"A ONE YEAR CROSS SECTIONAL STUDY TO ASSESS THE CLINICAL CORRELATION BETWEEN CAROTID INTIMA-MEDIA THICKNESS AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL"

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ENDORSEMENT

This is to certify that the dissertation entitled **"A ONE YEAR CROSS SECTIONAL STUDY TO ASSESS THE CLINICAL CORRELATION BETWEEN CAROTID INTIMA-MEDIA THICKNESS AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL"** is a bonafide research work done by **CANDIDATE REG NO. BG0113013**.

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LIST OF ABBREVIATIONS USED

µL	-	Micro liter
ACPA	-	Anti-citrullinated peptide antibodies
ACR	-	American College of Rheumatology
AD	-	Anno Domini
ADLs	-	Activities of daily living
ALP	-	Alkaline phosphatase
ALT	-	Alanine Transaminases
ANA	-	Antinuclear antibody
ANOVA	-	Analysis of variance
anti-CCP	-	Anti-cyclic citrullinated peptide antibodies
APR	-	Acute-phase response
ARA	-	American Rheumatoid Association
ASE	-	American Society of Echocardiography
AST	-	Aspartate Transaminases
BC	-	Before Christ
CAD	-	Coronary artery disease
CBC	-	Complete blood cell
CCA	-	Common carotid artery
CCP	-	Cyclic citrullinated peptide
CHD	-	Coronary heart disease
CIA	-	Collagen-induced arthritis
CIMT	-	Carotid intima-media thickness
cm/sec	-	Centimeters per second
cms	-	Centimeters

CRF	-	Chronic renal failure
CRP	-	C-reactive protein
cumm	-	Cubic millimeter
CURES	-	Chennai Urban Rural Epidemiology Study
CV	-	Cardiovascular
CVA	-	Cerebrovascular accident
CVD	-	Cardiovascular disease
DAS	-	Disease activity score
DC	-	Dendritic cells
DIP	-	Distal interphalangeal
DMARD	-	Disease-modifying antirheumatic drug
e.g.,	-	For example
EDV	-	End diastolic velocity
ELISA	-	Enzyme linked immunosorbant assay
ESR	-	Erythrocyte sedimentation rate
ESRD	-	End-stage renal disease
EULAR	-	European League Against Rheumatism
Fc	-	Fragment crystallizable
FMD	-	Flowmediated dilatation
g/dl	-	Grams per deciliter
GI	-	Gastrointestinal
HDL	-	High-density lipoprotein
HPA	-	Hypothalamic pituitary adrenal
Hs-CRP	-	Highly sensitive C-reactive protein
i.e.	-	That is

ICA	-	Internal carotid artery
IFN	-	Interferon
IgG	-	Immunoglobulin G
IgM	-	Immunoglobulin M
IHD	-	Ischaemic heart disease
IL	-	Interleukin
IMT	-	Intimal-Medial Thickness
IU/dL	-	International units per deciliter
IU/mL	-	International units per milliliter
LDL	-	Low-density lipoprotein
Lp-PL	-	Lipoprotein-associated phospholipase
MCP	-	Metacarpophalangeal joint
MCSF	-	Macrophage colony-stimulating factor
MetS	-	Metabolic Syndrome
mg/dl	-	Milligrams per deciliter
MHC	-	Major histocompatitibility complex
MHz	-	Mega Hertzs
mm	-	Millimeter
mm/Hr	-	Millimeters per hour
MMPs	-	Matrix metalloproteinases
MRI	-	Magnetic resonance imaging
MTP	-	Metatarsophalangeal joint
MTX	-	Methotrexate
n	-	Total number
NO	-	Nitric oxide

NSAIDs	-	Non steroidal anti-inflammatory drugs
NTG	-	Nitroglycerin
ox-LDL	-	Oxidation of low density lipoproteins
p	-	Probability
PAD	-	Peptidylarginine deiminase
PGs	-	Prostaglandins
PIP	-	Proximal interphalangeal joints
PSV	-	Peak systolic velocity
PVD	-	Peripheral vascular disease
r	-	Pearson's correlation co-efficient
RA	-	Rheumatoid arthritis
REACH	-	Rotterdam Early Arthritis Cohort
RF	-	Rheumatoid factor
ROC	-	Receiver operating characteristics
ROM	-	Range of motion
RR	-	Relative risk
SD	-	Standard deviation
SF	-	Synovial fluid
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvic transaminase
TCRs	-	T-cell receptor
TGF	-	Tumor growth factor
TIAs	-	Transient ischemic attacks
TNF	-	Tumor necrosis factor
U.S.	-	United States

UK	-	United Kingdom
ULN	-	Upper limit of normal
VAS	-	Visual analog scale
VEGF	-	Vascular endothelial growth factors
vs	-	Versus
WBC	-	White blood cell

ABSTRACT

Background and objectives

Rheumatoid arthritis (RA) is a chronic inflammatory disorder involving the joints with other organs including blood vessels and heart. There is increased of cardiovascular diseases in RA patients which is attributed to accelerated atherosclerosis. Carotid artery intima media thickness (CIMT) is noninvasive, reliable and economical test for assessment of atherosclerosis. The present study explored clinical relationship between CIMT with disease activity in patients with RA.

Materials and methods

This one year cross-sectional study was done in the Department of Medicine for a tertiary care hospital situated in North Karnataka. Based on the past three year hospital statistics, a total of 50 adult patients with RA were enrolled and evaluated for common carotid artery imaging to measure CIMT using high resolution B-mode ultrasonography. The disease severity was assessed based on Disease Activity Score (DAS) score.

Results

The male to female ratio was 6.14:1 and mean age was 49.88±12.12 years. With regard to clinical presentation, 76% of the patients had involvement of small joint of hand, 38% had tender joint count between 6 to 10 and swollen joint count of ≤5 (70%). Most of the patients presented with EULAR criteria score of 10 (28%). Based on DAS score, disease activity was severe in 44% and moderate in 48%. Based on the cut-off value of 0.57 for CIMT, majority of the

patients had raised CIMT. Mean CIMT was significantly differed with regard to duration of joint pain ($p=0.007$), tender joint count ($p<0.001$), swollen joint count ($p<0.001$), EULAR criteria score ($p<0.001$) and DAS score ($p<0.001$). Also significantly positive correlation was noted between CIMT and tender joint count ($r=0.711;R^2=0.506;p<0.001$), swollen joint count ($r=0.673;R^2=0.453;p<0.001$), EULAR criteria score ($r=0.611;R^2=0.373$; $p<0.001$) and DAS score ($r=0.729;R^2=0.532;p<0.001$).

Conclusion

The present study proposes strong relationship between CIMT and disease activity in RA hence CIMT can be a useful surrogate marker for detecting atherosclerosis in patients with RA.

Key words

Atherosclerosis; Carotid artery intima media thickness; Rheumatoid arthritis;

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that results in severe disability and premature mortality.[1] It is characterized by chronic inflammation of the synovial joints, which commonly leads to progressive joint destruction and consequent disability and reduction of quality of life.[2]

Rheumatoid arthritis affects 0.5 to 1% of the population.[3,4] Onset can occur at any age, but peaks between 30 and 50 years. Disability is common and significant. In a large U.S. cohort, 35% of patients with RA had work disability after 10 years.[5] The estimated prevalence of RA in developing countries is variable.[6] The prevalence of Rheumatoid Arthritis in India is estimated to be around 0.75%.[7] Projected to the whole population, this would give a total of about seven million patients in India.[8]

Like many autoimmune diseases, the etiology of RA is multifactorial. Genetic susceptibility is evident in familial clustering and monozygotic twin studies, with 50% of RA risk attributable to genetic factors. Smoking is the major environmental trigger for RA, especially in those with a genetic predisposition. Although infections may unmask an autoimmune response, no particular pathogen has been proven to cause RA.[5]

RA is characterized by inflammatory pathways that lead to proliferation of synovial cells in joints. Subsequent pannus formation may lead to underlying cartilage destruction and bony erosions. Overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-6, drives the destructive process.[5]

Patients with RA typically present with pain and stiffness in multiple joints. The wrists, proximal interphalangeal joints, and metacarpophalangeal joints are most commonly involved. Morning stiffness lasting more than one hour suggests an inflammatory etiology. Boggy swelling due to synovitis may be visible, or subtle synovial thickening may be palpable on joint examination. Patients may also present with more indolent arthralgias before the onset of clinically apparent joint swelling. Systemic symptoms of fatigue, weight loss, and low-grade fever may occur with active disease.[5]

In 2010, new classification criteria for RA were created in an effort to diagnose earlier which does not include presence of rheumatoid nodules or radiographic erosive changes, both of which are less likely in early RA. Symmetric arthritis is also not required allowing for early asymmetric presentation.[5]

Anti-citrullinated protein antibody is more specific for RA and may play a role in disease pathogenesis. Approximately 50 to 80 percent of persons with RA have rheumatoid factor, anti-citrullinated protein antibody, or both. C-reactive protein levels and erythrocyte sedimentation rate are often increased with active RA, and these acute phase reactants are part of the new RA classification criteria. C-reactive protein levels and erythrocyte sedimentation rate may also be used to follow disease activity and response to medication.[5]

Observational studies demonstrate that survival of patients with rheumatoid arthritis (RA) is significantly worse than in the general population, with life expectancy shortened by 3 to 18 years.[9,10] The morbidity and mortality caused by the disease are a consequence of local and systemic inflammatory processes that damage

cartilage, bone and soft tissue, as well as blood vessels and viscera. 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.[11]

Mortality due to coronary artery disease (CAD) has been found to be 59% higher in patients with RA when compared to general population.[12] This increase reflects the end-stage of persistence of a long standing or chronic inflammation and inflammation is considered as a pathogenetic factor for atherosclerosis. Studies linking the two conditions have provided data positively correlating RA and atherosclerosis. There appears to be a vascular involvement especially in seropositive RA with extra-articular features. The local vascular inflammation seems to induce diffuse endothelial dysfunction that initiates accelerated atherosclerosis.[13]

At present, several non-invasive imaging techniques offer a unique opportunity to study the relation between surrogate markers and the development of atherosclerosis in patients with RA. One of these is carotid intima-media thickness (CIMT) by high-resolution B-mode ultrasonography. It is a simple, reliable, inexpensive, non-invasive marker that is increasingly being used to detect subclinical atherosclerosis. This method has been approved in the assessment of subclinical atherosclerosis and considered as a good indicator of generalized atherosclerosis and coronary heart disease in subclinical stages in patients at risk.[10]

The CIMT corresponds to the width of the vessel intima and media (endothelium, connective tissue, and smooth muscles), which is also the site of lipid deposition and plaque formation. The increased CIMT reflects chronic vascular

thickening attributable to atherosclerosis or smooth muscle hypertrophy. The presence of atheromatous plaques represents more advanced stages of atherosclerosis.[10]

As an ethnic group, Asian Indians are predisposed to a high risk of metabolic syndrome, and premature atherosclerosis.[13] Thus, Indian patients with RA appear to be at a higher risk for developing atherosclerosis. However, sparse data are available regarding the burden of atherosclerosis among asymptomatic adult patients with RA in south India. Hence the present study was undertaken to find the correlation, between disease activity of rheumatoid arthritis and CIMT which is a marker of atherosclerosis so as to identify high risk RA patients who may benefit from active therapy to prevent clinical disease.

OBJECTIVES

The objective of this was to assess the clinical relationship between carotid intima media thickness with disease activity in patients with rheumatoid arthritis.

REVIEW OF LITERATURE

Historical note on rheumatic arthritis

The first known traces of arthritis dates back at least as far as 4500 BC. A text dated 123 AD, first describes symptoms which were very similar to that of rheumatoid arthritis. Morphological changes resembling RA was noted in skeletal remains of Native Americans found in Tennessee. In the Old World the disease is vanishingly rare before the 17th century and on this basis investigators believe it spread across the Atlantic during the Age of Exploration.[14]

The bones from the Tennessee site show no signs of tuberculosis even though it was prevalent at the time throughout the Americas.[15] Jim Mobley, at Pfizer, has discovered a historical pattern of epidemics of tuberculosis followed by a surge in the number of rheumatoid arthritis cases a few generations later. Mobley attributes the spikes in arthritis to selective pressure caused by tuberculosis. A hypervigilant immune system is protective against tuberculosis at the cost of an increased risk of autoimmune disease.[14]

Some of the paintings of Peter Paul Rubens may possibly depict the effects of rheumatoid arthritis. In his later paintings, his subject's hands showed, in the opinion of some physicians, increasing deformity consistent with the symptoms of the disease.[16] Rheumatoid arthritis appears to have been depicted in 16th century paintings as well.[17]

The first recognized description of rheumatoid arthritis was in 1800 by the French physician Dr Augustin Jacob Landré-Beauvais (1772–1840) who was based

in the famed Salpêtrière Hospital in Paris.[18] The name "rheumatoid arthritis" itself was coined in 1859 by British rheumatologist Dr Alfred Baring Garrod.[19]

Definition and classification

The first attempt to classify RA by the American Rheumatism Association (now, the American College of Rheumatology) was way back in 1956. These criteria incorporated 11 clinical, serological, radiological and histological features with 19 exclusions.[20,21] These sets classified disease as 'definite', 'probable' and 'possible' RA. The 'definite' group required 5 criteria with 6 weeks of symptoms while the 'probable' RA required 3 criteria with 4 weeks of joint symptoms.[20] The 1958 revision added the category of 'classic' RA for patients exhibiting 7 out of 11 criteria.[21] The criteria for RA were revised after a long gap of 25 years in 1987.[23] The 1987 ARA criteria were developed using RA cases and controls attending hospital clinics. The patients included had longstanding disease (mean disease duration 7.7 years). These criteria incorporated the typical features of symmetric inflammatory polyarthritis and did away with the categories of definite, possible and probable. These criteria were simple to use and required only one laboratory test, rheumatoid factor, and only one set of radiographs, posteroanterior view of hands and wrists.[21,23]

The 1987 criteria[23] were widely adopted all over the world and paved the way for uniformity in case inclusion. These criteria had a sensitivity of 91-94% and specificity of 89% when comparing RA with non-RA. These criteria served their purpose admirably well for several years.[21]

Over a period of time a few shortcomings became apparent. The first was the poor performance characteristics of 1987 criteria in early RA. This coincided with a shift in the focus in RA from 'established' to 'early disease'. Two things have fuelled interest in early RA: an explosion of targeted biologic therapies and the growing realization that time to treat is a key driver of outcome. The cut offs between 'early' and 'established' RA have progressively decreased.[21]

Over the past decade anti-citrullinated peptide antibodies (ACPA), also know as anti-cyclic citrullinated peptide antibodies (anti-CCP), have emerged as an important serologic marker for RA. These predict erosive disease and are poor prognostic markers.[24] These antibodies obviously do not find mention in the 1987 criteria which were formulated prior to the advent of ACPA.[23] Liao and colleagues attempted to incorporate ACPA in the 1987 criteria which improved upon the sensitivity of the ACR criteria, most remarkably for subjects with symptoms <6 months.[25] However, their attempt did not attract widespread attention. The latest attempt in remission, the 2010 criteria, aim to rectify many of these shortcomings.[26,27]

2010 ACR/EULAR Criteria for RA[26,27]

The 2010 ACR/EULAR classification criteria for rheumatoid arthritis

Joint involvement

- 1 large joint (0 points)
- 2-10 large joints (1 point)
- 1-3 small joints (2 points)
- 4-10 small joints (3 points)
- >10 joints [at least 1 small joint] (5 points)

Duration of synovitis

- Less than 6 weeks (0 points)
- 6 weeks or longer (1 point)

Serology

- RF/CCP negative (0 points)
- RF or CCP positive at low titer, <3 times upper limit of normal (ULN) (2 points)
- RF or CCP positive at high titer, defined as >3 times ULN (3 points)

Acute phase reactants

- Normal ESR/CRP (0 points)
- Abnormal ESR/CRP (1 point)

Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment; "Large joints" refers to shoulders, elbows, hips, knees, and ankles; "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

The 2010 criteria emerged as a joint initiative of American and European workers and were published simultaneously in the ACR and EULAR journals. The major aim was to permit early identification of poor prognosis arthritis much before the classic features of florid disease became apparent. These criteria, as shown above are meant to be applied to patients newly presenting with undifferentiated inflammatory synovitis. These incorporate factors that best discriminate between those patients who are and those who were not at high risk for persistent and/or erosive disease this being the appropriate current paradigm underlying the disease construct 'RA'.[21,26,27]

In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in four domains: number and site of involved joints (range 0–5), serological abnormality (range 0–3), elevated acute-phase response (range 0–1) and symptom duration (two levels; range 0–1). These criteria have done away with features that are typical of late disease, namely symmetry, rheumatoid nodules and radiographic changes. There is no longer insistence on disease duration of 6 weeks. The criterion of morning stiffness has been dispensed with and the serologic marker of ACPA included. This practically means that a patient with 1 small joint involvement (2 points), high levels of RF/ACPA (3 points) and high ESR/CRP (1 point) can be classified as RA even on day 1 of symptoms. These criteria have a provision whereby some patients can be classified as RA even if they do not fulfill the criteria. These include patients with erosive disease typical of RA with a history compatible with prior fulfillment of the

2010 criteria and patients with long-standing disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria.[21,26,27]

The performance characteristics of the 2010 ACR/EULAR criteria are being tested in early arthritis.[26,27] Alves et al.[28] applying these criteria to patients with early arthritis (<12 months) in the Rotterdam Early Arthritis Cohort (REACH) reported a sensitivity of 70% and equal specificity (70%). Using the cutpoint of 6 to start treatment, in this study 30% of persistent patients would not be treated, whereas 30% of the nonpersistent patients would have been. Lowering the cut-point to 4 increased sensitivity to 0.92 at the cost of specificity (0.33). Increasing it to 7 had a sensitivity of 0.53 and a specificity of 0.85. Similar results have been reported by other groups. Of the 301 patients with early arthritis (0-12 months), only 28% fulfilled the 1987 ACR criteria at baseline while 45% satisfied the 2010 ACR/EULAR criteria for RA.[29] Nearly one-third of the patients in this cohort who would have been labeled as undifferentiated arthritis using the 1987 criteria[23] met the 2010 criteria for RA.[26,27]

Overdiagnosis, however, remains an area of concern with the new criteria. More patients whose disease eventually resolved without ever requiring DMARD were classified at baseline as RA according to the 2010 criteria than with the 1987 criteria (8%) vs 2%; p=0.01) in a study from UK.[30]

Similar concerns have been voiced from India especially in context of infectious arthritis where patients with Chikungunya arthritis may easily satisfy the 2010 criteria.[31]

Clearly, the quest for ideal criteria is far from over. The 2010 criteria[26,27] for RA represent a significant advance but may need refinement in different populations and as new knowledge becomes available.[21]

Epidemiology

The prevalence of rheumatoid arthritis (RA) varies between 0.5% and 1% worldwide and is more common in women and in developed countries.[32] The prevalence of self-reported rheumatic disease confirmed by physician in population-based studies varies from a low of 14.8% in Pakistan to a high of 27.4% in Greece.[32]

Rheumatoid arthritis is a chronic systemic inflammatory illness with prevalence of approximately 0.75% in India.[7]

The prevalence rate of RA is approximately 1%, increasing with age and peaking at age 35-50 years. Women are affected by RA approximately 3 times more often than men,[33,34] but sex differences diminish in older age groups.[33]

Etiology

Like many autoimmune diseases, the etiology of RA is multifactorial. Genetic susceptibility is evident in familial clustering and monozygotic twin studies, with 50 percent of RA risk attributable to genetic factors. Genetic associations for RA include human leukocyte antigen-DR4, and -DRB1, and a variety of alleles called the shared epitope. Genome-wide association studies have identified additional genetic signatures that increase the risk of RA and other autoimmune diseases, including STAT4 gene and CD40 locus. Smoking is the major environmental trigger for RA, especially in those with a genetic predisposition.

Although infections may unmask an autoimmune response, no particular pathogen has been proven to cause RA. RA is characterized by inflammatory pathways that lead to proliferation of synovial cells in joints. Subsequent pannus formation may lead to underlying cartilage destruction and bony erosions. Overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-6, drives the destructive process.[5]

Risk factors

Older age, a family history of the disease, and female sex are associated with increased risk of RA, although the sex differential is less prominent in older patients. Both current and prior cigarette smoking increases the risk of RA (relative risk [RR] = 1.4, up to 2.2 for more than 40-pack-year smokers). Pregnancy often causes RA remission, likely because of immunologic tolerance. Parity may have long-lasting impact; RA is less likely to be diagnosed in parous women than in nulliparous women (RR = 0.61). Breastfeeding decreases the risk of RA (RR = 0.5 in women who breastfeed for at least 24 months), whereas early menarche (RR = 1.3 for those with menarche at 10 years of age or younger) and very irregular menstrual periods (RR = 1.5) increase risk. Use of oral contraceptive pills or vitamin E does not affect RA risk.[5]

Clinical features

Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown cause. The hallmark feature of this condition is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, although any joint lined by a synovial membrane may be involved. The severity of RA may fluctuate over time, but

chronic RA most commonly results in the progressive development of various degrees of joint destruction, deformity, and a significant decline in functional status. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant.[35]

Patients with rheumatoid arthritis may report difficulty performing activities of daily living (ADLs) (dressing, standing, walking, personal hygiene, using their hands). In addition to articular deterioration, constitutional symptoms, including fatigue, malaise, morning stiffness, weight loss, and low-grade fever, may be present. Rheumatoid arthritis has an insidious onset in most patients. It may begin with systemic features, such as fever, malaise, arthralgias, and weakness, before the appearance of overt joint inflammation and swelling. A small percentage of patients with this disease (approximately 10%) have an abrupt onset with the acute development of synovitis and extra-articular manifestations. Spontaneous remission is uncommon, especially after the first 3-6 months.[35]

Joint involvement is the characteristic feature of rheumatoid arthritis. In general, the small joints of the hands and feet are affected in a relatively symmetric distribution. In decreasing frequency, the MCP, wrist, PIP, knee, MTP, shoulder, ankle, cervical spine, hip, elbow, and temporomandibular joints are most commonly affected. Affected joints show inflammation with swelling, tenderness, warmth, and decreased range of motion (ROM). Atrophy of the interosseous muscles of the hands is a typical early finding. Joint and tendon destruction may lead to deformities such as ulnar deviation, boutonniere and swan-neck deformities, hammer toes, and, occasionally, joint ankylosis.[35]

Other commonly observed musculoskeletal manifestations include tenosynovitis (defined as inflammation of the tendon and its enveloping tendon sheath) and associated tendon rupture due to tendon and ligament involvement, most commonly involving the fourth and fifth digital extensor tendons at the wrist; periarticular osteoporosis due to localized inflammation; generalized osteoporosis due to systemic chronic inflammation, immobilization-related changes, or corticosteroid therapy; and carpal tunnel syndrome. Most patients with RA have muscle atrophy from disuse, which is often secondary to joint inflammation.[35]

Fingers

The boutonniere deformity, describes nonreducible flexion at the PIP joint along with hyperextension of the distal interphalangeal (DIP) joint of the finger. This deformity occurs as a result of synovitis stretching or rupturing the PIP joint through the central extensor tendon, with concomitant volar displacement of the lateral bands. When the lateral bands have subluxed far enough to pass the transverse axis of the joint, they become flexors of the PIP joint. Hyperextension of the DIP joint occurs as the tendons shorten with time. A compensatory and reducible hyperextension may occur at the MCP joint. Consequences of boutonniere deformity are loss of thumb mobility and pincher grasp. Swan-neck deformity of the finger describes hyperextension at the PIP joint with flexion of the DIP joint. The deformity may be initiated by (1) disruption of the extensor tendon at the DIP joint with secondary shortening of the central extensor tendon and hyperextension of the PIP joint, or (2) volar herniation of the PIP joint capsule due to weakening from chronic synovitis with subsequent tightening of the lateral bands and central

extensor tendon. The lateral bands may become shortened over time and lie dorsally, limiting PIP flexion and ineffectively extending the DIP joint.[35]

Tightness of intrinsic muscles (interossei, lumbricals) may cause major declines in mobility of the fingers. This characteristic is ascertained on examination when the PIP joint cannot be flexed while the MCP joint is fully extended, but it can be flexed if the MCP is in flexion (Bunnell test); primary PIP joint pathology would be evident with the MCP joint in either position. To assess this accurately, the phalanx must be aligned with the metacarpal, as the intrinsic muscles on the ulnar side are slack when ulnar deviation at the MCP joint exists, thus allowing more motion.[35]

Flexor tenosynovitis of the fingers is common and suggests a poor prognosis. "Triggering" of the finger occurs when thickening or nodule formation of the tendon interacts with the concomitant tenosynovial proliferation, trapping the tendon in a flexed position (stenosing tenosynovitis). Tendon rupture may occur due to infiltrative synovitis in the digit or bony erosion of the tendon at the wrist (especially the flexor pollicis longus). Arthritis mutilans (sometimes called opera glass hands) results if destruction is severe and extensive, with dissolution of bone. In the small joints of the hands, the phalanges may shorten and the joints may become grossly unstable. Pulling on the fingers during examination may lengthen the digit much like opening opera glasses, or the joint may bend in unusual directions merely under the pull of gravity.[35]

Metacarpophalangeal joints

Two typical deformities that alter the alignment of the palmar skeletal arches and the stability of the fingers may occur at the MCP joints: volar subluxation and ulnar deviation. Most cases of ulnar deviation are accompanied by counterpoised radial deviation of the wrist, roughly proportional to the degree of ulnar deviation of the fingers. The volar plate is firmer and more substantial than other portions of the MCP joint capsule and, therefore, effectively limits extension and dorsal movement at the joint. The greater strength of the flexor muscles relative to the extensor muscles causes volar migration of the proximal phalanx after synovial-based inflammation has weakened ligament and tendon insertions about the MCP joint capsule.[35]

Ulnar deviation occurs after synovitis has led to stretching and attenuation of the volar plate and collateral ligaments, allowing dislocation of the flexor tendon volarward and ulnarward. The supporting structures of the extensor tendons also may become attenuated or destroyed by synovial distention and invasion, loosening the tendons so that they no longer ride centrally and dorsally over the metacarpal head but move into the cleft between the MCP joints. If the extensor tendon subluxation is beyond the transverse axis of the MCP joint, the tendon becomes a flexor at that joint, further limiting the active extension of the fingers.[35]

Wrists

Multiple deformities may occur in the wrist. Disruption of the radioulnar joint with dorsal subluxation of the ulna (caput ulna), as well as rotation of the carpus on the distal radius with an ulnarly translocated lunate, is common. The

combination of an ulnar drift of the fingers and carpal rotation is known as a zigzag deformity. Shortening of the carpal height, due in part to cartilage loss, is seen with rotational deformities.[35]

Dorsal subluxation of the ulna often allows the ulnar styloid to be depressed volarly on examination, much like depressing a piano key. Subluxation may lead to rupture of the extensor tendons of the little, ring, and long fingers, because the end of the distal ulna is roughened secondary to erosion of bone and may abrade the tendons as they move back and forth during normal hand function, much like a rope being frayed while rubbing over a sharp rock. This process is especially likely to lead to tendon rupture if there is associated tenosynovitis. Entrapment of the median nerve as it passes through the carpal tunnel leads to decreased sensation on the palmar aspect of the thumb, index finger, and long finger and on the radial aspect of the ring finger; weakness and atrophy of the muscles in the thenar eminence also occurs. The less frequent entrapment of the ulnar nerve at the wrist causes decreased sensation over the little finger and the ulnar aspect of the ring finger and decreased interosseous muscle strength and mass.[35]

Elbow

Elbow involvement is often detected by palpable synovial proliferation at the radiohumeral joint and is commonly accompanied by a flexion deformity, such as in contractures. Olecranon bursal involvement is common, as are rheumatoid nodules in the bursa and along the extensor surface of the ulna. Rheumatoid arthritis commonly involves the shoulders and is manifested by tenderness, nocturnal pain, and limited motion. Initially, swelling occurs anteriorly, but it may be difficult to

detect and is present on examination in a minority of patients at any point in time. Rotator cuff degeneration secondary to synovitis may limit abduction and rotation. Superolateral migration of the humerus occurs with complete tears. Glenohumeral damage leads to pain with motion and at rest and typically leads to severely restricted motion or "frozen shoulder syndrome." Acromioclavicular arthritis is not as frequent or as disabling as the other manifestations of this disease.[35]

Feet and ankles

The ankle joint itself is rarely involved without midfoot or MTP involvement. The ankle does not often deform, as it is a mortise joint. Major structural changes occur in the midfoot and foot due to the combination of chronic synovitis and weight bearing. Posterior tibialis tendon involvement or rupture may lead to subtalar subluxation, which results in eversion and migration of the talus laterally. Midfoot disease leads to loss of normal arch contour with flattening of the feet. The MTP joints are inflamed in most patients and, due to the heavy loads they bear, commonly become deformed over time. The great toe typically develops hallux valgus (a bunion); subluxation of the phalanx at the MTP joint of the other toes predominantly occurs dorsally. The toes may exhibit compensatory flexion due to a fixed length of the flexor tendons, thus resulting in hammer toes (thought to look like piano hammers). The second and third metatarsal heads commonly protrude and may become the primary weight-bearing surface at the MTP joints. Calluses and pain upon weight bearing result.[35]

Knees

Rheumatoid arthritic knees may develop large effusions and abundant accumulation of synovium. Knee effusions and synovial thickening are common and are easily detected during the early course of the disease. Persistent effusions may lead to inhibition of quadriceps function by spinal reflexes, resulting in subsequent atrophy. Instability may develop after progressive loss of cartilage and weakening of ligaments; deformity may include genu valgus or varus and flexion deformities. The energy expenditure to stand or walk significantly increases if there are flexion deformities of the knees.[35]

Hips

The hips are commonly involved in rheumatoid arthritis; however, because of their deep location, their involvement is not always readily apparent early on during the course of the disease. Hips are difficult to examine by direct inspection or palpation. Limited motion or pain on motion and weight bearing are the hallmarks of hip involvement. The Patrick maneuver (flexion, external rotation, and abduction) is abnormal in this situation. A flexion deformity may be demonstrable by conducting a Thomas test, which is performed by flexing one hip (with the patient supine) while restricting pelvic motion by keeping the other hip in the neutral position on the examination table. If the hip cannot be maintained in the neutral position, a contracture is present.[35]

Cervical spine

Neck pain on motion and occipital headache are common manifestations of cervical spine involvement. Most patients with cervical spine involvement have a

history of the disease for more than 10 years. Clinical manifestations of early cervical spine disease consist primarily of neck stiffness that is perceived throughout the entire arc of motion. The atlantoaxial joint is a synovial-lined joint and is susceptible to the same proliferative synovitis and subsequent instability seen in the peripheral joints. Patients with severe destruction in the hands (arthritis mutilans) are very likely to have symptomatic cervical spine abnormalities, as are those patients taking significant amounts of corticosteroids for control of rheumatoid arthritis.[35]

Neurologic involvement ranges from radicular pain to a variety of spinal cord lesions that may result in weakness (including quadriparesis), sphincter dysfunction, sensory deficits, and pathologic reflexes. Transient ischemic attacks (TIAs) and cerebellar signs may reflect vertebral artery impingement from cervical subluxation or basilar artery impingement from upward migration of the dens. Tenosynovitis of the transverse ligament of C1 may lead to C1-C2 instability. Myelopathy secondary to rupture of the transverse ligament may lead to neurologic deficits. Radiculopathy is most common at the C2 root, although symptomatic subluxations may occur at any level.[31]

Symptoms of cervical myelopathy are gradual in onset and are often unrelated to either the development of or accentuation in neck pain. When neck pain does occur, it frequently radiates over the occiput region in the distribution of the C1-3 nerve roots. The Lhermitte sign, in which tingling paresthesia that descends through the thoracolumbar spine occurs as the cervical spine is flexed, is typically observed. During the physical examination, it is important to assess the following signs and symptoms like stiffness, tenderness, pain on motion, swelling, deformity, limitation of motion, extra-articular manifestations, rheumatoid nodules.[35]

Stiffness, Tenderness, and Pain on Motion

On physical examination, stiffness is determined by limitation of motion, which may vary with the time of day. Stiffness due to articular surface derangement or soft-tissue contractures about the joint does not vary with the time of day. Severe stiffness in the hands may improve with heat, but it is most effectively relieved with active exercise. These modalities reduce stiffness immediately after application, but unfortunately, they do not prevent the return of stiffness. Direct palpation can elicit joint tenderness, which can vary significantly among patients and with the method of application of force used. The examiner should try to apply approximately the same pressure for each patient examined to minimize variation over time.[35]

The enlarged synovial membrane, periarticular ligaments, and supporting structures are the major pain-sensitive structures. Muscles may also become tender, but rarely is this due to myositis. Muscle tenderness is not specific for RA. Severe muscle tenderness should suggest another differential diagnosis, including fibromyalgia or a regional pain disorder. Bony prominences are generally tender, as periarticular structures tend to be more vulnerable to palpation at these sites. Pain on motion is often used as a surrogate for tenderness in joints that are difficult to directly palpate due to overlying muscle and other tissues. Such areas include the cervical spine, shoulder, and hip. Pain on motion of the joint may be due to noninflammatory processes that also interfere with the joint's normal, almost frictionless motion, including damage of cartilage and bone. Additionally, joint instability or subluxation causes pain on motion because of musculotendinous imbalances across the joint. Documenting the positions of motion at which pain occurs can be useful.[35]

Swelling, Deformity, and Limitation of Motion

Enlargement of the synovial membrane is noted on physical examination as thickening of the synovium that may obscure joint margins. This thickening is most evident in the small joints of the hands and feet. In the MCP and MTP joints, the outline of the base of the proximal phalanx may become indistinct, and in the PIP joints of the fingers, a fusiform swelling is noted due to the anatomy of the synovial reflections. If synovial proliferation is abundant, a doughy texture may be felt due to the resultant soft-tissue mass. Such synovial proliferation is commonly identified in the PIP, MCP, elbow, ankle, MTP, and knee joints, as well as in the flexor tendons of the fingers, the common extensor compartment of the dorsal wrist, and the extensor carpi ulnaris tendon sheath. Joint effusions may also contribute to swelling by distending the joint. When the effusion is put under increased pressure with joint flexion, the synovium may be forced between articular structures and a portion becomes trapped and separated from the rest of the joint, forming a Baker cyst. More fluid is forced into the structure with subsequent loading of the distended joint, and a 1-way valve effect may prevent the fluid from returning to the joint.[35]

Baker cysts may be seen in most peripheral joints and are most commonly recognized in the knee.[36] The larger the effusion, the more likely a painful cyst will develop. Rupture of a Baker cyst at the knee may resemble acute thrombophlebitis, with distal dissection of inflammatory joint contents along fascial planes as far as the ankle and dorsal foot. Deformity of the joint may develop over time as articular and supporting structures are damaged by the inflammatory process. By the time deformity has developed, the diagnosis of rheumatoid arthritis is in little doubt; however, recognition of the inflammatory aspects of the arthritis before the

development of deformity is required for optimal management of RA. Loss of cartilage from proteolytic and mechanical degradation, combined with stretching and weakening of the periarticular ligaments and their attachments, allows forces acting across the joints to deform them. The small joints in the hands and feet are most commonly deformed in this manner; more than 10% of patients with RA develop deformity of the small joints of the hands within the first 2 years of the disease, and at least 33% develop such deformities over time. Joint instability is seen if disruption of supporting structures has occurred.[35]

Limitation of motion occurs as a result of articular surface damage, joint and tendon sheath swelling, or alteration of joint supporting structures. Effusion may limit joint motion through pain or by causing sufficient tightness of the joint capsule to impede joint mobility. Fibrosis involving tendons and muscles may limit normal joint motion and result in flexion contractures. Joint deformities and subluxations invariably limit motion because of mechanical factors.[35]

Extra-Articular Manifestations

Rheumatoid arthritis is a systemic disease, and most individuals with the disease experience extra-articular manifestations such as generalized malaise and fatigue. Rarely, a patient presents with extra-articular manifestations before the onset of arthritis. Some of these manifestations are more common in men (pleural involvement, vasculitis, pericarditis), but the proportion of men and women who have other manifestations is similar to that of RA overall. Rheumatoid nodules occur in approximately 25% of patients with RA, but they occur in less than 10% of patients during the first year of the disease. These lesions are most commonly found

on extensor surfaces or sites of frequent mechanical irritation. The olecranon process, proximal ulna, back of the heel, occiput, and ischial tuberosities are common periosteal sites for rheumatoid nodule development. Nodules may also form in subcutaneous tissues of the finger, in toe and heel pads, in tendons, and in viscera. RF is almost invariablypresentinpatientswith rheumatoid nodules; the absence of RF suggests other diagnoses.[35]

Frequently, there is a discrepancy between the level of articular inflammation and the progression of nodule formation. Patients with rheumatoid nodulosis have a great number of nodules, usually subcutaneous, and may have little active synovitis. In a similar fashion, patients whose articular inflammation responds well to treatment with methotrexate (MTX) may have a seemingly paradoxical rapid increase in the number of nodules.[35]

Organ Systems

Rheumatoid arthritis affects several organ systems, such as cutaneous, cardiac, pulmonary, gastrointestinal, renal, vascular, hematologic, neurologic, ocular. Subcutaneous nodules (rheumatoid nodules) develop in many patients with rheumatoid arthritis whose RF value is abnormal, often over pressure points (olecranon). Vasculitic lesions of the skin may manifest as palpable purpura or skin ulceration (leg ulceration). Additionally, palmar erythema and pyoderma gangrenosum may be noted.[35]

Cardiovascular morbidity and mortality are increased in patients with RA. Nontraditional risk factors appear to play an important role. Myocardial infarction, myocardial dysfunction, and asymptomatic pericardial effusions are common;

symptomatic pericarditis and constrictive pericarditis are rare. Myocarditis, coronary vasculitis, valvular disease, and conduction defects are occasionally observed. Rheumatoid arthritis involvement of the lungs may take several forms, including pleural effusions, interstitial fibrosis, nodules (Caplan syndrome), and bronchiolitis obliterans organizing pneumonia. Methotrexate therapy can induce interstitial fibrosis that may be difficult to distinguish from that which naturally occurs in patients with RA.[35]

Intestinal involvement, as with kidney involvement, is often secondary to associated processes such as medication effects, inflammation, and other diseases. The liver is often affected in patients with Felty syndrome (RA, splenomegaly, and neutropenia). The kidneys are usually unaffected directly by RA. Secondary involvement is common, including that due to medications (NSAIDs, gold, cyclosporin), inflammation (amyloidosis), and associated diseases (Sjogren syndrome with renal tubular abnormalities). Vasculitic lesions can occur in any organ but are most commonly found in the skin. Lesions may present as palpable purpura, skin ulcers, or digital infarcts. Most active patients have an anemia of chronic disease. Several hematologic parameters parallel disease activity, including normochromic-normocytic anemia, thrombocytosis, and eosinophilia, although the latter is uncommon. Leukopenia is a finding in patients with Felty syndrome.[35]

Nerve entrapment is common, such as with the median nerve in carpal tunnel syndrome. Vasculitic lesions, mononeuritis multiplex, and cervical myelopathy may cause serious neurologic consequences. Peripheral myopathy may be noted as well.[35]

Diagnostic tests

No test results are pathognomonic for rheumatoid arthritis; instead, the diagnosis is made using a combination of clinical, laboratory, and imaging features. Potentially useful laboratory studies in suspected RA include the following:[35]

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Complete blood cell (CBC) count
- Rheumatoid factor (RF) assay
- Antinuclear antibody (ANA) assay
- Anticyclic citrullinated peptide antibody (anti-CCP) assay (currently used in the 2010 ACR/EULAR classification criteria)
- Anti-RA33 antibody assay

These studies fall into three categories: markers of inflammation, hematologic parameters, and immunologic parameters.

Markers of inflammation

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level are associated with disease activity. In addition to the ESR and the CRP level, the CRP value over time correlates with radiographic progression.[35]

Hematologic parameters

The CBC count commonly demonstrates anemia of chronic disease and correlates with disease activity; it improves with successful therapy. Hypochromic

anemia suggests blood loss, commonly from the GI tract (associated with NSAIDs). Anemia may also be related to disease-modifying antirheumatic drug (DMARD) therapy. Thrombocytosis is common and is also associated with disease activity. Thrombocytopenia may be a rare adverse event of therapy and may occur in patients with Felty syndrome. Leukocytosis may occur but is usually mild. Leukopenia may be a consequence of therapy or a component of Felty syndrome, which may then respond to DMARD therapy.[35]

Radiography

Radiography remains the first choice in imaging RA, as it is inexpensive, cheap, and easily reproducible and allows easy serial comparison for assessment of disease progression. Views of the hands, wrists, knees, feet, elbows, shoulders, hips, cervical spine, and other joints should be assessed with radiographs when indicated. Note that erosions may be present in the feet, even in the absence of pain and in the absence of erosions in the hands.[35]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) provides a more accurate assessment, as well as earlier detection of lesions, but the cost of the examination and the small size of the joints involved limit widespread use. This modality is used primarily in patients with abnormalities of the cervical spine; early recognition of erosions based on MRI images has been sufficiently validated.[35]

Ultrasonography

Ultrasonography of specific joints based on radiographs may have a role as well. This technique allows recognition of effusions in joints that are not easily accessible (hip joints, shoulder joints in obese patients) and of cysts (Baker cysts). In addition, high-resolution sonograms may allow visualization of tendon sheaths, changes and degree of vascularization of the synovial membrane, and even erosions; however, this needs further validation. Ultrasonography may be used as an office-based procedure.[35]

Bone scanning

Bone scan findings may help to distinguish inflammatory from noninflammatory changes in patients with minimal swelling, and densitometry findings are useful for helping to diagnose changes in bone mineral density that are indicative of osteoporosis.[35]

Joint Aspiration

Consider joint aspiration when making the definitive diagnosis of rheumatoid arthritis or when ruling out coexistent infection or crystal arthritis in an acutely swollen joint. New-onset monoarticular arthritis or an unusual pattern of a joint flare in a patient with RA should encourage strong consideration for joint aspiration and evaluation. Analyze fluid for Gram stain, cell count, culture, and overall appearance. In patients with RA, synovial fluid analysis typically reveals inflammation (WBC count >2000/µL), with WBC counts generally from 5,000-50,000/µL. Usually, neutrophil predominance (60-80%) is observed in the synovial fluid (in contrast with mononuclear cell predominance in the synovium). Because of

a transport defect, glucose levels of synovial fluids (as well as pleural and pericardial fluids) in patients with RA are often low compared with serum glucose levels.[35]

Histology

Early in the disease process, there is an influx of inflammatory cells into the synovial membrane, with subsequent angiogenesis, proliferation of chronic inflammatory (mononuclear) cells and resident synovial cells, and marked histologic changes a 2-cell-layer lining membrane changes to a thickened membrane that often has villous projections into the joint space. The lymphoplasmacytic infiltration of the synovium with neovascularization seen in rheumatoid arthritis is similar to that seen in other conditions characterized by inflammatory synovitis. Early rheumatoid nodules are characterized by small-vessel vasculitis and later by granulomatous inflammation.[35]

Immunologic parameters

Immunologic parameters include autoantibodies (RF, anti-RA33, ANA), and RF is an immunoglobulin (IgM) antibody directed against the Fc fragment of IgG that is present in approximately 60-80% of patients with rheumatoid arthritis over the course of their disease; however, it is present in fewer than 40% of patients with early RA. RF values fluctuate somewhat with disease activity, although high-titered RF generally remains present even in patients with drug-induced remissions. RF is not specific for RA, as it is also present in other connective tissue diseases, infections, and autoimmune disorders, as well as in 1-5% of healthy people.[35]

Pathophysiology

Although the exact cause of RA remains unknown, recent findings suggest a genetic basis for disease development. More than 80% of patients carry the epitope of the HLA-DRB1*04 cluster, and patients expressing two HLA-DRB1*04 alleles are at elevated risk for nodular disease, major organ involvement and surgery related to joint destruction.[37]

Single-nucleotide polymorphism genotyping across the MHC has identified additional alleles related to RA risk, including those found on the conserved A1-B8-DR3 (8.1) haplotype and those near the HLA-DPB1 gene. Other RA-associated loci are PTPN22, PADI4, STAT4, TRAF1-C5 and TNFAIP3, although non-MHC risk alleles may represent only 3-5% of the genetic burden of RA. Environmental factors, such as smoking and infection, may also influence the development, rate of progression and severity of RA.[37]

Various immune modulators (cytokines and effector cells) and signalling pathways are involved in the pathophysiology of RA. The complex interaction of immune modulators is responsible for the joint damage that begins at the synovial membrane and covers most IA structures. Synovitis is caused by the influx or local activation, or both, of mononuclear cells (including T cells, B cells, plasma cells, dendritic cells, macrophages and mast cells) and by angiogenesis. The synovial lining then becomes hyperplastic, and the synovial membrane expands and forms villi. The osteoclast-rich portion of the synovial membrane, or pannus, destroys bone, whereas enzymes secreted by neutrophils, synoviocytes and chondrocytes degrade cartilage.[37,38]

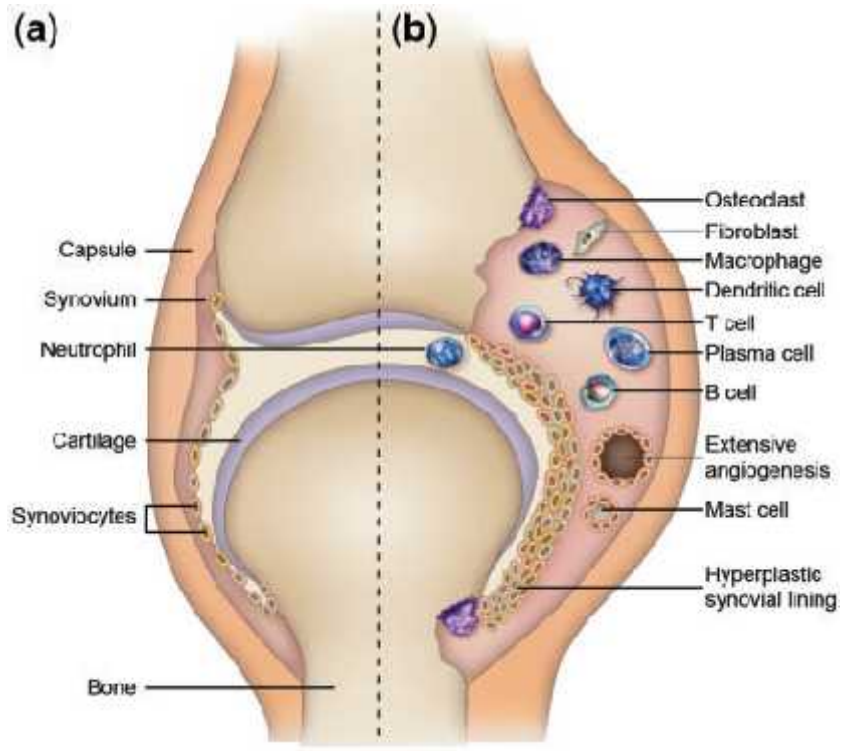


Figure 1. Schematic view of a normal joint (a) and a joint affected by RA (b). The joint affected by RA (b) shows increased inflammation and cellular activity[38]

In addition to joint symptoms, many patients experience extra-articular or systemic manifestations, or both. Extra-articular manifestations include rheumatoid nodules, vasculitis, pericarditis, keratoconjunctivitis sicca, uveitis and rheumatoid lung. Systemic manifestations include acute-phase protein production, anaemia, cardiovascular disease (CVD), osteoporosis, fatigue and depression.[37]

Effector cells involved in the pathobiology of RA

The earliest event in RA pathogenesis is activation of the innate immune response, which includes the activation of dendritic cells by exogenous material and autologous antigens.[37]

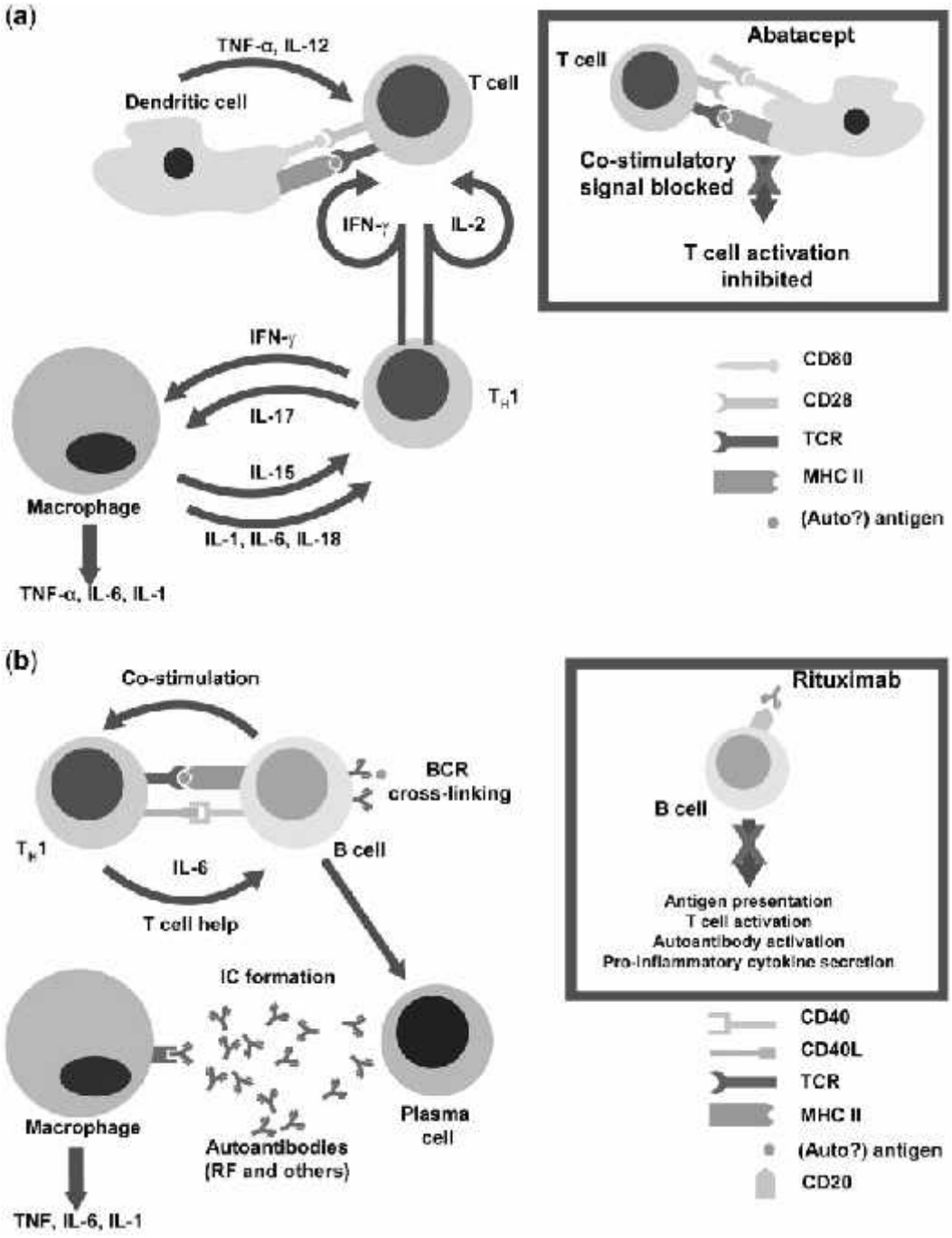


Figure 2. Consequences of the activation of effector cells by cytokines. (a) Effects on T cells. The inset depicts the mechanism of action of abatacept, which inhibits T-cell co-stimulation. (b) Effects on B cells. The inset depicts the mechanism of action of rituximab, which selectively depletes CD20+ B cells[37-39]

Antigen-presenting cells, including dendritic cells, macrophages and activated B cells, present arthritis-associated antigens to T cells. Concurrently, CD4+ T cells that secrete IL-2 and IFN-g infiltrate the synovial membrane. As noted previously, most patients with RA carry the epitope of the HLA-DRB1*04 cluster. These alleles share a homologous amino acid sequence on the HLA-DR b-chain that confers binding of specific peptides and affects antigen presentation to TCRs. Disease-associated HLA-DR alleles may present arthritis-related peptides, leading to the stimulation and expansion of autoantigen-specific T cells in the joints and lymph nodes. B cells contribute to RA pathogenesis not only through antigen presentation, but also through the production of antibodies, autoantibodies and cytokines. RF and anti-CCP autoantibodies are common in patients with RA. B lymphocytes express cell surface proteins, including immunoglobulin and differentiation antigens such as CD20 and CD22.[37,39]

Autoantibodies can form larger immune complexes that can further stimulate the production of pro-inflammatory cytokines, including TNF-a, through complement and Fc-receptor activation. T- and B-cell activation result in increased production of cytokines and chemokines, leading to a feedback loop for additional T-cell, macrophage and B-cell interactions.[37-38] In addition to antigen presentation, macrophages are involved in osteoclastogenesis and are a major source of cytokines, including TNF-a, IL-1 and IL-6.[37-38]

Within the synovial membrane there is a great increase in activated fibroblast-like synoviocytes, which also produce inflammatory cytokines, PGs and MMPs. Synoviocytes contribute to the destruction of cartilage and bone by secreting MMPs into the SF and by direct invasion into these tissues.[38]

Cytokines and the impact on effector cells

It is well established that pro-inflammatory cytokines (e.g. IL-6 and TNF-a) are involved in the pathogenesis of RA. TNF-a and IL-6 play dominant roles in the pathobiology of RA; however, IL-1, VEGF and perhaps IL-17 also have a significant impact on the disease process.. Through complex signal pathways, these cytokines activate genes associated with inflammatory responses, including additional cytokines and MMPs involved in tissue degradation; this is discussed in subsequent sections.[37,38]

AnIL-17-secretingsubsetofCD4+ cells[i.e.Th17(TH17)] that has a critical role in synovitis has recently been implicated in the pathogenesis of many inflammatory and autoimmune diseases, including RA. The presence of TH17 cells in the SF and peripheral blood of patients with RA suggests the involvement of this potent proinflammatory cytokine in RA pathology.[37] An in vivo study has shown that CIA was markedly suppressed in IL-17-deficient mice.[40] Additionally, the ubiquitous expression of IL-17 receptor (IL-17R) on fibroblasts, endothelial cells, epithelial cells and neutrophils indicates that this cytokine has the potential to influence a number of pathways and effector cells involved in RA.[37]

Actions of cytokines that play major roles in RA pathobiology[37]

TNF-α

Local effects

- Increased monocyte activation, cytokine release, PG release.
- Increased polymorphonuclear leucocyte priming, apoptosis and oxidative burst.

- T-cell apoptosis, clonal regulation, TCR dysfunction.
- Increased endothelial cell adhesion molecule expression, cytokine release.
- Decreased synovial fibroblast proliferation, collagen synthesis [20] Increased MMP and cytokine release.

Systemic effects

- Acute-phase protein production.
- HPA axis dysregulation (fatigue and depression).
- CVD promotion.

IL-6

Local effects

- Osteoclast activation.
- Neutrophil recruitment
- Pannus formation via promotion of VEGF production
- B-cell proliferation and antibody production
- T-cell proliferation and differentiation

Systemic effects

- Acute-phase protein production
- Anaemia (via hepcidin production)
- CVD promotion
- Osteoporosis
- HPA axis dysregulation (fatigue and depression)

IL-1

Local effects

- Increased synovial fibroblast cytokine, chemokine, MMP and PG release

- Increased monocyte cytokine, reactive oxygen intermediate and PG release [
- Osteoclast activation
- Endothelial cell adhesion molecule expression

Systemic effects

- Acute-phase protein production
- CVD promotion
- HPA axis dysregulation (fatigue and depression)

IL-17

- Recruitment of monocytes and neutrophils by increasing local chemokine production
- Facilitation of T-cell infiltration and activation
- Amplification of immune response (e.g. by induction of IL-6 production)
- Increased synovial fibroblast cytokine and MMP release Osteoclastogenesis and cartilage damage
- Synergistic activity with IL-1b, TNF-a and IFN-g

VEGF

- Angiogenesis, contributing to pannus formation

Role of cytokines in RA joint effects

Inflammation TNF-a, IL-6 and IL-1 are key mediators of cell migration and inflammation in RA.[39] IL-6, in particular, acts directly on neutrophils through membrane-bound IL-6R, which in turn contributes to inflammation and joint destruction by secreting proteolytic enzymes and reactive oxygen intermediates.

Furthermore, an in vitro study with fibroblasts from patients with RA demonstrates the role of IL-6 in promoting neutrophil recruitment by activated fibroblasts. Although untreated fibroblasts were able to recruit neutrophils, recruitment was inhibited in the presence of anti-IL-6 antibody. The authors concluded that while IL-6 can directly recruit neutrophils, recruitment may also occur indirectly through fibroblasts.[41]

Bone and cartilage destruction

Osteoclasts are multinucleated cells formed by the fusion of mononuclear progenitors of the monocyte/macrophage family. The primary mediators of bone destruction, these cells populate the synovial membranes of patients with RA and are polarized on bone. Macrophage-driven osteoclastogenesis requires the presence of macrophage colony-stimulating factor (MCSF) and results from the interaction of the RANK and the RANK ligand (RANKL). RANKL expression is regulated by pro-inflammatory cytokines such as TNF-a, IL-1, IL-6 and IL-17. MCSF, IL-6 and IL-11 can also support human osteoclast formation from peripheral blood mononuclear cells by a RANKL-independent mechanism. The principal cause of bone erosion is the pannus, which is found at the interface with cartilage and bone. Angiogenesis is a key process in the formation and maintenance of pannus because invasion of cartilage and bone requires increased blood supply.[37]

In patients with RA, many pro-angiogenic factors are expressed in the synovium, but VEGF, a potent cytokine, plays the central role in new blood vessel development. VEGF is both a selective endothelial cell mitogen and an inducer of vascular permeability. In cultured synovial fibroblasts from patients with RA, IL-6,

in the presence of sIL-6R and in synergy with IL-1b and TNF-a, induces VEGF production.[37] Conversely, anti-IL-6R mAb therapy significantly reduced VEGF concentrations in these cultures, further demonstrating the role of IL-6 in VEGF production. Cartilage degradation in RA occurs when TNF-a, IL-1 and IL-6 activate synoviocytes, resulting in the secretion of MMPs into the SF. Cytokines also activate chondrocytes, leading to the direct release of additional MMPs into the cartilage.[38,39]

Role of cytokines in systemic effects of RA

Acute-phase protein production

The acute-phase response (APR) is the change in the concentration of certain plasma proteins, such as CRP, hepcidin, serum amyloid A, haptoglobin and fibrinogen, following protein synthesis alterations within hepatocytes. IL-6 has the greatest effect on acute-phase protein levels, although IL-1, TNF-a, TGF-b1 and IFN-g are also contributory. Elevated levels of CRP, a major acute-phase protein, can be detected within 4h of injury, with peak values usually occurring within 24 72h.[37,42]

Although an APR generally lasts for only a few days, some components may persist indefinitely. Increased levels of CRP may exacerbate disease-related tissue damage and contribute to the development of further complications, such as CVD.[42]

A prospective observational study that evaluated patients within 1 year of their RA diagnosis and then 3 years later found that an elevated baseline CRP level was a significant predictive factor for radiographic damage at the latter evaluation.[43]

Anaemia

After CVD, the most common systemic manifestation of RA is anaemia, which occurs more frequently during the early stage of the disease. In patients with early RA, IL-6 levels are significantly higher in patients with anaemia than in persons without anaemia. Additionally, haemoglobin levels are inversely correlated with IL-6 levels.[37]

IL-6 is required for the induction of hepcidin during inflammation and rapidly induces hypoferraemia in humans. Hepcidin, a peptide produced by hepatocytes, is thought to be the principal iron-regulatory hormone and the key mediator of anaemia in patients with chronic disease. Plasma hepcidin inhibits iron release from macrophages in the spleen and iron uptake in the duodenum.[37]

In vivo data in wild-type mice have shown that after a turpentine-induced inflammatory response, liver hepcidin expression is increased and serum iron is decreased. Conversely, in IL-6 knockout mice, hepcidin levels are reduced, whereas iron levels are slightly increased in response to turpentine treatment.[44] In humans, serum hepcidin levels have been shown to be highest in patients with RA and anaemia, whereas the lowest levels are reported in healthy adults.[45]

Osteoporosis

Osteoporosis is a common systemic manifestation of RA. The increased prevalence observed in this patient population consequently results in an elevated risk of bone fracture. In vivo data support a major role for IL-6 in RA-related osteoporosis. IL-6 transgenic mice, which have high circulating levels of IL-6, have osteopaenia, a condition involving accelerated bone resorption caused by increased

osteoclastogenesis and reduced bone formation caused by decreased osteoblast activity. However, IL-6-deficient mice with oestrogen deficiency after ovariectomy do not experience an increase in the number of osteoclast precursors or bone loss.[37]

Fatigue and depression

Persistent fatigue and high rates of depression are commonly reported in patients with RA. Corticotropin-releasing hormone, a key regulator of the hypothalamic-pituitary-adrenal (HPA) axis and the overall stress system, is associated with fatigue, dysthymia, irritability and depression.[37]

Case-control studies have demonstrated that the HPA axis is dysregulated to varying degrees in patients with RA.[46-48] HPA axis dysregulation has been reported to be caused in part by the release of various cytokines, including TNF-a, IL-1 and IL-6. Thus the fatigue and depression frequently observed in persons with RA are primarily mediated by the up-regulation of cytokines known to be associated with its pathology.[37]

CVD

The incidence of CVD events in patients with RA is more than three times that in the general population, and this increase is not entirely explained by traditional risk factors.[37] RA is associated with a spectrum of pro-atherogenic changes linked to systemic inflammation. Release of TNF-a, IL-6 and IL-1 from synovial tissue alters the function of distant tissues, including adipose tissue, skeletal muscle, liver and the vascular endothelium. These changes result in insulin resistance, dyslipidaemia, increased global oxidative activity and endothelial dysfunction. RA-related dyslipidaemia is characterized by low total and high-density

lipoprotein (HDL) cholesterol, elevated triglyceride and lipoprotein(a) levels and an increase of small, dense low-density lipoprotein (LDL) species.[49]

Although the reduction in inflammation in patients with severe RA following treatment with a biologic agent may result in increased levels of total, HDL and LDL cholesterol (and perhaps triglycerides), inflammation reduction decreases CVD risk.[37]

Contrary to understanding of the link between hyperlipidaemia and CVD, the increases in total cholesterol, LDL and triglyceride levels that may follow treatment for severe inflammation should be considered a consequence of inflammation reduction, not a CVD risk factor.[37]

IL-6 plasma concentrations are elevated in patients with RA, and the potentially detrimental cardiovascular consequences of these elevations are suggested by the results of a prospective case control study in 404 healthy men who participated in the Physicians' Health Study.[50]

Median IL-6 plasma concentrations at baseline were significantly higher in men who experienced a first myocardial infarction than in those who remained free of CVD during the 6-year follow-up. Furthermore, each quartile increase in the baseline IL-6 concentration was associated with a 38% increase in the risk of future myocardial infarction.[50]

Subclinical Atherosclerosis

Patients with conditions such as RA are associated with an increase mortality compared with the general population. A major part of the excess mortality has been

attributed to cardiovascular disease (CVD). The results of a recent systematic review showed that RA is associated with a 60% increase in the risk of CVD-related death. In particular, inflammation in RA is now considered as an independent risk factor for the development of atherosclerosis.[51]

Both RA and atherosclerosis are complex polygenic diseases with shared disease mechanism. There is increasing evidence that chronic inflammation and immune dysregulation contributes to accelerated atherogenesis and plays a role in all stages of atherosclerosis (i.e., atherogenesis, atheroma progression, and the development of thrombosis). Further, the increased cardiovascular morbidity and mortality in patients with RA cannot be entirely explained by traditional risk factors, such as type 2 diabetes mellitus, Metabolic Syndrome (MetS) and smoking habit. This article reviews the data supporting the association of RA with CVD, the possible mechanism for atherosclerosis, and discusses potential strategies for the prevention of atherosclerosis in such patients.[51]

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) alpha and interleukin (IL)-6, and increased expression of leukocyte adhesion molecules.[52] Patients with RA have elevated levels of the acutephase reactant C reactive protein (CRP), a marker of inflammation associated with increased cardiovascular risk. Moreover, CRP causes endothelial dysfunction by decreasing endothelial nitric oxide synthase, a potent antiatherogenic factor.[53] Patients with RA with elevated erythrocyte sedimentation rate (ESR) have a higher rate of cardiovascular death than those without elevated ESR. This inflammatory marker also increases linearly with increased carotid artery intima-media thickness

in both patients with RA and healthy controls.[54] Immune system plays an important role in the progression and development of atherosclerotic disease and associated complications. Atherosclerosis is in fact now considered as an autoimmune disease.[52-55]

The presence of inflammatory cells, such as macrophages and activated lymphocytes within atherosclerotic plaque, is a strong indicator of immune system involvement. Furthermore, the inflammatory burden in RA and other rheumatologic diseases increases the process of oxidation of low density lipoproteins (ox-LDL), responsible for the formation and progression of atherosclerotic plaque. ox-LDL amplifies the inflammatory response through the expression of adhesion molecules by endothelial cells and through the production of pro-inflammatory cytokines (TNF alpha, IL-1, IL-6) by macrophages.[54,55]

Mature dendritic cells (DC) express CCL17 that favoring T-lymphocytes recruitment; moreover the presence of modified or native LDL, induce up-regulation of co-stimulatory molecules on DCs that lead to T-lymphocyte proliferation. Modified LDL determine the formation of new antigenic epitopes which can be presented by DCs and brought to clonal expansion of LDL-specific T-lymphocytes. Indeed, about 10% of all T-lymphocytes detectable in human atherosclerotic plaques specifically recognize modified or native LDL. Of note, LDL-specific T-lymphocytes are also present in the circulation.[56]

The elevated levels of pro inflammatory cytokines can elicit a systemic inflammatory state that could lead to pro-atherogenic phenotype: 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: systemic release of IL-1, IL-17, IL-6, and TNF-α, produced in synovial tissue in RA patients, promotes 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.[57]

CRP and other factors local released by leukocytes, contributes to early endothelial dysfunction and damage. Immunological abnormalities such as auto-antibodies production may be involved in endothelial dysfunction and in the process of progression and rupture of the atherosclerotic plaque. Rheumatoid factor could be found in the atheroma as immunocomplex and is associated with impaired endothelial function and increased mortality.[58]

Atherosclerotic vascular involvement and cardiac abnormalities including pericardial, myocardial, and endocardial involvement, were higher among anti citrullinated peptide antibodies (ACPA) positive RA patients.[59] Citrullinated proteins, including citrullinated fibrinogen, are present within atherosclerotic plaque, and co-localized with peptidylarginine deiminase type 4 (PAD-4). Moreover, ACPA serum levels correlates with subclinical atherosclerosis indices. These, and other observations, support the hypothesis that citrullinated epitopes within the atherosclerotic plaque may be targeted by RA-associated ACPAs, thus forming immune complexes capable of locally perpetuating plaque inflammation and progression.[60]

Several studies demonstrated that endothelial dysfunction plays a central role in the pathogenesis of atherosclerosis, promotes early atherosclerotic changes and is predictive for the development of cardiovascular events. Patients with RA have a greater prevalence of arterial atherosclerotic plaques than controls and the presence of atherosclerotic plaques correlate with disease duration, radiological damage index and systemic inflammation.[61-65]

Early detection of subclinical atherosclerosis in RA could be useful to prevent cardiovascular events, death and disability. Different non-invasive methods are available to detect atherosclerosis and to estimate risk of cardiovascular events. These tools include functional and morphological assessment of artery physiology.[55]

The normal, healthy endothelium regulates vascular tone and structure and exerts anticoagulant, anti-platelet, and fibrinolitic properties. The maintenance of vascular tone is accomplished by the release of numerous dilator and constrictor substances. The major vasodilator substance released by the endothelium is nitric oxide (NO). Endothelial dysfunction occurs when NO bioavailability is reduced.[55,61,62]

Among different methods, the assessment of flowmediated dilatation (FMD) is one of the most used to assess the endothelial function in vivo, with a non invasive approach. FMD reflects the ability of brachial artery to dilate after reactive hyperaemia induced by shear stress. It depends on the endothelial production of agents with vasomotor action, specifically NO.[55]

Traditional cardiovascular risk factors, such as smoking, obesity, abnormal glucose or lipid dysmetabolism and hypertension, could alter endothelial function

and have been related with impaired FMD. Moreover, impaired FMD predicts the risk of future cardiovascular events and it is a surrogate marker of general atherosclerosis.[55]

Endothelial function could also be assessed with administration of sublingual nitroglycerin (NTG). NTG induces a vasodilatation that is endothelium-independent to production of local NO.[66] In RA patients, FMD is impaired, compared to controls, independent to the presence of classical atherosclerosis risk factors. RA patients showed similar FMD impairment than those with diabetes, supporting the theory that RA is an independent risk factor for atherosclerosis. Endothelial dysfunction in these patients seems to be related to disease activity (DAS28), disease duration, HLA-DRB1 shared epitope and inflammatory indices.[67]

Furthermore, in RA patients disease activity, assessed by DAS28, ESR and CRP, predicts the magnitude of endothelial dysfunction. FMD is impaired even in patients with early disease, suggesting that atherosclerotic process starts early.[55] Few studies demonstrate NTG-mediated vasodilatation impairment in RA patients.[68]

Hannawi et al.[68] in a longitudinal study on 20 patients with early RA found that both FMD and NTG-mediated vasodilatation were significantly lower in patients in respect to control and negatively correlated with age and CRP.

Mortality and mortality of RA is related to atherosclerosis

Large epidemiological studies from the last few decades have confirmed that patients with RA are 60% more likely to suffer a CV event than subjects from the general population. The major complication in patients with RA is the development of cardiovascular events due to accelerated atherosclerosis.[51]

A recent Dutch, cross-sectional study found that age- and gender-adjusted odds ratios for CV diseases derived from these cohorts were 3.1 for patients with RA. Further, up to 13% non-diabetic RA patients developed CVD (coronary, cerebral and peripheral arterial diseases).[69]

Multiple studies have confirmed that the excess mortality in RA is largely attributed to CV death. A recent meta-analysis of 24 studies showed a 50% increased risk of CV death overall.[12]

RA patients have a 2 to 3 fold risk of myocardial infarction, a 2 fold risk of congestive heart failure, a 2 increase risk of sudden death and a 1.7 fold increased risk of strokes. Accordingly, clinicians should be aware of the high risk and provide close surveillance of CVD in patients with RA.[51]

Carotid intima-media thickness

An approach to assess the presence and extent of subclinical atherosclerosis is carotid ultrasonography. In the general population, carotid ultrasound has been used for cardiovascular risk stratification; Intimal-Medial Thickness (IMT) and plaque are associated with clinical CVD and have independent prognostic value for such CV events.[70]

CIMT is the area of tissue starting at the luminalintimal interface and the media-adventitia interface of CCA. Since B-mode (bright-mode) ultrasonography is a safe, noninvasive, and cost-effective to measure CIMT, a recent study more precisely defined CIMT as the double-line pattern visualized by B-mode vascular ultrasound formed by two parallel echogenic lines representing junction of the vessel lumen with intima and media-adventitia interface.[71]

Guidelines for CIMT measurements

The American Society of Echocardiography (ASE) in a consensus statement has standardized the technique for CIMT assessment.[72,73] Adherence to the prescribed imaging protocol and close attention to instrumentation are critical in CIMT measurement as small errors can classify patients in different risk categories. Ultrasound imaging in CIMT uses transducers that produce acoustic or sound waves. Two types of transducers, sector phased-array and linear phased-array, are used in ultrasound imaging. Linear phased-array transducers (version A and version B) have an advantage over sector phased-array because of its improved image quality. Presently, these transducers are helping clinicians in making accurate diagnosis with improved image quality, ergonomics, and trapezoid imaging formats.[74]

The current guidelines recommend the use of state-of-the art linear-array ultrasound transducers that can operate at a fundamental frequency of at least 7 MHz to scan carotid arteries. Depending on scanning protocol, the specifi c predetermined bilateral sites in the vicinity of carotid bifurcation are selected for taking CIMT measurements. Other segments of the carotid artery used for CIMT measurement are CCA and the internal carotid artery (ICA). CIMT of the CCA has better reproducibility than ICA or carotid bifurcation due to its ease of access and proximity to the surface and runs relatively parallel to the skin.[72]

The consensus statement on use of CIMT from ASE has recommended adhering to carotid ultrasound scanning technique and procedures to facilitate high-quality, reproducible images, and requires both sonographer and patient to be positioned properly to obtain high-quality images. CIMT testing is conducted in

supine position on scan bed with head of the patient resting comfortably, and neck slightly hyper-extended and rotated in direction opposite to the probe. A wedge pillow at an angle of 45° standardizes lateral rotation. Optimization of images is done by adjusting patient's neck position especially in anterior scanning planes, and rolled towels are given under neck and legs for comfort. With the use of external landmarks such as the Meijer arc or similar device, transducer angle is standardized. Height and location of ultrasound system keyboard and monitor, examination bed, and chair are adjusted accordingly to avoid any musculoskeletal injuries to patients.[73]

The six values of mean CIMT (three on each side) are obtained and averaged to get mean CIMT.[75] Reliance on a single absolute threshold abnormality will result in under-detection of diseases in younger individuals and over-detection in older individuals.[72]

In healthy middle-aged adults, CIMT values between 0.6 and 0.7 mm have been considered normal, while CIMT of 1 mm or more has been associated with signifi cant increased absolute risk of CHD. In healthy Indian adults, the average and maximum CIMT values reported were 0.67 and 0.70 mm, respectively. The measurement of CIMT varies with age and values >1.0 mm are considered abnormal in younger population and confer increased absolute risk of CHD.[72]

The present consensus on echocardiography reported CIMT values ≥75th percentile as the upper limit of normal across age, gender, and race/ethnicity, and served as the indicators of increased CVD risk. CIMT values increase with age and

are generally more in men than women. Thickness of CIMT has been reported to be the highest in African Americans, least in Hispanics, and intermediate in Whites.[72]

IMT is calculated based on the protocol incorporating all three carotid segments (i.e., distal common carotid, carotid artery bifurcation, and proximal internal carotid arteries). A strong correlation between incident CVD and increasing CIMT has been reported in the age group of 42-74 years. But comparatively strong relationship between increasing risk factor burden, emerging risk factors, and CIMT has been observed in young adults aged 18-42 years.[72]

Advantages of CIMT Ultrasonographic assessment of CIMT has several advantages in clinical practice over angiography in observing atherosclerotic vascular changes and development of atherosclerosis.[76-78]

- CIMT can be used repeatedly and reproducibly with no adverse effects on the patients. It can be performed noninvasively with no risk of vessel dissection, vessel closure, or coronary spasm

- CIMT scanning protocol can detect atherosclerotic diseases in early and asymptomatic stages

- CIMT directly visualizes vasculature unlike indirect biomarkers such as low-density LDL-C or even the more advanced biomarkers like high-sensitivity C-reactive protein or lipoprotein-associated phospholipase A2 (Lp-PLA2)

- CIMT with plaque interrogation can be performed in any basic ultrasound ambulatory setting with favorable speed and cost factors

- CIMT can be easily quantified via automated boundary detection software, and the carotid interrogation is radiation free and thus safer than other imaging tests such as coronary calcium scoring or CT-CAG

- CIMT allows for observation of the arterial wall, the actual site of the atherosclerotic disease, rather than the lumen

- CIMT is not dependent on calcification of the plaque as are some of the other assessment tools such as coronary artery calcification score.

Asian Indians have been an ethnically vulnerable race for developing metabolic syndrome and diabetes, both of which are well-known contributors to the pathogenesis of atherosclerotic vascular disease. The subclinical diabetes is reported as an important vascular risk for Asian Indians. Additionally, atherosclerosis is known to develop in patients of hypertension, chronic autoimmune vasculitides or arthritis, polycystic ovarian syndrome, and in patients receiving dialysis.[72]

The Chennai Urban Rural Epidemiology Study (CURES-2), an epidemiological study published in 2004, reported association of CIMT and arterial stiffness with retinopathy in Asian Indians who were at a high risk group for diabetes and CAD.[79]

The data from this study showed an association between early atherosclerosis and diabetic retinopathy in urban South Indian population. A prospective study in 2006 reported efficacy of CIMT in predicting the prevalence of CAD in a patient population of end-stage renal disease (ESRD) using CAG as standard. The study reported that CIMT can be used as a screening tool for the evaluation of CAD in

patients with ESRD, and in the absence of other risk factors, patients with IMT less than 0.75 mm may not need a pre-transplant CAG.[80]

In 2008, Mahajan et al.[81] published a study that was regarded as the second only Indian study examining the extent of atherosclerosis in rheumatoid arthritis (RA) patients. The study reported that RA patients had significantly greater CIMT values than age-sex-matched controls, indicating the association of RA with premature atherosclerosis.

A recent study by Madhuri et al.[82] reported relation of the CIMT with age and found a signifi cant association between advancing age and CIMT.

Another group studied association between CIMT and prevalent CAD in Indian subjects and found significantly increased CIMT in patients with established CAD.[83]

In 2 studies[84,85] of Asian patients and in a study from Poland, carotid IMT was increased in patients with RA compared with matched controls.[84] In addition, patients with RA had a similar carotid IMT and prevalence of carotid plaque as with age- and gender-matched patients with type 2 diabetes mellitus. The result thus suggested that both diseases contribute equally to the development of premature atherosclerosis.[85]

A meta-analysis was performed involving 22 studies to estimate the overall mean carotid IMT difference between RA and control groups.[86]

In 17 of the studies, patients with RA had a statistically significantly greater carotid IMT. The overall mean carotid IMT difference was 0.09 mm, indicated an

approximately 15% increased cardiovascular risk.[71] Grover S. et al.[87] reported that, one-third of Indian RA patients had subclinical atherosclerosis. Age and tender joint count were independent predictors of abnormal CCA IMT.

However, this was not confirmed by a study from the United States, showing no significant difference in carotid IMT and carotid plaque between patients with RA and control.[88]

Nonetheless, carotid IMT was correlated positively with inflammatory markers both in patients with RA and controls, suggesting that systemic inflammation played a significant role in the development of atherosclerosis. The presence of carotid plaques is a more reliable predictor of cardiovascular events than IMT.[89]

In a cross-sectional study of 98 patients with RA, Salmon and Roman[90] demonstrated that the presence of carotid atherosclerotic plaques was greater than controls (44% vs. 15%, $p<0.01$). The same result was similarly shown by and Stamatelopoulos and colleagues[85] (48% vs. 10%, $p<0.01$). The clinical importance for the presence of carotid plaque, but not carotid IMT, was demonstrated by a study involving 105 patients with RA, that demonstrated patients with bilateral carotid plaques were associated with a worse CVD event survival (Hazard ratio = 6.31).[91]

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2014 to December 2014.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2014 to December 2014.

Place

This study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Source of Data

The present study was comprised of patients with rheumatoid arthritis and willing to undergo carotid artery imaging to measure CIMT using high resolution B-mode ultrasonography.

Sample size

The present study included a total of 50 patients with rheumatoid arthritis.

Sampling method

The sample size was determined based on the 80% of average hospital statistics on patients with RA for the last three years. During the past three years average 53 patients with RA attended the hospital and considering 80% of 53 a sample size of 43 was calculated. However, during the study period 50 patients fulfilled the selection criteria and were enrolled.

Selection criteria

Inclusion Criteria

- Patients above the age of 18 years and below the age of 80 years.
- Patients diagnosed with RA based on the history, clinical examination and the new jointly published ACR and EULAR criteria.

Exclusion Criteria

- Current or recent (within the past 3 months) pregnancy.
- Patients with history suggestive of
    - Type 2 Diabetes Mellitus
    - Hypertension
    - Coronary artery disease
    - Cerebro-vascular disease,
    - Peripheral vascular disease.
    - Chronic hepatic failure
    - Chronic renal failure
    - Endocrinopathies like hypothyroidism
    - Cushing's Syndrome.

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Procedure

Demographic data such as age and sex were recorded. History of other co-morbid conditions such as, hypertension, diabetes mellitus, previous stroke, personal history such as habits of alcohol consumption, smoking, were noted. A thorough physical examination was conducted for vitals (pulse rate, blood pressure and respiratory rate) followed by systemic examination. During the clinical examination the number of tender joints(t), the number of swollen joints(t) were observed. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Diagnosis of Rheumatoid arthritis

The diagnosis of RA was based on the history, clinical examination and new classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[18,19] The criteria establishes a point value between 0 and 10. Patients with a point total of 6 or higher were unequivocally classified as an RA patient, provided he has synovitis in at least one joint and given that there is no other diagnosis better explaining the synovitis.

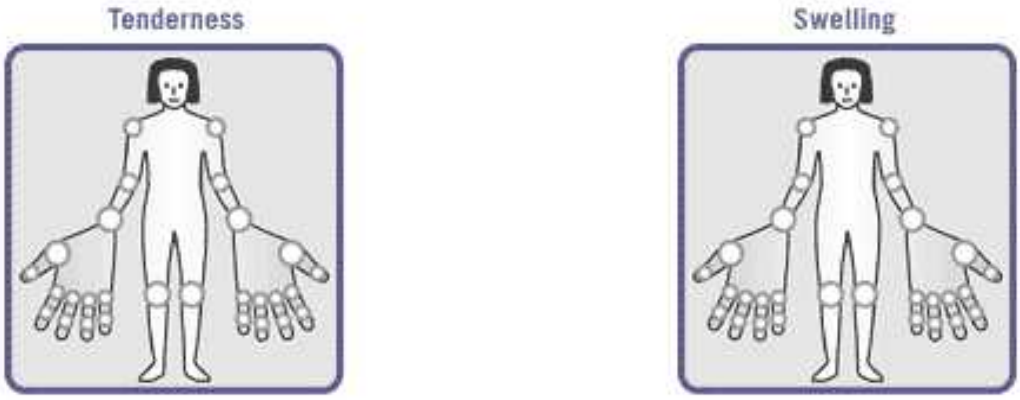


Figure 3. Tender and swollen joint counts

Informed Consent

Patients were screened for the eligibility and those fulfilling the selection criteria were briefed about the nature of the study. The patients expressing their willingness to participate in the study were enrolled after obtaining a written informed consent (Annexure I).

Investigations

Blood samples were collected from the patients with all aseptic precautions. 10 ml of venous blood was collected from median cubital vein by disposable plastic syringe. The needle was detached from the nozzle and blood transferred immediately in to a dry, clean, ionized, graduated, screw capped plastic test tube with a gentle push to avoid hemolysis. Then the patient's blood samples were sent to the laboratory for assessment of

- Erythrocyte sedimentation rate (ESR)
- Highly sensitive C-reactive protein (Hs-CRP)
- Renal function tests

- Liver function tests
- RA factor
- Anti CCP antibody
- High Resolution B-mode Ultrasonography mode to measure the CIMT

Anti-CCP antibody test was done using ELISA method. Patients with anti-CCP titres more than 10 IU/dL were considered as positive.

Outcome variables

Severity of rheumatoid arthritis

The severity of the disease was calculated using Disease Activity Score 28 (DAS 28) score. The Disease Activity Score (DAS) combines single measures such as tender joint count, swollen joint count, ESR, visual analog scale (VAS) score into an overall, continuous measure of RA disease activity. The use of a single index has advantages, because simultaneous interpretation of several measures of RA disease activity is difficult. The DAS28 is analogous to the DAS but includes simplified 28-joint counts based on clinical assessment of joint counts and drawing a blood sample for ESR or CRP.[92]

Fomula for calculation of Disease Activity Score (DAS)[93,94]

DAS28 (3) = [0.56*sqrt (t28) + 0.28*sqrt (sw28) + 0.70*Ln (ESR)] * 1.08 + 0.16

Interpretation

A DAS28 score of higher than 5.1 was considered as indicative of high disease activity, whereas a DAS28 below 3.2 was considered as low disease activity. A patient was considered to be in remission if they have a DAS28 lower than 2.6.[92]

Carotid intima medial thickness

The carotid intimal-medial thickness was determined by imaging of common carotid artery using a high frequency B-mode ultrasonography. High resolution B mode, colour Doppler, and pulse Doppler ultrasonography of both carotid arteries were performed with an ultrasound machine PHILIPS HD-11 equipped with a 7.5 MHz linear array transducer. Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans the probe was rotated 90˚ to obtain and record a longitudinal image of the anterior and posterior walls. The maximum IMT was measured at the near and far walls of the common carotid artery, the bifurcation, and the internal carotid arteries and was expressed as a mean aggregate value.

The IMT was assessed as normal if it did not exceed 1 mm. With regard to the plaque, its maximum diameter was assessed and included in further analysis. Furthermore, the grade of stenosis in the carotid and vertebral arteries was assessed through the increase in the peak systolic and end diastolic velocities (according to the criteria of Hood at al.[95]), with a view to establishing the frequency of concomitant CAD and severe carotid and vertebral atherosclerosis. The carotid and vertebral atherosclerosis was considered severe when the grade of stenosis was >70%. When Doppler ultrasound indicated severe stenosis of the carotid or vertebral

artery, the actual grade of stenosis was confirmed by standard angiography. All scans were obtained by the same experienced sonographer, who had no prior knowledge of the patients' clinical and angiographic characteristics.

Statistical analysis

The data obtained was coded and entered into the Microsoft Excel Spreadsheet (Annexure III). The data was analysed using SPSS version 20. The categorical data was expressed in terms of rates, ratios and percentages. To find the differences in categorical characteristics Chi square or Fisher's exact test were used. Continuous data was compared using independent sample 't' test. In case of more than two mean the comparison was done using one way ANOVA. The correlation of CIMT and disease severity was determine using Pearson's correlation co-efficient. A probability value (p value) of less than or equal to 0.050 at 95% confidence interval was considered as statistically significant.

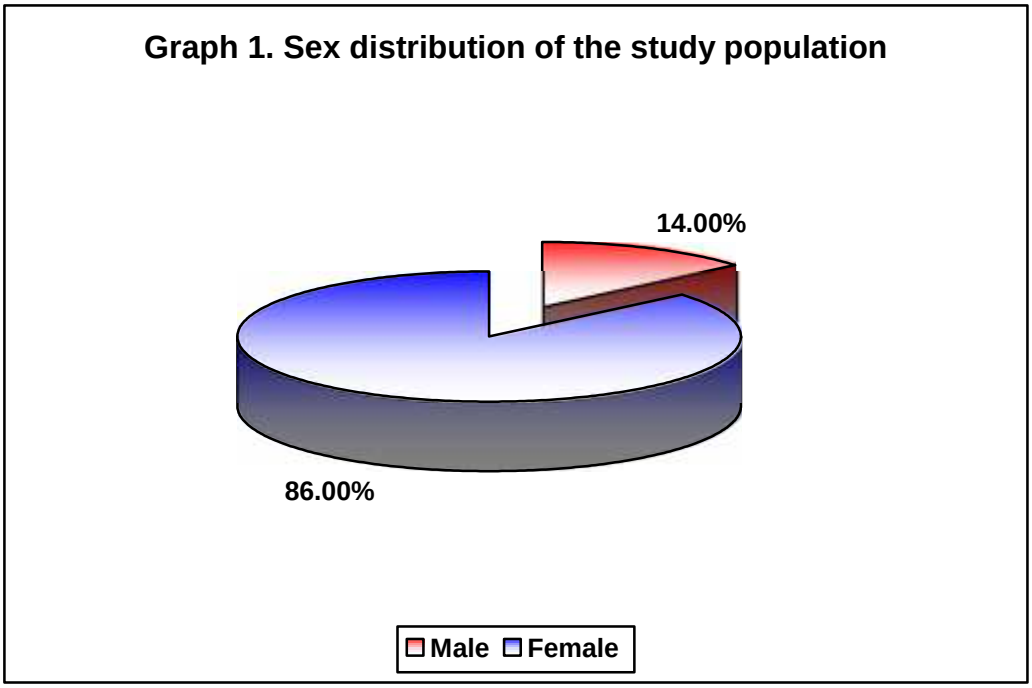
RESULTS

This one year cross sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 50 patients who present with rheumatoid arthritis were investigated for carotid artery imaging to measure CIMT using high resolution B-mode ultrasonography from January 2014 to December 2014.

The data obtained was analysed and the final observations were tabulated as below.

Table 1. Sex distribution of the study population

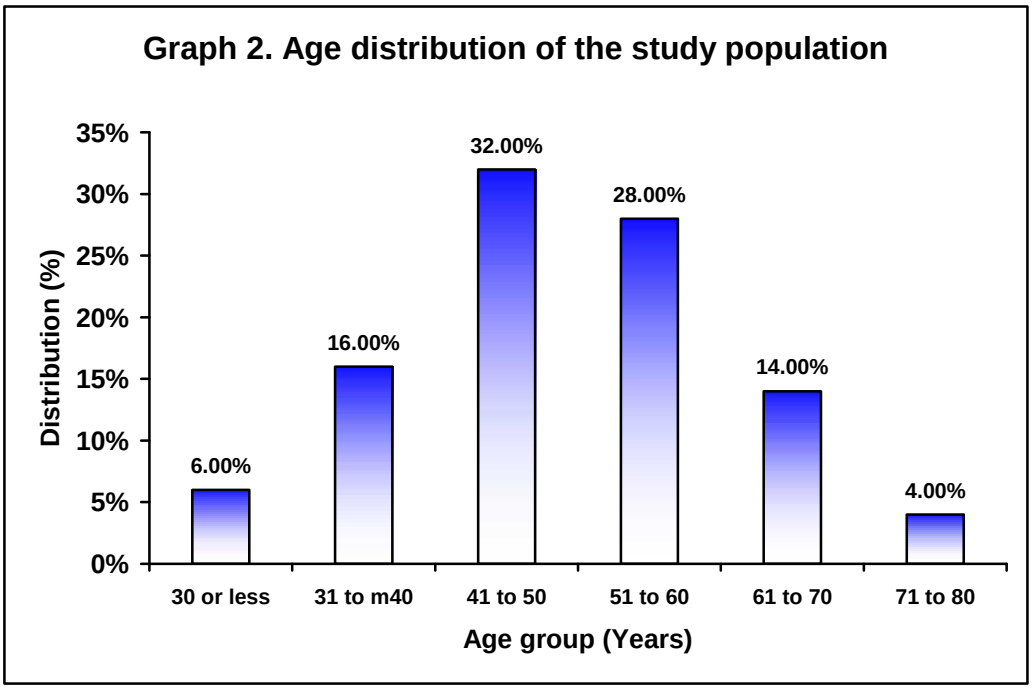
Sex distribution	Distribution (n=50)	
	Number	**Percentage**
Male	7	14.00
Female	43	86.00
Total	**50**	**100.00**



In the present study 86% of the patients were females and 14% were males. The female to male ratio was 6.14:1.

Table 2. Age distribution of the study population

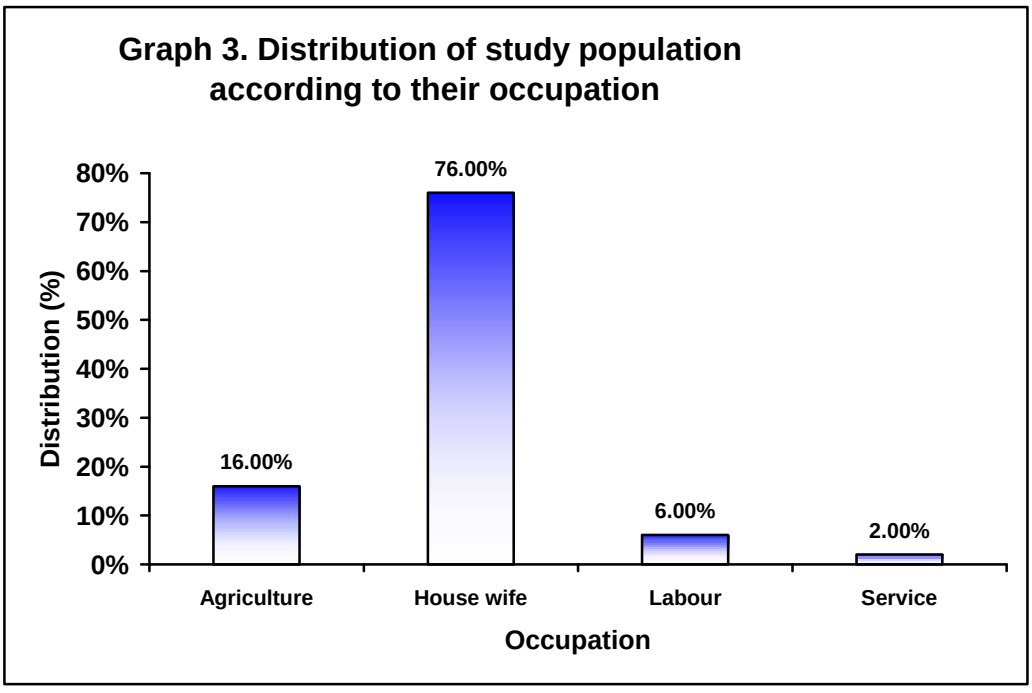
Age group (Years)	Distribution (n=50)	
	Number	**Percentage**
30 or less	3	6.00
31 to 40	8	16.00
41 to 50	16	32.00
51 to 60	14	28.00
61 to 70	7	14.00
71 to 80	2	4.00
Total	**50**	**100.00**



In this study most of the patients presented with age between 41 to 50 years (32%) and 51 to 60 years (28%). The mean age was 49.88 ± 12.12 years and median age was 50 year (Range - 20 to 78 years)

Table 3. Distribution of study population according to their occupation

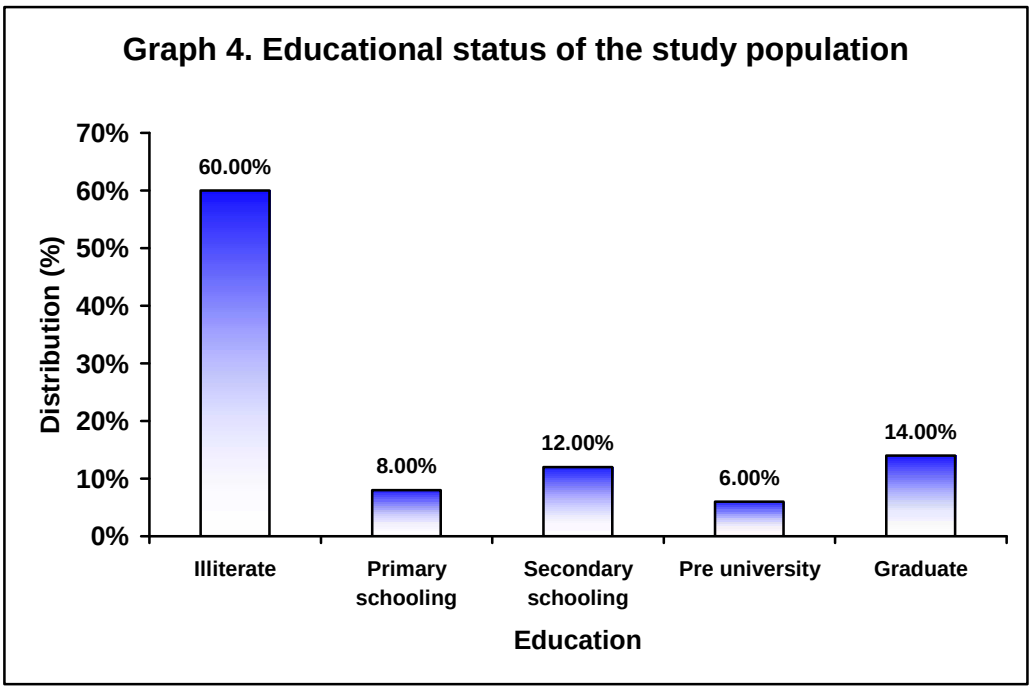
Occupation	Distribution (n=50)	
	Number	**Percentage**
Agriculture	8	16.00
House wife	38	76.00
Labour	3	6.00
Service	1	2.00
Total	**50**	**100.00**



In the present study majority of the patients were housewives (76%).

Table 4. Educational status of the study population

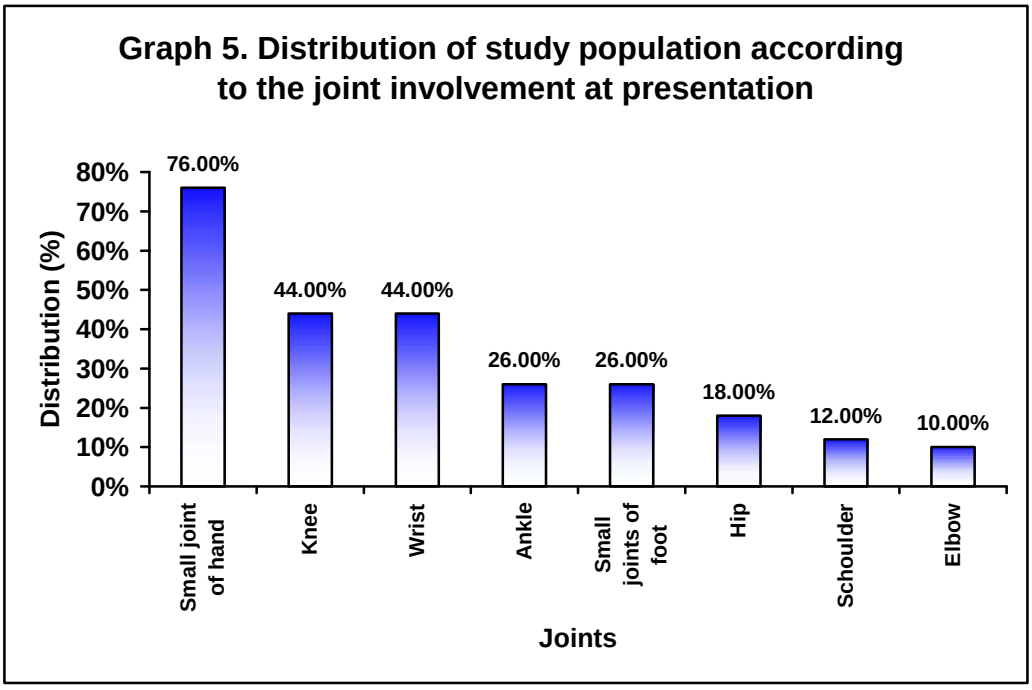
Education	Distribution (n=50)	
	Number	**Percentage**
Illiterate	30	60.00
Primary schooling	4	8.00
Secondary schooling	6	12.00
Pre university	3	6.00
Graduate	7	14.00
Total	**50**	**100.00**



In this study 60% of the patients were illiterates while 14% and 12% of the patients completed graduation and secondary schooling respectively.

Table 5. Distribution of study population according to the joint involvement at presentation

Joints	Distribution (n=50)	
	Number	Percentage
Small joint of hand	38	76.00
Wrist	22	44.00
Knee	22	44.00
Ankle	13	26.00
Small joints of foot	13	26.00
Hip	9	18.00
Shoulder	6	12.00
Elbow	5	10.00



In the present study majority of the patients reported involvement of small joints of hand (76%) followed by knee and wrist (44% each).

Table 6. Distribution of study population according to the history of RA

Variables	Findings	Distribution	
		No	**%**
Duration of joint pain (Years)	≤ 1	37	74.00
(n=50)	2 to 5	10	20.00
	5 to 10	3	6.00
	Total	**50**	**100.00**
History of rheumatoid arthritis	Present	14	28.00
(n=50)	Newly diagnosed	36	72.00
	Total	**50**	**100.00**
Duration of rheumatoid arthritis	≤ 3	8	57.14
(n=14)	4 to 6	2	14.29
	7 to 9	3	21.43
	10 or more	1	7.14
	Total	**14**	**100.00**
Treatment history	Yes	14	100.00
(n=14)	No	0	0.00
	Total	**14**	**100.00**

In the present study majority of the patients (74%) reported duration of joint pain as ≤ 1 year. The mean duration of joint pain was 1.45 ± 2.16 years and median duration was 0.50 years with range being 0.04 as minimum to 10 years as maximum.

The history of RA was reported by 14 (28%) patients and among, them 8 patients (57.14%) had ≤ 3 years duration of RA. The mean duration of disease among the patients with history of RA was 3.62 ± 3.25 years and median duration of RA was 2 years with range 2 months being minimum and 10 years being maximum.

Table 7. Distribution of study population according to the tender and swollen joint count

Variables	Findings	Distribution (n=30)	
		No	**%**
Tender joint count	≤ 5	12	24.00
	6 to 10	19	38.00
	11 to 15	11	22.00
	16 to 20	7	14.00
	> 20	1	2.00
	Total	**50**	**100.00**
Swollen joint count	≤ 5	35	70.00
	6 to 10	11	22.00
	11 to 15	3	6.00
	16 to 20	1	2.00
	Total	**50**	**100.00**

In the present study 38% of the patients had involvement of 6 to 10 tender joint count and 70% of the patients had ≤ 5 swollen joint counts.

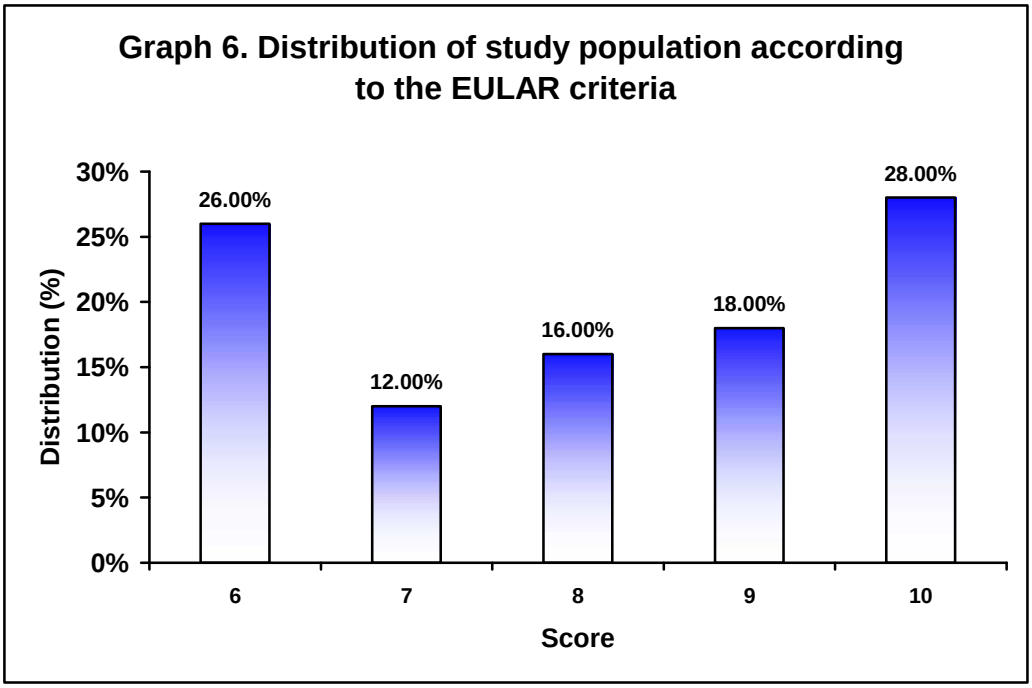
Table 8. Distribution of study population according to the RA factor and anti CCP antibody test findings

Variables	Findings	Distribution (n=30)	
		No	**%**
RA factor	Positive	44	88.00
	Negative	6	12.00
	Total	**50**	**100.00**
Anti CCP antibodies	Positive	18	36.00
	Negative	32	64.00
	Total	**50**	**100.00**

In this study RA factor was positive in 88% of the patients and Anti CCP antibodies were positive in 36% of the patients.

Table 9. Distribution of study population according to the EULAR criteria

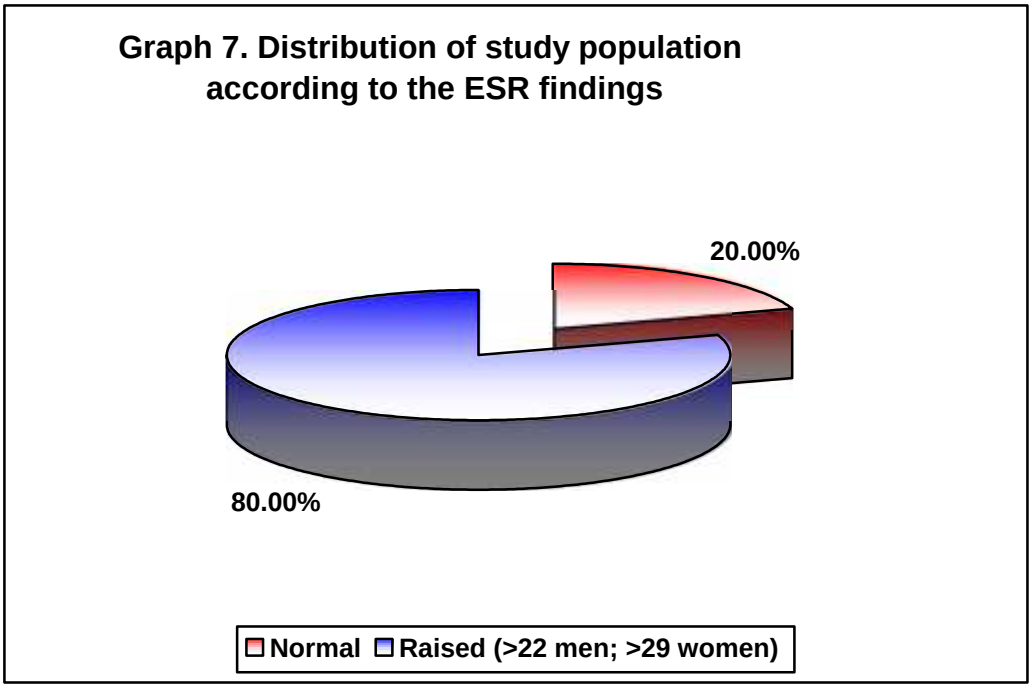
Score	Distribution (n=50)	
	Number	Percentage
6	13	26.00
7	6	12.00
8	8	16.00
9	9	18.00
10	14	28.00
Total	**50**	**100.00**



In the present study the EULAR criteria score in 26% and 28% of the patients was 6 and 10 respectively. In the remaining score of 9, 8 and 7 were noted in 18%, 16% and 12% respectively. The mean EULAR criteria score was noted as 8.10 ± 1.58 with median score of 8 (Range 6 to 10)

Table 10. Distribution of study population according to the ESR findings

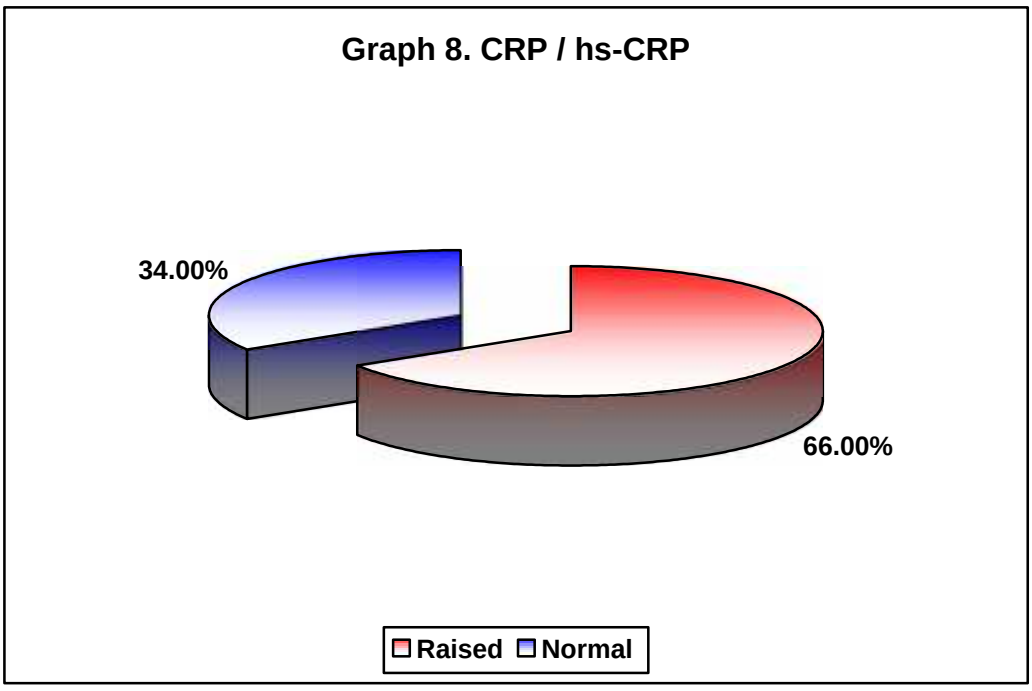
ESR (mm/Hr)	Distribution (n=50)	
	Number	**Percentage**
Normal	10	20.00
Raised (>22 men; >29 women)	40	80.00
Total	**50**	**100.00**



In this study ESR was raised in 80% of the patients. The mean ESR value was 50.68 ± 24.73 mm /Hr and median ESR was noted as 47 mm/Hr (Range 12 to 107).

Table 11. Distribution of study population according to the CRP/hs-CRP findings

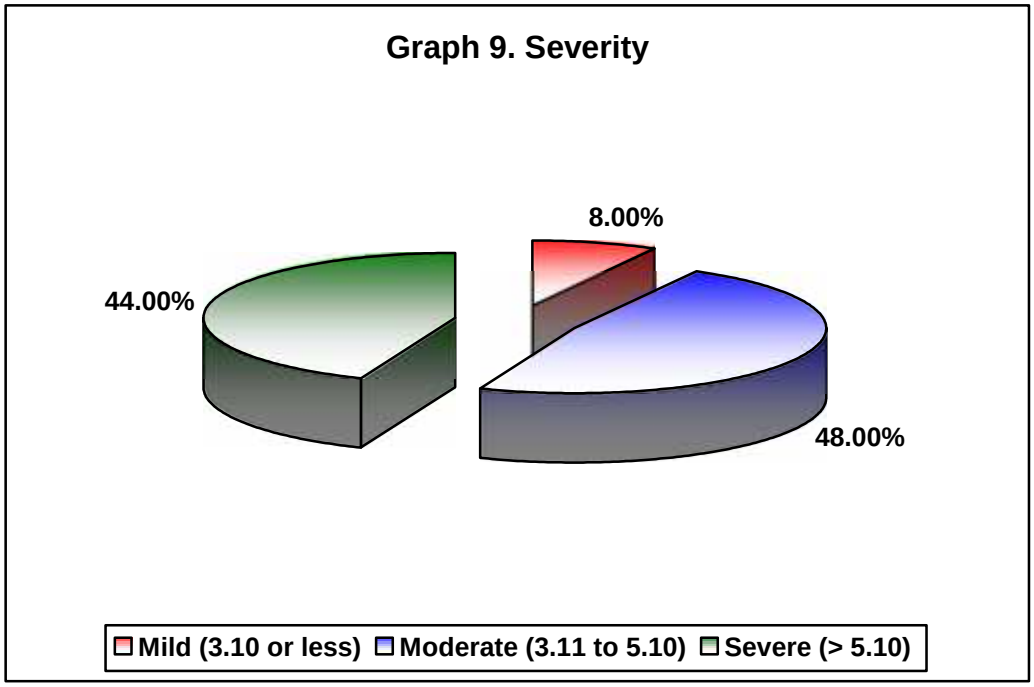
CRP / hs-CRP	Distribution (n=50)	
	Number	**Percentage**
Raised	33	66.00
Normal	17	34.00
Total	**50**	**100.00**



In the present study CRP was raised in 66% of the patients.

Table 12. Distribution of study population according to the disease severity

DAS 28 score	Distribution (n=50)	
	Number	**Percentage**
Mild (3.10 or less)	4	8.00
Moderate (3.11 to 5.10)	24	48.00
Severe (> 5.10)	22	44.00
Total	**50**	**100.00**



In this study based on DAS 28 scores severe disease was present in 44% of the patients while 48% had moderate disease activity. The mean DAS 28 scores were noted as 4.91 ± 1.11 and median scores were 4.95 (Range 2.73-7.26).

Table 13. Haematological, renal and liver profile of study population

Characteristics	Mean (n=50)		Median (n=50)		
	Mean	**SD**	**Median**	**Minimum**	**Maximum**
Uric acid (mg/dl)	3.78	1.25	3.50	1.90	6.70
Haemoglobin (g/dl)	11.08	1.27	11.25	8.40	14.30
Total count (cells/cumm)	8803.00	2928.96	8500.00	3600.00	16200.00
Platelet count (Lakhs/cumm)	3.36	1.14	3.36	0.48	6.50
Blood urea (mg/dL)	21.77	6.95	21.00	10.00	39.00
Serum creatinine (mg/dL)	0.87	0.23	0.84	0.47	1.57
Total bilirubin (mg/dL)	0.72	0.30	0.80	0.13	1.40
Direct bilirubin (mg/dL)	0.33	0.24	0.20	0.03	0.90
Indirect bilirubin (mg/dL)	0.39	0.21	0.38	0.10	0.90
SGOT (IU/mL)	25.18	19.47	19.50	12.00	137.00
SGPT (IU/mL)	34.08	25.81	28.50	10.00	173.00

The haematological, renal and liver profile of the study population is as depicted in table 13.

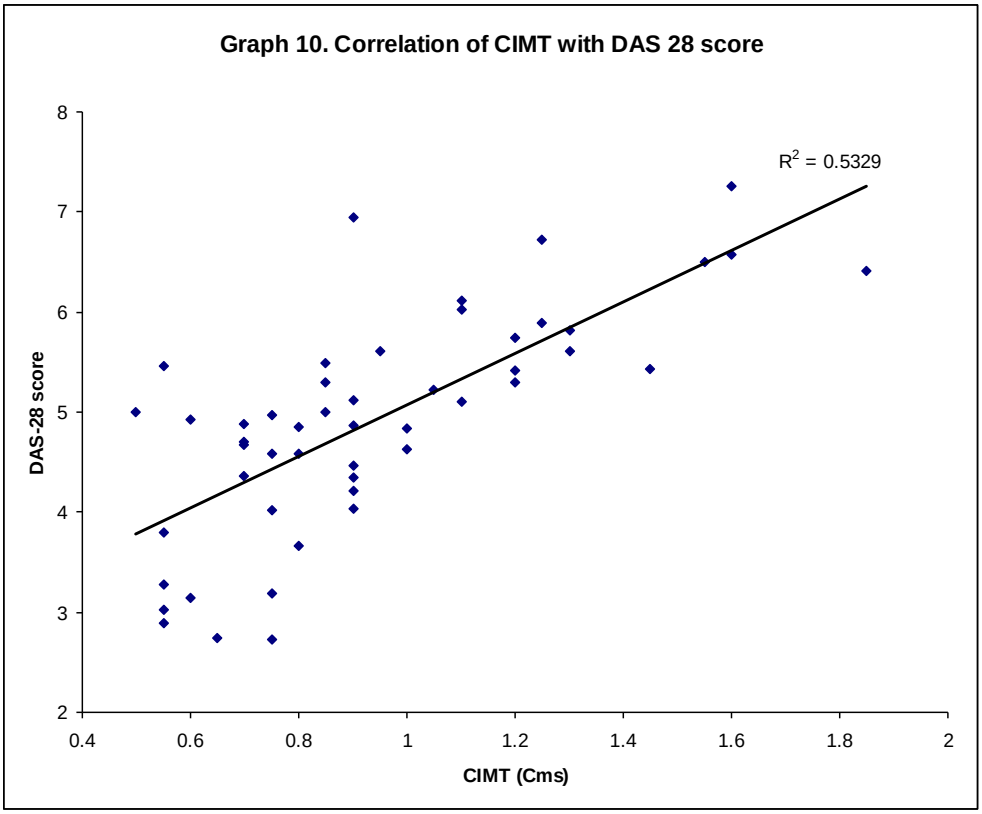
Table 14. Carotid doppler study findings

Variables	Mean (n=50)		Median (n=50)		
	Mean	**SD**	**Median**	**Minimum**	**Maximum**
RIGHT CCA - CIMT (in cms)	0.94	0.34	0.90	0.40	1.80
PSV (cm/sec) RIGHT Side	69.72	17.51	69.00	38.00	117.00
EDV (cm/sec) RIGHT Side	21.12	7.16	20.50	10.00	41.00
LEFT CCA - CIMT (in cms)	0.93	0.32	0.90	0.30	1.90
PSV (cm/sec) LEFT Side	73.18	17.33	69.50	47.00	137.00
EDV (cm/sec) LEFT Side	22.72	8.72	20.50	8.00	42.00
Mean CIMT (Cms)	0.94	0.31	0.90	0.50	1.85

The carotid doppler findings are as shown in table 14. It was observed that, the mean CIMT was 0.94 ± 0.31 cms and median CIMT was 0.90 cms with with minimum being 0.50 cms and maximum being 1.85 cms.

Table 15. Comparison of mean CIMT with DAS 28 score

DAS 28 score	Patients (n)	CIMT (Cms)	
		Mean	**SD**
Mild (3.10 or less)	4	0.63	0.10
Moderate (3.11 to 5.10)	24	0.76	0.14
Severe (> 5.10)	22	1.19	0.30
F value		**24.335**	
p value		**<0.001**	

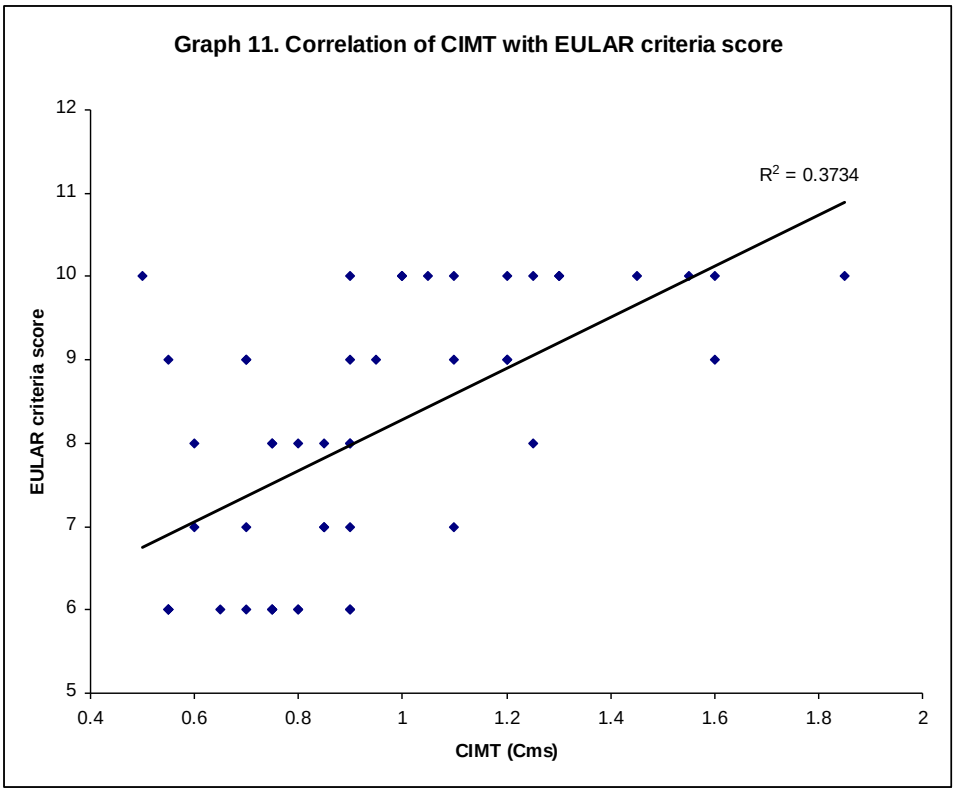


r=0.729; R^2=0.532; p<0.001

In the present study significant rise in CIMT was observed with respect to disease severity based on DAS 28 score (p<0.001). Further there was strong positive correlation between CIMT and DAS 28 scores (**r=0.729; R^2=0.532; p<0.001)**

Table 16. Comparison of mean CIMT with EULAR criteria score

EULAR criteria score	Patients (n)	CIMT (Cms)	
		Mean	SD
6	13	0.71	0.13
7	6	0.83	0.17
8	8	0.85	0.19
9	9	0.99	0.32
10	14	1.22	0.34
F value		7.464	
P value		**<0.001**	

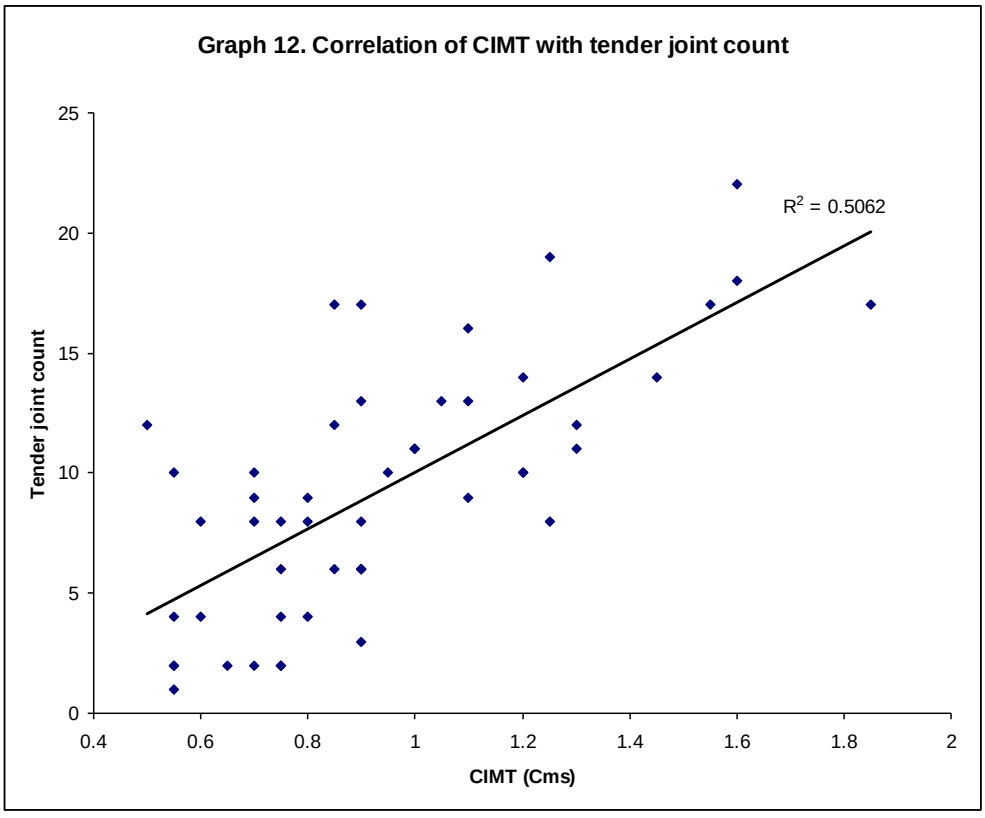


r=0.611; R^2=0.373; p<0.001

In this study, there was a trend showing significant rise in mean CIMT values with respect to increase in EULAR criteria score (p<0.001). Also EULAR criteria score showed strong positive correlation with CIMT (**r=0.611; R^2=0.373; p<0.001)**

Table 17. Comparison of mean CIMT with tender joint count

Tender joint count	Patients (n)	CIMT (Cms)	
		Mean	**SD**
5 or less	12	0.68	0.12
6 to 10	19	0.87	0.20
11 to 15	11	1.06	0.26
16 to 20	7	1.30	0.38
> 20	1	1.60	-
F value		11.348	
P value		**<0.001**	

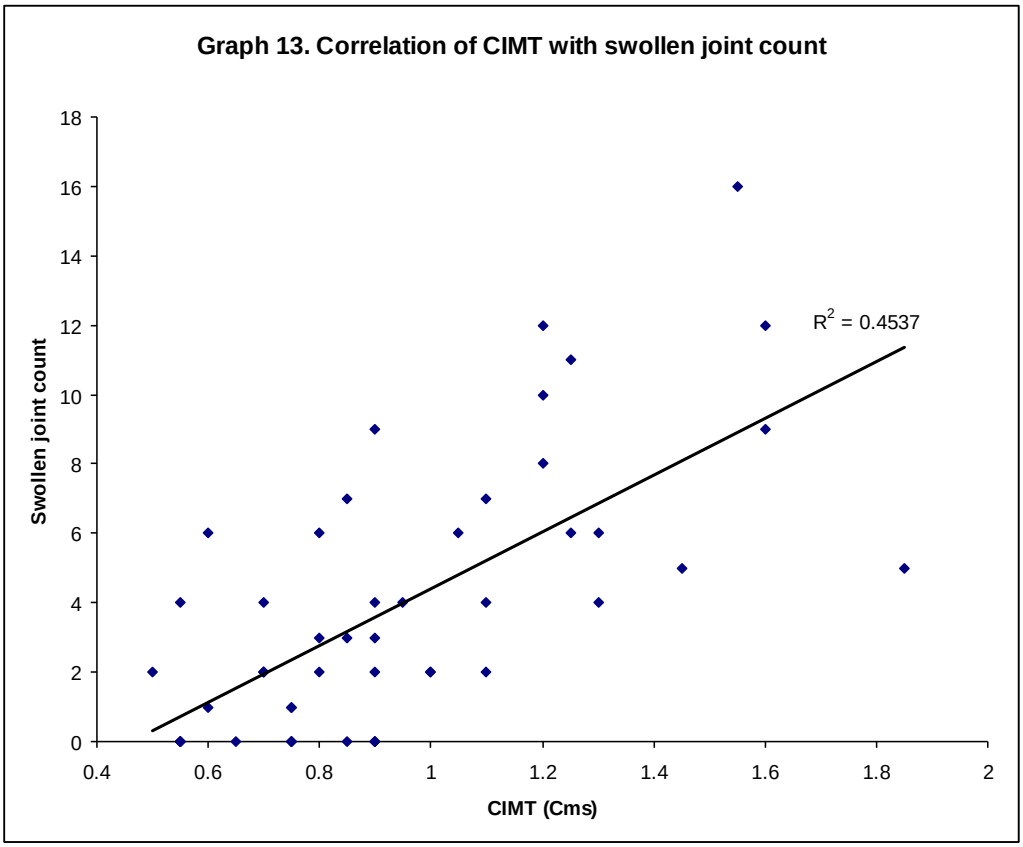


r=0.711; R^2=0.506; p<0.001

In the present study the mean CIMT significantly increased as the number of tender joint counts increased (p<0.001). Further there was strong positive correlation between CIMT and the number tender joint counts (**r=0.711; R^2=0.506; p<0.001)**

Table 18. Comparison of mean CIMT with swollen joint count

Swollen joint count	Patients (n)	CIMT (Cms)	
		Mean	**SD**
5 or less	35	0.84	0.28
6 to 10	11	1.08	0.28
11 to 15	3	1.35	0.22
16 to 20	1	1.55	-
F value		6.298	
P value		**0.001**	

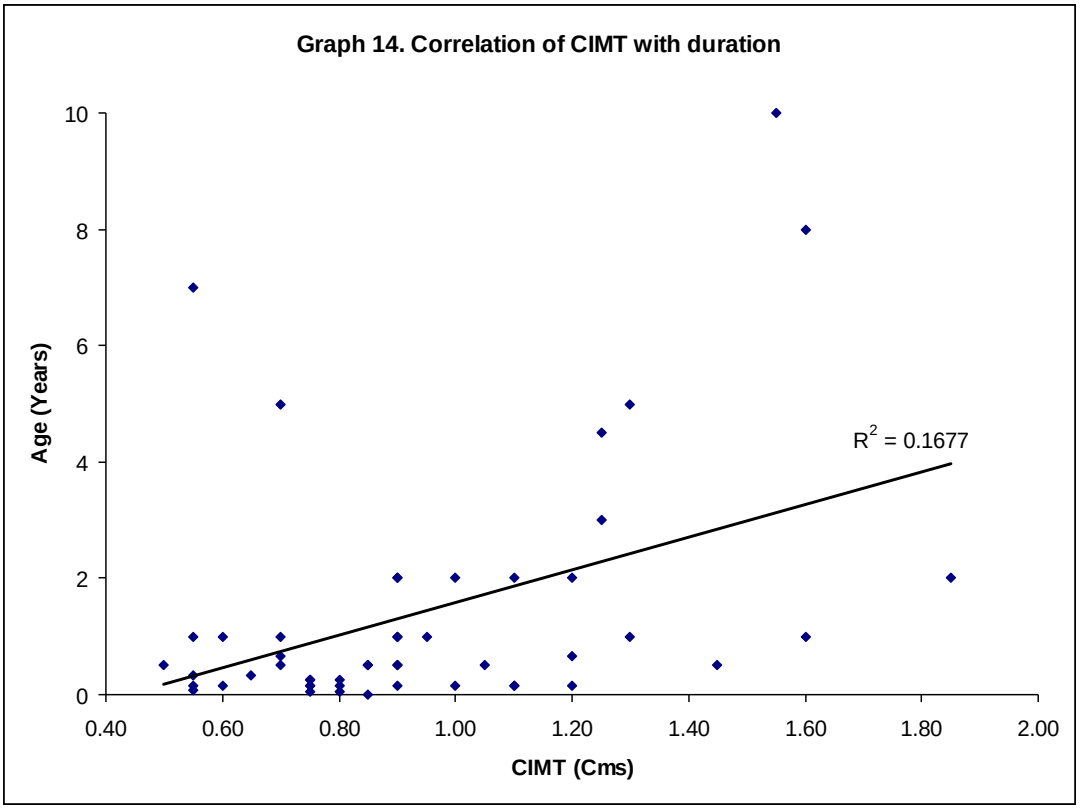


r=0.673; R^2=0.453; p<0.001

In this study, there was a trend showing significant rise in mean CIMT values with respect to increase in swollen joint count (p=0.001). Also the mean CIMT showed strong positive correlation with swollen joint count (**r=0.673; R^2=0.453; p<0.001)**

Table 19. Comparison of mean CIMT in different durations

Joint pain duration (Years)	Patients (n)	CIMT (Cms)	
		Mean	SD
1 or less	37	0.86	0.26
2 to 5	10	1.15	0.31
5 to 10	3	1.23	0.59
F value		5.480	
p value		**0.007**	



r=0.409; R^2=0.167; p<0.001

In the present study the significant increase in mean CIMT levels was noted as there was increase in duration (p=0.007). The CIMT levels showed moderate positive correlation with the duration (**r=0.409; R^2=0.167; p<0.001)**

Table 20. Comparison of mean CIMT with RA factor

RA factor	Patients (n)	CIMT (Cms)	
		Mean	SD
Positive	44	0.91	0.31
Negative	6	1.13	0.30

p = 0.138

In the present study the mean CIMT was comparable in patients with RA factor positive and RA factor negative (p=0.138).

Table 21. Comparison of mean CIMT with anti CCP antibodies

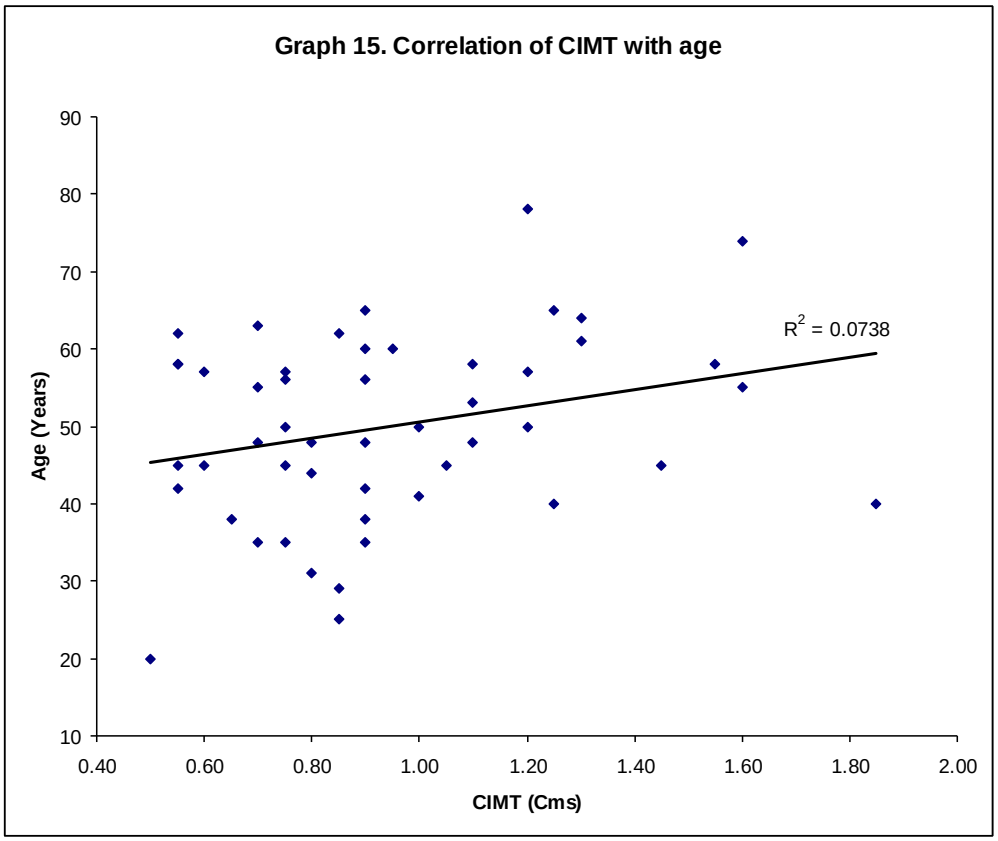
Anti CCP antibodies	Patients (n)	CIMT (Cms)	
		Mean	SD
Positive	18	1.02	0.30
Negative	32	0.90	0.32

p = 0.189

In this study the mean CIMT levels were comparable among the patients with positive Anti CCP antibodies and negative Anti CCP antibodies (p=0.189).

Table 22. Comparison of mean CIMT in different age groups

Age group (Years)	Patients (n)	CIMT (Cms)	
		Mean	SD
30 or less	3	0.73	0.20
31 to 40	8	0.98	0.40
41 to 50	16	0.88	0.25
51 to 60	14	0.94	0.34
61 to 70	7	0.98	0.31
71 to 80	2	1.40	0.28
F value		1.304	
p value		0.279	



r=0.271; R^2=0.073; p<0.001

In this study, the mean CIMT levels increased with increase in age but same was not true statistically (p=0.279). Also the mean CIMT showed weak positive correlation with age (**r=0.271; R^2=0.073; p<0.001)**

Table 23. Comparison of mean CIMT in males and females

Sex	Patients (n)	CIMT (Cms)	
		Mean	SD
Male	7	0.81	0.28
Female	43	0.96	0.32

p = 0.228

In the present study the mean CIMT was high in females compared to males but the difference was statistically not significant (p=0.228).

DISCUSSION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder involving the joints (nonsuppurative proliferative synovitis) along with other organ involvement including blood vessels and heart.[1,5] It is associated with disability, shortened life expectancy, and increased mortality.[11,12] It is reported that, survival of patients with RA is significantly worse than in the general population, with life expectancy shortened by 3 to 18 years.[10] The excessive mortality is largely attributable to cardiovascular (CV) disease. Patients with RA have a 2 to 3 fold increased risk of myocardial infarction, a 2-fold increased risk of heart failure and sudden death, and a 1.7-fold increased risk of stroke.[10]

The increased cardiovascular risk in RA patients has been attributed to accelerated atherosclerosis which has been found to be independent of the traditional risk factors. Inflammation, increased levels of homocysteine, homoeostatic imbalance, decreased mobility, low levels of antioxidants8, side-effects of medication, and dyslipidaemia have been attributed to cause accelerated atherosclerosis in RA.[96]

However, the mechanism of the increased CV event rate can not be explained only by the presence of traditional CV risk factors. In healthy populations, it has been established that systemic markers of inflammation independently predict CV events and mortality. It seems that chronic systemic inflammation is the most important contributor in the development of accelerated atherosclerosis in RA patients.[10]

Atherosclerosis is an inflammatory disease and so there are striking parallels between the inflammatory and immunological mechanism operating in atherosclerotic plaque and in rheumatoid synovitis. The common pathogenic features in the affected tissues include an abundance of activated macrophages which release or induce inflammatory mediators, including cytokines (e.g., interleukin 1 and TNF), growth factors, adhesion molecules with matrix metalloproteinases, and an infiltrate of T-cells. RA and atherosclerosis are associated with elevated levels of acute phase reactants- CRP, serum amyloid A, ESR, fibrinogen, and secondary phospholipase.[96]

The Indirect evidence of accelerated atherosclerosis in RA comes from studies using CIMT as a marker of atherosclerotic burden and cardiovascular risk. This measurement is a noninvasive and economical test which is quite reliable and sensitive for assessment of atherosclerosis. Increased atherosclerosis in carotid arteries holds true for atherosclerosis for multiple vascular beds including coronaries, and so measurement of carotid IMT is an important surrogate marker of increased cardiovascular risk including acute coronary syndrome.[96] However to date very few studies[96] have evaluated the relationship of disease activity in RA patients with CIMT. Hence this study was designed to assess the clinical relationship between CIMT with disease activity in patients with rheumatoid arthritis.

The present one year cross sectional study was conducted from January 2014 to December 2014 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Fifty patients who presented with rheumatoid arthritis were investigated for CIMT using high resolution B-mode ultrasonography.

It is reported that, women are affected by RA approximately three times more often than men,[33,34] but sex differences diminish in older age groups.[33] In the present study also females outnumbered males. Of the 50 patients studied, 86% of the patients were females and 14% were males with male to female ratio of 1:6.14. The direct comparison of sex distribution was not possible due to limited number of similar studies. However a case control study by Jassim NAI et al.[97] from Iraq also reported 43 females and 9 males out of the 52 patients with RA. The sex distribution pattern observed in the present study was also comparable with a case control study done by Singh S. et al.[96] from India who reported 27 males and 63 females out of 90 patients with RA with male:female ratio as 1:2.4. Lawrence (1998) also reported that, RA occurs 2.5 times in women compared to men.[98]

Literature reveals that, the maximum incidence of RA is between 35 to 50 years and the incidence and prevalence of RA generally rises with increasing age until about age 70, then declines.[99] In this study also nearly one third of the study population (32%) presented with age from 41 to 50 years followed by and 51 to 60 years (28%). The mean age was 49.88 ± 12.12 years and median age was 50 year with youngest patient having 20 years of age and oldest being 78 years. The mean age observed in the present study was comparable with a case control study by Jassim NAI et al.[97] from Iraq who reported mean age of 47.46±11.37 years in patients with RA.

In the present study out of 50 patients, history of RA was reported by 14 (28%) patients and 36 (72%) patients presented with history of joint pain and they were diagnosed to have RA. Out of 14 patients with history of RA, 8 patients (57.14%) reported duration of RA as ≤ 3 years and mean duration among these

patients was 3.62 ± 3.25 years. Also all these patient were on treatment. In 36 patients who were newly diagnosed with RA, the duration of joint pain was ≤1 year in 31 (86.11) patients and remaining 5 (13.89%) patients had duration of joint pain between 2 to 5 years. These findings suggest that though majority of the cases were newly diagnosed to have RA they had long standing untreated disease.

In the present predominance of joint pain pertaining to small joints of hand (76%) and knee and wrist joint (44% each) was noted. More than one third of the study population (38%) had of 6 to 10 tender joint count and more than two third (70%) were found to have ≤ 5 swollen joint counts. Based on tender and swollen joint count the EULAR criteria score was found to be 10 in 28% of the patients and 6 in 26% of the patients and the score was 8.10 ± 1.58. These findings demonstrate that majority of the patients had severe disease activity which was also evident by raised ESR levels and RA factor positivity.

In the present study ESR was profoundly raised in majority of the patients that is 80% of the patients were found to have ESR above normal reference range and there was a rise of almost 1.5 time in mean ESR (50.68 ± 24.73 mm /Hr). ESR can aid in the diagnosis of RA, but it cannot be used solely for diagnosing RA. It is very useful when used with other parameters as outlined in the American College of Rheumatology guidelines,[23] in the diagnosis and follow-up of RA patients.

Palosuo T et al[100] and van Boekel MA[101] indicated that rheumatoid arthritis is more severe in patients with rheumatoid factor positivity. In this study also majority of the patients were found to have positive RA factor (88%).

There are several studies which conclude that anti-CCP antibodies identify patients with significantly greater disease activity more reliably than rheumatoid factor.[102] A meta analysis conducted by Nishimura et al[102] also concluded that Anti-CCP antibodies are more specific than RF for diagnosing rheumatoid arthritis and may better predict erosive disease. The present study was no exception and supports this hypothesis. Despite of 80% of the patients with raised ESR and 88% of the patients with positive RA factor, severity of the disease as calculated by DAS 28 scores revealed moderate disease activity in 48% of the patients while severe disease activity was noted in 44%. The mean DAS 28 scores were also suggestive of moderate disease activity (4.91 ± 1.11; Range 2.73 to 7.26).

In the present study the mean CIMT was 0.94±0.31 cms and median CIMT was 0.90 cms. The minimum CIMT noted was 0.50 cms and maximum being 1.85 cms. The mean CIMT noted in the present study was similar to that of a case control study by Sing H. et al.[96] who reported mean CIMT in RA group as 0.80 ± 0.15 mm. Balaraju G. et al.[103] in India conducted a case control study to find the correlation between inflammation (severity and duration) to intima media thickness (As a marker of atherosclerosis) in RA and found mean CIMT as 0.798 ± 0.19 mm in RA subjects.

In this study, the mean CIMT levels significantly raised with disease severity that is, in four patients with mild disease activity the mean CIMT was 0.63 ± 0.10 cms which increased to 0.76 ± 0.14 cms in 24 patients with moderate disease activity. Further there was 2 fold rise in mean CIMT that is, 1.19 ± 0.30 cms in 22 patients with severe disease activity compared to those having mild disease activity. This rising trend was statistically significant ($F=24.335$; $p<0.001$). Furthermore,

there was strong positive correlation between CIMT and DAS 28 scores suggesting increase in CIMT with rise in DAS 28 scores ($r=0.729$; $R^2=0.532$; $p<0.001$). Similar trend of mean CIMT values and correlation was noted with regard to EULAR criteria score ($p<0.001$; $r=0.611$), swollen joint count ($p<0.001$; $r=0.711$) and swollen joint count ($p<0.001$; $r=0.673$). The head to head comparison of the findings observed in the present study was not possible due to lack similar studies in the literature. However, several studies have reported higher CIMT in patients with RA and positive association as well as correlation of CIMT with disease severity with different study designs and using definition of RA.

A study showed that the CIMT was significantly higher in RA patients (0.66±0.11mm) than in control subject (0.58±0.086 mm) ($p=0.003$). Similar results was concluded by Kumeda Y. et al.[104] whom found IMT of the common carotid artery of (0.641 ± 0.127 mm) in patients which was higher than the control subjects (0.576 ± 0.115 mm) ($P=0.0001$). Mohan A et al.[13] in 2014 estimated the mean CIMT among patients with RA in Tirupati India and reported significantly higher CIMT value in RA patients than normal healthy controls. Recently (2015) Balaraju G. et al.[103] in India found higher mean CIMT in RA subjects (0.798 ± 0.19 mm) when compared to controls (0.591 ± 0.11 mm). The mean values of common carotid IMT for mild, moderate and severe activity sub-groups based on the DAS 28 Score were 0.77 ± 0.14; 0.78 ± 0.15 and 0.8 ± 0.17 mm respectively; these values when compared with each other were found to be statistically non-significant ($p>0.05$).

Despite the methodological differences and variation in sample size the finding of the present study corroborate with the studies[13,103,104] in the literature. These findings indicate higher CIMT in patient with RA and; a positive association

as well as correlation, of CIMT with disease severity. However in contrast to these findings, a case control study by Balaraju G. et al.[103] in India reported mean CIMT as 0.798 ± 0.19 mm in RA subjects compared to 0.591 ± 0.11 mm ($p<0.001$) but did not differ when compared to disease activity.

The rise in CIMT levels among the patients with RA can be attributed to the following mechanisms. Firstly, it has recently been hypothesized that inflammation plays a major role in the process of atherosclerosis.[52] Previous studies have demonstrated that atherosclerosis shares many similarities with other inflammatory diseases.[105,106] 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,[107,108] a low-grade inflammatory response might have enhanced the arterial wall changes in these patients. The second possible explanation for the advanced arterial wall changes in RA patients is impaired physical activity. The third possible explanation is that the arterial wall changes progressed in the RA patients as bone destruction progressed. There is evidence that atherosclerosis progresses significantly faster in patients with enhanced bone destruction than in those with less bone destruction.[109,110] The increase in common carotid artery IMT in RA patients can be explained by an increase in calcium mobilization from bone due to enhancement of bone destruction, leading to enhanced development of atherosclerosis.[111]

Most studies emphasize an association between the disease duration and CIMT, as well as with atherosclerotic plaques.[10,96] The present study supports this observation. Higher CIMT value and symptoms of subclinical atherosclerosis were noticed in patients with longer disease duration as significant rise in mean CIMT levels was noted with increase in duration (p=0.007). Also the CIMT levels showed moderate positive correlation with the duration (r=0.409; R^2=0.167; p<0.001). These findings were consistent with a case control study by Balaraju G. et al.[103] in India who reported that, CIMT increased significantly with duration of disease. Gonzales et al.[112] in their study had found disease duration as one of the best predictor for the development of severe morphologic expression of atherosclerotic disease. Del Rincon et al.[113] and Mahajan et al.[81] also had similar observations. This may be due to more years of exposure to increased inflammation, and other factors like increased arterial stiffness[113] and prothrombotic marker in RA patients.[114]

In this study the mean CIMT values were comparable in males and females (p=0.228). Similar observations were reported in a study by Merza RR et al.[115] from Iraq in 2014 where the relation between the gender and the CIMT not reach a statistical significant level (p=0.445).

In the present study, mean CIMT levels in different age groups were also nearly equal (p=0.279) and showed weak positive correlation with age (r=0.271; R^2=0.073; p<0.001). Furthermore, no statistically significant difference was noted with positive and negative RA factor (p=0.138) as well as anti CCP antibodies (p=0.189). In contrast, Merza RR et al.[116] in their study from Iraq in 2014 found that patients with seropositive (RF) have higher CIMT (0.72 ± 0.10mm) than those with sero-negative (0.57 ± 0.08mm) (p<0.001). Furthermore, they demonstrated

significant relationship between the age and the CIMT (p=0.008) this is due to the disease course and chronic inflammatory processes. but the intimal thickness increase in RA males was greater than RA females (0.70 ± 0.13mm) (0.66 ± 0.11mm) respectively and this might indicate more severe vascular involvement in RA males than in RA females.

Overall the present study showed higher CIMT in patients with RA and significant strong correlation with not only disease severity but other characteristics of RA including EULAR criteria score, tender and swollen joint count and duration.

However, a major limitation of CIMT as a marker for atherosclerosis is that there is no clear "threshold" for demarcating 'normal' and 'abnormal' values[117] which was the limitation of the present study also. This limited the study to explore the association of several aspect like age, gender, EULAR criteria score, disease severity, ESR and CRP.

In some Indian studies, arbitrary cut-offs, such as, 1 standard deviations (sd)[118] or 2 sd[119] above the mean value obtained for control subjects have been used; or, without defining a cut-off, comparison of mean CIMT values between cases and controls[81] have been used to explain the significance of CIMT measurements. However, these methods do not appear to be the ideal methods for defining the cut-off value[13] hence were not considered in the present study. The consensus statement from the American Society of Echocardiography[73] 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.

However, a study by Mohan et al.[13] in Tirupati, India attempted 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. The CIMT measurements obtained from patients with angiographically proven CAD and age- and gender-matched normal control subjects were used to construct an ROC curve and a cut-off value of 0.57 was derived. The performance of this cut-off value in detecting asymptomatic atherosclerosis among patients with RA was very similar to the 75th percentile value of CIMT in normal control subjects. Thus, these cut-off values of CIMT appeared to be appropriate for screening for asymptomatic (subclinical) atherosclerosis among adult patients with RA. However, this study by Mohan et al.[13] had certain limitations like the study design was a cross-sectional study which limits the study from looking for clinical events that reflect the consequences of atherosclerosis in long term and the number of male participants was small which make the cut-off value largely applicable to women.

CONCLUSION

Patients with rheumatoid arthritis, a chronic inflammatory disease involving joints are at high risk of atherosclerosis as measured by CIMT. There is strong relationship of CIMT with not only the disease per se, but also with the disease severity as determined by DAS 28 score which takes into account various characteristics like tender and swollen joint counts, EULAR criteria score and duration of disease. However no relationship of CIMT was found with RA factor, anti CCP antibodies, age and sex.

SUMMARY

Rheumatoid arthritis is a chronic inflammatory disorder and these patients are at a higher risk for developing atherosclerosis The CIMT by high-resolution B-mode ultrasonography is a simple, reliable, inexpensive, non-invasive marker that is increasingly being used to detect subclinical atherosclerosis. This study was aimed to explore clinical relationship between CIMT and disease activity in patients with RA.

The present one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 50 adult patients with RA were enrolled and evaluated for common carotid artery imaging to measure CIMT using high resolution B-mode ultrasonography. The disease severity was assessed based on Disease Activity Score (DAS) score.

The male to female ratio was 6.14:1 and mean age was 49.88±12.12 years. With regard to clinical presentation, 76% of the patients had involvement of small joint of hand, 38% had tender joint count between 6 to 10 and swollen joint count of ≤5 (70%). Most of the patients presented with EULAR criteria score of 10 (28%). Based on DAS score, disease activity was severe in 44% and moderate in 48%. Based on the cut-off value of 0.57 for CIMT, majority of the patients had raised CIMT. Mean CIMT was significantly differed with regard to duration of joint pain ($p=0.007$), tender joint count ($p<0.001$), swollen joint count ($p<0.001$), EULAR criteria score ($p<0.001$) and DAS score ($p<0.001$). Also significantly positive correlation was noted between CIMT and tender joint count

($r=0.711;R^2=0.506;p<0.001$), swollen joint count ($r=0.673;R^2=0.453;p<0.001$), EULAR criteria score ($r=0.611;R^2=0.373$; $p<0.001$) and DAS score ($r=0.729;R^2=0.532;p<0.001$).

There is a strong relationship between CIMT and disease activity in RA which makes measurement of CIMT as a useful marker for detecting atherosclerosis.

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ANNEXURE I – CONSENT FORM

TITLE OF RESEARCH STUDY: "A ONE YEAR CROSS SECTIONAL STUDY TO ASSESS THE CLINICAL CORRELATION BETWEEN CAROTID INTIMA-MEDIA THICKNESS AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL."

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Introduction and Purpose

Cardiovascular involvement is the leading cause of mortality in patients with Rheumatoid Arthritis. This increased cardiovascular risk is attributed to accelerated atherosclerosis. Carotid Intima Media Thickness measurement is used as a tool to measure this accelerated atherosclerosis.

Procedure

If you agree to be part of the research study, you will be asked the relevant history of joint involvement, coronary heart disease, cerebrovascular disease, chronic hepatic and renal failure, hypothyroidism etc; and will be subjected to relevant clinical examinations like enumerating the number of tender and swollen joints and routine general examination of other systems. Relevant blood investigations like liver function, renal function test, ESR will be done. You will also have to give blood samples for the necessary investigations. Finally you will be undergoing B-mode ultrasound estimation of carotid Intima Media Thickness.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

The benefits you receive from undergoing these tests are enormous and far reaching. These tests act as an early marker to predict increased cardiovascular risk etc, so that appropriate lifestyle changes and treatment made will reduce the morbidity and mortality rates associated with the disease.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

In case of any injury related to the study, treatment will be made available at the free hospital of K.L.E.S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. There is no compensation or payment for such medical treatment by law.

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

Questions

In case of the queries during study or in future you may contact following persons

1. **Dr. **** ********
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   Belgaum – 590 010
   Phone No.: ***** ******

3. **Dr. ***** *********
   Jawaharlal Nehru Medical College,
   Ethical Committee for Human Research,
   Phone Number: ***** *****

Consent Statement:

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant : _____ Signature / Thumb print _____

Name of the Witness _____ Signature/ Thumb print _____

Investigator Name: _____ Signature :_____

Date: Place

ANNEXURE II – PROFORMA

TITLE OF RESEARCH STUDY: "A ONE YEAR CROSS SECTIONAL STUDY TO ASSESS THE CLINICAL CORRELATION BETWEEN CAROTID INTIMA-MEDIA THICKNESS AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL."

Case Number :

Name :

Age / Sex :

In Patient Number :

Address :

Occupation :

Education : literate / illiterate

Complaints at presentation

Past history

History suggestive of –

IHD / CVA / PVD / Endocrinopathies / CRF

Known Case of Rheumatoid Arthritis

If yes, since how long -

Treatment history

Physical examination

Tender Joint Count (t)

Swollen Joint Count (sw)

ESR

DAS (28-3) Score

RA-factor	:	Positive / Negative
Blood Urea	:	
Serum Creatinine	:	
Liver Function Test	:	
Total Bilirubin	:	
Direct Bilirubin	:	
Aspartate Transaminases (SGOT/AST)	:	
Alanine Transaminases (SGPT/ALT)	:	
Alkaline Phosphatase (ALP)	:	
Carotid -Intima-Media Thickness	:	

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
Ag	-	Agriculturist
CCP	-	Cyclic citrullinated peptide
cm/sec	-	Centimeters per second
CRF	-	Chronic renal failure
CRP	-	C-reactive protein
CVA	-	Cerebrovascular accident
DAS	-	Disease activity score
EDV	-	End diastolic velocity
ESR	-	Erythrocyte sedimentation rate
EULAR	-	The European League Against Rheumatism
F	-	Female
G	-	Graduate
g/dl	-	Grams per decilitre
Hs CRP	-	Highly sensitive C-reactive protein
HS	-	Higher secondary school
HW	-	House wife
IHD	-	Ischaemic heart disease
Il	-	Illiterate
IU/mL	-	International units per milliliter
L	-	Labour
M	-	Male

mg/dL	-	Milligrams per decilitre
NA	-	Not available
ND	-	Newly detected
PS	-	Primary schooling
PSV	-	Peak systolic velocity
PUC	-	Preuniversity college
PVD	-	Peripheral vascular disease
RA	-	Rheumatoid arthritis
RFT	-	Renal function test
S	-	Student
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvic transaminase