"PREVELANCE OF ANTI CCP ANTIBODIES IN PATIENTS WITH RHEUMATOID ARTHRITIS" – ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MRC, BELGAUM

By

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Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.

in

GENERAL MEDICINE

Under the Guidance of

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Professor

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BELGAUM, KARNATAKA

MAY - 2012

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ACKNOWLEDGEMENT

I take this opportunity to extend my gratitude and sincere thanks to all those who have helped me to complete this dissertation.

I am extremely indebted and remain grateful forever to my respected teacher and guide, **Dr. REKHA S. PATIL MD**, Professor of Medicine, for her constant able guidance and constant encouragement in preparing this dissertation during my post-graduate course.

I am extremely grateful to my respected teacher and co-guide, **Dr. DHANITA KHANNA MD, DM (rheumatology and immunology),** for her able guidance, supervision, invaluable suggestions, and kind help in the preparation of this dissertation.

It gives me immense pleasure to express my deep sense of gratitude to my Professor and Head of Department of Medicine **Dr. V. A. KOTHIWALE MD, PhD,** the person who has mastered the art of clinical medicine, for his excellent guidance, encouragement and constant inspiration during my P.G. Course.

I am extremely grateful to **Dr. V. G. SOMANNAVAR MD** and **Dr. B. SRINIVAS MD**, Professor, Department of medicine for his excellent guidance and kind help in the preparation of this dissertation.

It gives me immense pleasure to express my deep sense of gratitude to **Dr. DNYANESH MORKAR MD** and **Dr. ANJALI METGUDMATH MD** for their encouragement and advice.

I am very much thankful to **Dr. P. K. PHADNIS** MD **Dr. ARATHI DARSHAN** MD**, Dr. PRAKASH BABALICHE** MD**, Dr. RAJU BADIGER** MD**, Dr. MADHAV PRABHU** MD**, Dr. POORNIMA PATIL** MD**, Dr. RAJEEV MALIPATIL** MD**, Dr. JAYPRAKASH APPAJIGOL** MD**, and Dr. NAVEEN ANGADI** MD for their guidance and encouragement during my postgraduate course.

I extend my sincere thanks to my Post-graduate Colleagues**, Dr. HARSHAVARDHAN RAO.B, Dr. CHANDRAMOULI REDDY, Dr. HEMANTH KUMAR, Dr. RANJAN MODI, Dr. PAKALPATI SASANKA, Dr. SNEHA SIRDESHPANDE, and Dr. VEENA MUNAVALLI** who had helped me in preparing this dissertation.

I must give my sincere thanks to my **PARENTS** for their moral support and constant encouragement.

Last but not the least my heartfelt thanks to all **PATIENTS** who formed this study group and co-operated wholeheartedly.

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LIST OF ABBREVIATIONS USED

Ab	-	Antibody
ACPA	-	Anticitrullinated Protein Antibody
ACR	-	American College of Rheumatology
AD	-	Anno Domini
ADL	-	Activities Of Daily Living
ANA	-	Antinuclear Antibody
Anti-CCP	-	Anticyclic Citrullinated Peptide Antibody
APC	-	Antigen-Presenting Cells
BC	-	Before Christ
CBC	-	Complete Blood Count
CD4	-	Cluster Of Differentiation 4
CNS	-	Central Nervous System
CRP	-	C reactive protein
CT	-	Computerized Tomography
DAS28	-	Disease Activity Score 28-joint counts
DIP	-	Distal Interphalangeal Joints
DJD	-	Degenerative joint disease
DMARD	-	Disease Modifying Anti Rheumatic Drugs
ELISA	-	Enzyme-Linked Immunosorbent Assay
ESR	-	Erythrocytic Sedimentation Rate
EULAR	-	European League Against Rheumatism
FGF	-	Fibroblast Growth Factor
HLA	-	Human Leukocyte Antigen
IFN	-	Interferon

IL	-	Interleukins
IU	-	International Units
MAS	-	Macrophage Activation Syndrome
MCP	-	Metacarpophalangeal Joint
MHC	-	Major Histocompatibility Complex
MRI	-	Magnetic resonance imaging
MTP	-	Metatarsophalangeal
MTX	-	Methotrexate
NSAID	-	Nonsteroidal Anti-Inflammatory Drugs
PAD	-	Peptidyl Arginine Deiminase
PDGF	-	Platelet-derived growth factor
PIP	-	Proximal Interphalangeal Joints
PIP	-	Proximal Interphalangeal
RA	-	Rheumatoid Arthritis
RF	-	Rheumatoid factor
RNA	-	Ribonucleic acid
SLE	-	Systemic Lupus Erythematosus
TGF	-	Transforming Growth Factor
TNF	-	Tumor necrosis factors
UA	-	Undifferentiated Arthritis
ULN	-	Upper Limit Of Normal
VAS	-	Visual analogue scale

ABSTRACT

Background and objectives

Anti-cyclic-citrullinated-peptide antibodies (anti-CCPs) hold promise for earlier and more accurate diagnosis of rheumatic arthritic (RA) disease, improved prognostic information, and have been implicated in RA pathogenesis. The present study was undertaken to find prevalence of anti CCP antibodies in patients with RA, to assess the positivity of anti CCP antibody in subsets of RA factor positive and negative patients and to correlate anti CCP positivity with severity of rheumatoid arthritis.

Methodology

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010 on 100 patients with history, suggestive of RA and fulfilling ACR Criteria 1987. The severity of the disease was calculated using Disease Activity Score 28 (DAS 28) score.

Results

In the present study females outnumbered male (77% vs 23%) with male to female ratio of 1:3.34. The mean age was 44.74 ± 11.62 years. RF was positive in 77% and negative in 23% of all patients and anti CCP was found to be positive in only 43 % and negative in 57% of the patients. 94% of the patients were having severe disease while 6% had moderate disease. The sensitivity of CCP in measuring RF was 55.7%. The specificity of CCP in measuring RF is 35.9%, that

is among those who were RF negative, 35.9% were also CCP negative. In RA positive subset of patients anti-CCP positive titres had significantly positive correlation with severity of RA disease.

Interpretation and conclusion

Anti-CCP titres were found to have a positive correlation with the severity of the disease. Anti-CCP should be used along with RF in patients with clinical suspicion of RA.

Keywords

Anti-CCP antibody; Rheumatoid arthritis; Rheumatoid factor;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

Chapter 1

Introduction

INTRODUCTION

Rheumatoid arthritis (RA) is a common, systemic autoimmune disease affecting 0.5 to 1% of the population.[1,2] 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.[3] Disease outcome may vary from mild symptoms to severe systemic disease when joint destruction is accompanied by extraarticular manifestations (rheumatoid nodules, vasculitis).

Mortality in the latter group is significantly increased compared to the former group and the general population.[4,5] The morbidity and mortality it causes are a consequence of local and systemic inflammatory processes that damage cartilage, bone and soft tissue, as well as blood vessels and viscera.

Until recently, treatment for RA was limited, and severe joint damage and overall debility were common. Early and aggressive intervention with new and effective biological treatments can alter the course of the disease, lengthen life, and improve function,[6] but better molecular markers for diagnosis and prognosis are needed to identify RA patients earlier and fine-tune therapeutic choices to the individual patient. Serological testing for rheumatoid factor is complicated by moderate sensitivity and specificity, and high rates of positivity in other chronic inflammatory and infectious diseases such as Sjögren's syndrome and chronic viral hepatitis.[7] The reported sensitivity and specificity of rheumatoid factor in current studies may be falsely elevated by the inclusion of rheumatoid factor as a

diagnostic criteria in the commonly used American College of Rheumatology diagnostic criteria for RA.[8]

With more sophisticated and effective therapies becoming available[9] and with the understanding that early intervention is crucial in preventing irreversible joint damage,[10-12] it is more and more important to diagnose RA at a very early stage in the disease. Although the 1987 American College of Rheumatology (ACR; formerly, American Rheumatism Association) classification criteria for RA[13] are often used in clinical practice as diagnostic tool for RA, they are not very well suited for the diagnosis of early RA.[8,13-15]

The ACR criteria rely heavily on the expression of clinical symptoms of RA, but in early RA these clinical parameters are often not (yet) manifest. Therefore, a specific and sensitive (serological) marker, which is present very early in the disease, is needed. Rheumatologists need to be able to target the use of potentially toxic and expensive drugs to those patients where the benefits clearly outweigh the risks.[15,16] Therefore a good marker should ideally be able to predict the erosive or nonerosive progression of the disease.

Fortunately, the cyclic citrullinated peptide (anti-CCP) antibodies meet the demands for a good and useful marker for early RA. Anti-cyclic-citrullinated-peptide antibodies hold promise for earlier and more accurate diagnosis of disease, improved prognostic information, and have been implicated in RA pathogenesis. If the physician is to intervene optimally during a patient's window of opportunity before irreversible damage occurs, such a biomarker may be very useful, when used in combination with other diagnostic features.[17]

In view of the above, the present study was undertaken to find the prevalence of anti CCP antibodies in patients with rheumatoid arthritis, to assess the positivity of anti CCP antibody in subsets of RA factor positive and negative patients and to correlate anti CCP positivity with severity of rheumatoid arthritis.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

Primary

- To find the prevalence of anti CCP antibodies in patients with RA

Secondary

- To assess the positivity of anti CCP antibody in two subsets of patients 1) RA factor positive and 2) RA factor negative patients.
- To correlate anti CCP positivity with severity of rheumatoid arthritis.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

RHEUMATIC ARTHRITIS

History

The first known traces of arthritis date back at least as far as 4500 BC. A text dated 123 AD first describes symptoms very similar to rheumatoid arthritis. It 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.[18]

An anomaly has been noticed from investigation of Precolumbian bones. The bones from the Tennessee site show no signs of tuberculosis even though it was prevalent at the time throughout the Americas.[19] 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.[18]

The art of Peter Paul Rubens may possibly depict the effects of rheumatoid arthritis. In his later paintings, his rendered hands show, in the opinion of some physicians, increasing deformity consistent with the symptoms of the disease.[20] Rheumatoid arthritis appears to have been depicted in 16th century paintings.[21] However, it is generally recognized in art historical circles

that the painting of hands in the sixteenth and seventeenth century followed certain stylised conventions, most clearly seen in the Mannerist movement. It was conventional, for instance to show the upheld right hand of Christ in what now appears a deformed posture. These conventions are easily misinterpreted as portrayals of disease. They are much too widespread for this to be plausible.[18]

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.[22] The name "rheumatoid arthritis" itself was coined in 1859 by British rheumatologist Dr Alfred Baring Garrod.[23]

Background

Rheumatoid arthritis (RA) 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. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant.

Early therapy with disease-modifying antirheumatic drugs (DMARDs) has become the standard of care, as it not only can more efficiently retard disease progression than later treatment but also may induce more remissions. Many of the newer DMARD therapies, however, are immunosuppressive in nature, leading to a higher risk for partially masked serious bacterial, and sometimes fungal, infections.

Cervical spine involvement usually affects C1-C2 and may potentially cause serious neurologic consequences. Patients who are to undergo intubation or procedures that may involve manipulation of the neck should undergo careful evaluation of the cervical spine.

Optimal care of patients with RA requires an integrated approach of pharmacologic and nonpharmacologic therapies, such as DMARDs, biologics, NSAIDs, analgesics, glucocorticoids, and immunomodulators.

ACR Criteria for RA

Historically, the diagnosis of RA was based on American College of Rheumatology (ACR) 1987 criteria.[8] These criteria were based on the persistence of arthritic symptoms over time. This classification system failed to identify patients with early inflammatory arthritis. Over the last decade, it has been recognized that early therapeutic intervention significantly improves clinical outcomes and reduces irreversible joint damage and disability. With this focus, the ACR and European League Against Rheumatism (EULAR) have devised new classification criteria for early arthritis, which assess joint involvement, autoantibody status, and acute-phase response and symptom duration.[23]

The ACR and EULAR revised criteria for the classification of RA in newly presenting patients, those with erosive disease typical of RA, and those with inactive disease with or without treatment.[23]

A joint collaborative of American and European rheumatologists developed new classification criteria for RA. These criteria are designed to

identify patients with unexplained inflammatory arthritis in at least one peripheral joint and a short duration of symptoms who would benefit from early therapeutic intervention. This new classification criteria represents a paradigm shift from the 1987 American College of Rheumatology criteria, which lacked sensitivity to detect early RA.[24]

According to the 2010 RA classification criteria[24] patients who should be tested are those (1) with at least one joint with definite clinical synovitis and (2) whose synovitis is not better explained by another disease (lupus, psoriatic arthritis, gout).

The following is a score-based algorithm for RA based on 4 areas: joint involvement, serology test results, acute phase reactant test results, and patient self-reporting of signs/symptom duration. A score of 6 of 10 or greater must be met for a classification of definitive RA. Patients with a score that falls below 6/10 may be reassessed over time.

Joint involvement consists of swelling or tenderness upon examination. The presence of synovitis may be confirmed on imaging studies. Points are allocated as follows:

- 1 large joint (shoulders, elbows, hips, knees, ankles) = 0 points
- 2-10 large joints = 1 point
- 1-3 small joints (with or without involvement of large joints) (MCP, PIP, second-fifth MTP, thumb IP, and wrist joints) = 2 points
- 4-10 small joints (with or without involvement of large joints) = 3 points

- More than 10 joints (at least 1 small joint, plus any combination of large and additional small joints or joints such as temporomandibular, acromioclavicular, sternoclavicular) = 5 points

At least 1 serology test result is needed for classification. Points are allocated as follows:

- Negative RF and negative anti CCP = 0 points
- Low-positive RF or low-positive anti CCP = 2 points
- High-positive RF or high-positive anti CCP = 3 points

Negative results are defined as IU values that are less than or equal to the upper limit of normal (ULN) for the reporting laboratory/assay. Low-positive results are defined as IU values greater than the ULN but no more than 3-fold the ULN for reporting laboratory/assay. High-positive results are IU values that are more than 3-fold greater than the ULN reporting laboratory/assay. When RF is available only as a positive or negative, a positive result should be scored as low-positive RF.

At least 1 test acute-phase reactant test result is needed for classification. Local laboratory standards determine normal/abnormal results. Points are allocated as follows:

- Normal CRP and normal ESR = 0 points
- Abnormal CRP or abnormal ESR = 1 point

Patient-reported duration of synovitis signs/symptoms of joints clinically involved at the time the patient is assessed, with or without treatment. Points are allocated as follows:

- Shorter than 6 weeks = 0 points
- 6 weeks or longer = 1 point

Two studies evaluated the diagnostic accuracy of the 2010 ACR/EULAR criteria[23] and the 1987 ACR criteria for rheumatoid arthritis.[8] One study found that diagnostic accuracies of the ACR/EULAR score and ACR 1987 criteria were not statistically different. Some improvements were noted of the ACR/EULAR criteria; however, this was attributed to the use of exclusion criteria in the algorithm.[24] The other study also found that the 2010 ACR/EULAR criteria and the 1987 ACR criteria achieved similar results, with the 2010 version being slightly more sensitive.[25]

Measurement of Progression of Disease

To determine progression, patients are categorized by clinical and radiologic criteria into 4 stages, as follows:

Stage I (early RA): No destructive changes observed upon roentgenographic examination; radiographic evidence of osteoporosis is possible

Stage II (moderate progression): Radiographic evidence of periarticular osteoporosis, with or without slight subchondral bone destruction; slight cartilage destruction is possible; joint mobility is possibly limited, but no joint deformities

are observed; adjacent muscle atrophy is present; extra-articular soft-tissue lesions (nodules, tenosynovitis) are possible.

Stage III (severe progression): Radiographic evidence of cartilage and bone destruction in addition to periarticular osteoporosis; joint deformity (subluxation, ulnar deviation, hyperextension) without fibrous or bony ankylosis; muscle atrophy is extensive; extra-articular soft-tissue lesions (nodules, tenosynovitis) are possible.

Stage IV (terminal progression): Presence of fibrous or bony ankylosis, along with criteria of stage III

Measurement of Disease Remission

To be considered in remission, patients must meet at least 5 of the conditions below for at least 2 consecutive months:

- Duration of morning stiffness not exceeding 15 minutes
- No fatigue
- No joint pain
- No joint tenderness or pain with motion
- No soft-tissue swelling in joints or tendon sheaths

An ESR level of less than 30 mm/h in a female or less than 20 mm/h in a male.

Measurement of Functional Status

Patients with rheumatoid arthritis are categorized into 4 functional classes:

- Class I - Completely able to perform usual activities of daily living
- Class II - Able to perform usual self-care and vocational activities but limited in avocational activities
- Class III - Able to perform usual self-care activities but limited in vocational and avocational activities
- Class IV - Limited in ability to perform usual self-care, vocational, and avocational activities

Usual self care activities include, dressing, feeding, bathing, grooming and tolerating. Avocational (recreational and leisure) and vocational (work, school, home making) activities are patient desired and age and sex specific.

Epidemiology

Worldwide, the annual incidence of rheumatoid arthritis is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking at age 35-50 years. Rheumatoid arthritis affects all populations, although the disease is much more prevalent in some groups (5-6% in some Native American groups) and much less prevalent in others (black persons from the Caribbean region). First-degree relatives of individuals with RA are at an increased risk (2- to 3-fold) of the disease. Disease concordance in monozygotic twins is approximately 15-20%, suggesting that nongenetic factors

play an important role. Because the worldwide frequency of RA is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role.

Women are affected by RA approximately 3 times more often than men,[26,27] but sex differences diminish in older age groups.[26] In investigating whether the higher rate of RA among women could be linked to certain reproductive risk factors, a study from Denmark found that the rate of RA was higher in women who had given birth to just 1 child than it was in women who had delivered 2 or 3 offspring.[28] However, no increased rate was found in women who were nulliparous or who had a history of lost pregnancies. Time elapsed since pregnancy also is significant; in 1- to 5-year postpartum period a decreased risk for RA has been recognized, even in those with higher-risk HLA markers.[29]

The Denmark study also found a higher rheumatoid arthritis risk among women with a history of preeclampsia, hyperemesis during pregnancy, or gestational hypertension.[28] The authors suggested that this portion of the data indicated that a reduced immune adaptability to pregnancy may exist in women who have a predisposition to the development of RA or that there may be a link between fetal microchimerism (in which fetal cells are present in the maternal circulation) and RA.

In India, the prevalence of rheumatoid arthritis (0.75%) is similar to that in the West. In China, Indonesia, and the Philippines, in contrast, rheumatoid arthritis appears rare (prevalence below 0.4%), in both urban and rural settings.

The rarity of rheumatoid arthritis in rural Africa contrasts with the high prevalence of the disease in Jamaica, where over 2% of the adult population are affected. In a study in Latin America, rheumatoid arthritis was the reason for seeking medical advice in 22% of rheumatology clinic patients. These differences probably reflect variations in the interactions between genetic and environmental factors. Rheumatoid arthritis may be less severe in Asia and West Africa than in western countries. No such difference has been found for Jamaica or southern and eastern Africa. In China and India, the genetic profile associated with rheumatoid arthritis is not uniform. Thus, associations with antigens other than HLA DR4 have been demonstrated. This genetic variability may reflect the heterogeneity of the Chinese and Indian populations. It may also support the theory of a shared epitope. In southern Africa, most rheumatoid arthritis patients carry the HLA DR4 antigen.

Etiology

The cause of RA is unknown. Genetic, environmental, hormonal, immunologic, and infectious factors may play significant roles. Socioeconomic, psychologic, and lifestyle factors like consumption of tobacco may exacerbate the disease and influence disease outcome.

Infectious agents

For many decades, numerous infectious agents have been suggested to induce RA. Among these are Mycoplasma organisms, Epstein-Barr and rubella viruses, and others. This supposition is further supported indirectly by the following:

- Occasional reports of flu like disorders preceding the start of arthritis.
- The inducibility of arthritis in experimental animals with different bacteria or bacterial products (streptococcal cell walls).
- The presence of bacterial products, including bacterial RNA, in patients' joints.
- The activity of several agents that have antimicrobial effects as disease-modifying drugs (gold salts, antimalarials, minocycline)

Hormones

Sex hormones may play a role in RA, as evidenced by the disproportionate number of females with this disease, its amelioration during pregnancy, its recurrence in the early postpartum period, and its reduced incidence in women using oral contraceptives. Hyperprolactinemia may be a risk factor for RA.[30]

Immunologic factors

All of the major immunologic elements play fundamental roles in the initiation, propagation, and maintenance of the autoimmune process of RA. The exact orchestration of the cellular and cytokine events that lead to pathologic consequences, such as synovial proliferation and subsequent joint destruction, is complex. It involves T and B lymphocytes, antigen-presenting cells (APCs) (B cells, macrophages, dendritic cells), and numerous cytokines. Aberrant production and regulation of both proinflammatory and anti-inflammatory cytokines and cytokine pathways are found in RA.

T cells are assumed to play a pivotal role in the initiation of RA, and the key player in this respect is assumed to be the T helper 1 (Th1) CD4 cells. (Th1 cells produce IL-2 and interferon [IFN] gamma.) These cells may subsequently activate macrophages and other cell populations, including synovial fibroblasts. Macrophages and synovial fibroblasts are the main producers of the proinflammatory cytokines TNF-alpha and IL-1. Experimental models suggest that synovial macrophages and fibroblasts may become autonomous and thus lose responsiveness to T-cell activities in the course of the disease.

B cells are important in the pathologic process and may serve as antigen-presenting cells. B cells also produce numerous autoantibodies and secrete cytokines.

The hyperactive and hyperplastic synovial membrane is ultimately transformed into pannus tissue and invades cartilage and bone, the latter being degraded by activated osteoclasts. The major difference between RA and other forms of inflammatory arthritis, such as psoriatic arthritis, does not lie in their cytokine patterns but rather in the highly destructive potential of the RA synovial membrane and in the local and systemic autoimmunity. Whether these 2 events are linked is unclear; however, the autoimmune response conceivably leads to the formation of immune complexes that activate the inflammatory process to a much higher degree than normal. This theory is supported by the much worse prognosis of RA among patients with positive RF results.

Pathophysiology

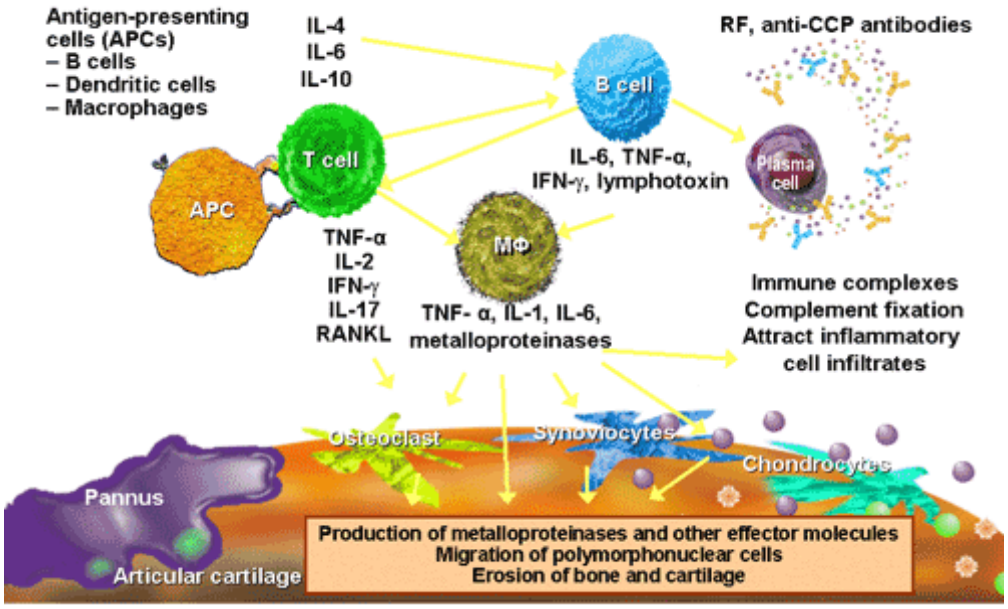


Figure 1. Cellular pathophysiology of Rheumatoid Arthritis

The pathogenesis of RA is not completely understood. An external trigger (infection, trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals. Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation.

CD4+ T-cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of rheumatoid arthritis (RA), whereas B lymphocytes produce autoantibodies (rheumatoid factors [RFs]). Abnormal production of numerous cytokines, chemokines, and

other inflammatory mediators (eg, tumor necrosis factor alpha [TNF-alpha], interleukin [IL]–1, IL-6, transforming growth factor beta [TGF-beta], IL-8, fibroblast growth factor [FGF], platelet-derived growth factor [PDGF]) has been demonstrated in patients with RA. Ultimately, inflammation and exuberant proliferation of synovium (pannus) leads to destruction of various tissues, including cartilage, bone, tendons, ligaments, and blood vessels. Although the articular structures are the primary sites involved by RA, other tissues are also affected.

Clinical features[31]

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.

Juvenile rheumatoid arthritis is the most common form of childhood arthritis. In most patients, the immunogenic associations, clinical pattern, and functional outcome are different from adult-onset RA.

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.

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.

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.

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.

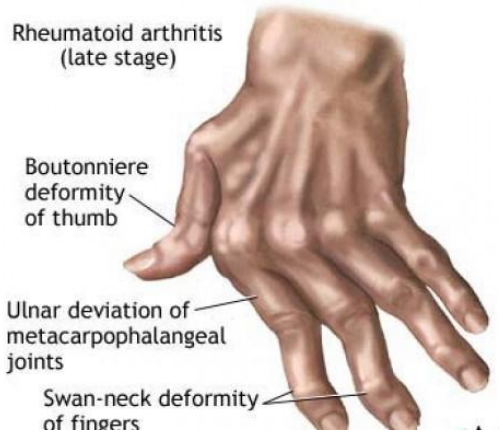


Figure 2. Clinical manifestations of rheumatoid arthritis – Hand

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

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.

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.[31]

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.

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.[31]

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.

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.[31]

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.[31]

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.[31]

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.[31]

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.[31]

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.

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.

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.[31]

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.

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.[31]

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.

Baker cysts may be seen in most peripheral joints and are most commonly recognized in the knee.[32] 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.

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.[31]

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.

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.[31]

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.

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.

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.

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.[31]

Diagnostic Considerations

The differentiation of rheumatoid arthritis from other diseases of connective tissue can be difficult; however, certain clinical features are helpful. Rheumatic fever is characterized by the migratory nature of the arthritis, an elevated anti-streptolysin O titer, and a more dramatic and prompt response to aspirin. Carditis and erythema marginatus may occur in adults, but chorea and subcutaneous nodules virtually never do. Butterfly rash, discoid lupus erythematosus, photosensitivity, alopecia, a high titer to anti-DNA, renal disease, and central nervous system (CNS) abnormalities suggest the diagnosis of systemic lupus erythematosus (SLE)

Degenerative joint disease (DJD) is not associated with constitutional manifestations; in contrast to the morning stiffness of RA, the joint pain from

degenerative joint disease is characteristically relieved by rest. Signs of articular inflammation prominent in RA are usually minimal in degenerative joint disease, and in contrast to RA, osteoarthritis spares the wrist and the MCP joints. While in the early years of disease, gouty arthritis is almost always intermittent and monoarticular; in later years, it can become a chronic polyarticular process that mimics RA. Gouty tophi can at times resemble rheumatoid nodules. The early history of intermittent monoarthritis and the presence of synovial urate crystals are distinctive features of gout.

Pyogenic arthritis can be distinguished by chills and fever, demonstration of the causative organism in joint fluid, and the frequent presence of a primary focus elsewhere (gonococcal arthritis). Chronic Lyme disease typically involves only 1 joint, most commonly the knee, and is associated with positive serologic tests. Human parvovirus B19 infection in adults can occasionally mimic RA. Polymyalgia rheumatica occasionally causes polyarthritis in patients older than 50 years, but these patients have chiefly proximal muscle pain and stiffness and remain negative for RF.

A variety of cancers produce paraneoplastic syndromes, including polyarthritis. One form is hypertrophic pulmonary osteoarthropathy, which is most often produced by lung and gastrointestinal carcinomas. Hypertrophic pulmonary osteoarthropathy is characterized by a rheumatoid-like arthritis associated with clubbing, periosteal new bone formation, and a negative RF. Diffuse swelling of the hands with palmar fascitis also has been reported with a variety of cancers, especially ovarian carcinoma.[31]

Complications

Rheumatoid arthritis itself is not fatal, but complications of the disease may shorten survival by years in some individuals. In general, RA is progressive and cannot be cured, but in some patients, the disease gradually becomes less aggressive and symptoms may even improve. However, if bone and ligament destruction and any deformities have occurred, the effects are permanent.

Joint disability and pain with daily life are common. Affected joints can become deformed, and the performance of even ordinary tasks may be very difficult or impossible. According to one survey, 70% of patients with RA believe the disease prevents them from living a fully productive life. In 2000, a study in England found that approximately one third of individuals stop working within 5 years of the onset of disease.[31]

Rheumatoid arthritis is a systemic disease that can affect other parts of the body in addition to joints. These effects include the following:[31]

- Peripheral neuropathy (affects nerves, most often those in the hands and feet, and can result in tingling, numbness, or burning)
- Anemia
- Scleritis (inflammation of the blood vessels in the eye that can result in corneal damage, scleromalacia, and, in severe cases of nodular scleritis, perforation)
- Infections (patients with RA have a higher risk for infections; immunosuppressive drugs further increase that risk)

- GI problems (patients with RA may experience stomach and intestinal distress, but lower rates of stomach and colorectal cancers have been reported in RA patients)
- Osteoporosis (more common than average in postmenopausal women with RA; the hip is particularly affected; risk for osteoporosis appears to be higher than average in men with the disease who are older than 60 y)
- Lung disease (a small study found a high prevalence of pulmonary inflammation and fibrosis in patients with newly diagnosed RA but may be associated with smoking)
- Heart disease (RA can affect blood vessels and increase the risk for coronary ischemic heart disease)
- Sjogren syndrome (keratoconjunctivitis sicca is a common complication of RA; oral sicca and salivary gland enlargement are less common)
- Felty's syndrome (characterized by splenomegaly, leukopenia, and recurrent bacterial infections; may respond to DMARDs)
- Lymphoma and other cancers (RA-associated immune system alterations may play a role; aggressive treatments for RA may help prevent such cancers)
- Macrophage activation syndrome (MAS) (life-threatening complication of RA; includes persistent fever, weakness, drowsiness, and lethargy; requires immediate treatment with high-dose steroids and cyclosporin A)
- 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.

APPROACH CONSIDERATIONS

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:[31]

- 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 3 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.[31]

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.[31]

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.[31]

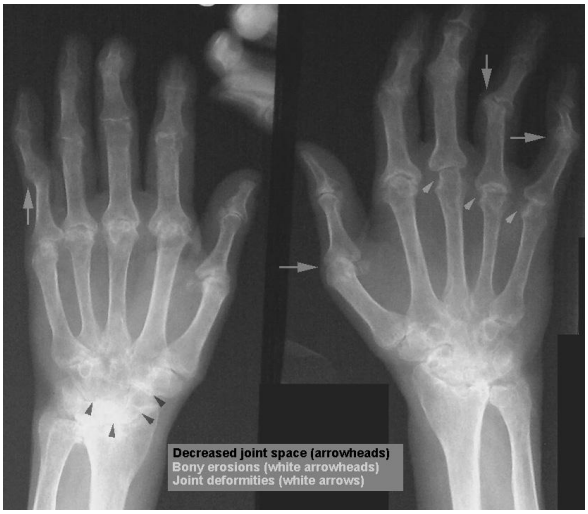


Figure 3. Radiographic changes of hand in rheumatoid arthritis

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.[31]

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.[31]

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.[31]

Hand Imaging in Rheumatoid Arthritis

Hand imaging in rheumatoid arthritis can include radiography, MRI, ultrasonography, and CT scanning (minimal role). Radiography is the mainstay of imaging RA in the hands. The modality is cheap and easily reproducible, and it allows easy serial comparison for assessment of disease progression. The main disadvantage of this modality is the absence of specific radiographic findings in early disease, since visualization of erosions may only be seen later.[31]

MRI has been shown to be more sensitive than radiography to early changes in RA, and in the appropriate clinical setting, it is more accurate than plain radiography in the diagnosis of the disease. However, a systematic literature review concluded that the widespread use of MRI for the diagnosis of early RA and for helping determine the prognosis of early RA is not currently recommended, although MRI bone edema may be predictive of progression in certain RA populations.[33]

Ultrasonography has been applied to the assessment of RA with the goal of improving on the current standard of conventional radiography. Similar to

MRI, ultrasonography serves as an early diagnostic tool and can help in evaluating the cause of joint swelling in a patient with RA.[31]

Spine Imaging in Rheumatoid Arthritis

Spinal imaging in rheumatoid arthritis involves radiography, MRI, CT scanning. The mainstay of imaging the rheumatoid spine remains plain radiography. Only half the patients with radiographic evidence of atlantoaxial subluxation are actually symptomatic. The role of plain radiography is to establish if the patient has risk factors for cord compression. The major role for CT scanning and MRI evaluation is in the preoperative assessment of the 2 main indications for surgical intervention, namely neurologic deficit and severe pain.[34,35] However, although CT scanning can document bone damage and alignment abnormalities, especially with more detailed multiplanar reconstruction, MRI has become the preferred modality for evaluation of the spinal cord and neural elements.[36]

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.[31]

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.[31]

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.[31]

Although antinuclear antibodies are present in approximately 40% of patients with rheumatoid arthritis, test results for antibodies to most nuclear antigen subsets are negative.

Studies of anti-CCP antibodies suggest a sensitivity and specificity equal to or better than those of RF, with an increased frequency of positive results in early RA; the presence of both anti-CCP antibodies and RF is highly specific for RA. Additionally, the presence of anti-CCP antibodies, like that of RF, indicates a worse prognosis.

ANTI-CCP ANTIBODIES

Historical background of citrullinated peptide antibodies and assays

The discovery of anti-CCP antibodies evolved from previous work examining autoantibodies in sera from RA patients that were distinct from rheumatoid factor. The first citrulline-binding autoantibodies in RA sera were discovered by Nienhuis *et al*. in 1964,[37] as an autoantibody able to bind to perinuclear granules in normal human buccal mucosa cells, and were named antiperinuclear factor. Antiperinuclear factor was found in 48% of patients with RA, and only 1% of healthy controls. The specificity of antiperinuclear factor for citrulline was not appreciated until years later, however. In 1979, Young *et al*. reported that RA sera contained antibodies that reacted to the keratinized layer of

epithelium.[38] These antibodies were called anti-keratin antibodies, and were only found in RA patients.[38]

Subsequent studies demonstrated that anti-keratin antibodies and antiperinuclear factor recognized a similar epitope, and were perhaps the same antibody.[39,40] It was also discovered that conversion of arginine to citrulline on peptides was essential for anti-keratin antibody and perinuclear factor binding.[41,42] Therefore, antiperinuclear factor and anti-keratin antibodies can be broadly categorized as anti-citrullinated-peptide antibodies. There is evidence for abnormal citrullination of various peptides in a diverse array of human diseases, including RA, psoriasis, and multiple sclerosis.[43] The formation of antibodies to citrullinated peptides seems to be specific for RA patients, however.

Assays for the detection of anti-citrullinated peptide antibodies using linear stretches of citrullinated peptide proved difficult to standardize, but an assay using a cyclic citrullinated peptide (CCP) resulted in greater reproducibility.[44] This test for anti-CCP antibodies was made commercially available, and is currently known as the anti-CCP1 assay. A second-generation assay was devised by screening a large library of citrulline-containing peptides with RA sera to identify the epitopes with the highest yield. This assay is now known as the anti-CCP2 assay, and has slightly better performance characteristics than anti-CCP1.[45] Anti-CCP2 is currently the most widely used anti-citrullinated peptide assay.[17]

Prevalence, sensitivity, and specificity of anti-CCP antibodies for RA

Several studies have examined the performance characteristics of anti-CCP antibodies in RA, using both the anti-CCP1 and anti-CCP2 assays. Sensitivity and specificity using the anti-CCP1 assay ranged from 44% to 56% and 90% to 97%, respectively.[46-48] Detection of antibody with CCP2 assays resulted in improved sensitivity (64–89%), and specificity (88–99%).[49-52] Rheumatoid factor sensitivity ranged from 59% to 79% and specificity from 80% to 84% in the same groups.[49-52] Many patients in the study groups had both rheumatoid factor and anti-CCP antibodies, but a significant number had only one or the other. Some of the variability in the sensitivity and specificity between studies may relate to slightly different cut-off points for positivity, and differences in disease duration, severity and other clinical characteristics of the groups being tested.[17]

Studies of anti-CCP antibodies have been done in early arthritis patients with <6 months of joint symptoms. Many did not have an obvious clinical diagnosis at inception, but attempts were made to establish diagnoses at later dates, often 1–2 years after initial presentation. The physicians making the clinical diagnoses were usually blinded to the laboratory information. Anti-CCP antibody testing showed sensitivity ranging from 39% to 50%, and specificity from 93% to 98% in the patients who were eventually diagnosed with RA, compared to the other non-RA patients.[44,53-57] Rheumatoid factor showed a sensitivity of 31% to 54% and specificity of 91% to 93% for the eventual diagnosis of RA when the test was done at first presentation, although rheumatoid factor was one of the criteria for the diagnosis of RA in these studies.[44,53-57]

Study designs evaluating anti-CCP antibodies in RA

Study	Location	Assay	RA patients (*n*)	Control population 1	Control population 2	Anti-CCP Sensitivity	Specificity control 1[a]	Specificity control 2[a]
Bizzaro[46]	Italy	CCP1	98	Non-RA inflammatory disease + infectious disease	NA	44%	97%	NA
Bas[47]	Switzerland	CCP1	196	Non-RA inflammatory disease	Healthy donors	56%	90%	99%
Zeng[48]	China	CCP1	191	Non-RA inflammatory disease + infectious disease	Healthy donors	47%	97%	100%
Lee[49]	US	CCP2	103	Non-RA arthritis	NA	66%	90%	NA
Suzuki[50]	Japan	CCP2	549	Non-RA inflammatory disease	NA	89%	88%	NA
Vallbracht[51]	Germany	CCP2	295	Suspected rheumatic disease	Healthy donors	64%	96%	99%
De Rycke[52]	Belgium	CCP2	118	Suspected rheumatic disease	NA	74%	99%	NA

Non-RA inflammatory disease, idiopathic inflammatory disease other than RA, such as systemic lupus, Crohn's disease, etc. Infectious disease, chronic viral infections, tuberculosis, etc. Non-RA arthritis, other inflammatory and non-inflammatory arthritic disorders such as osteoarthritis, lupus, etc. Suspected rheumatic disease, patients being evaluated for possible rheumatic disease in the hospital or clinic setting. NA, not applicable. [a]If two control groups were studied, the specificity is calculated for each control group separately.

Some patients who were eventually diagnosed with RA had either rheumatoid factor or anti-CCP antibodies. The combination of both rheumatoid factor and anti-CCP antibodies predicted RA with a sensitivity of 30% to 39% and a specificity of 98% to 100%. Overall, the high specificity of anti-CCP antibodies for RA does not seem to differ significantly between early and established disease.

Sensitivity and specificity of anti-CCP antibodies for rheumatoid arthritis

Study	RF sensitivity	RF specificity	RF+ and CCP+	RF^- and CCP+	RF+ and CCP^-
Bizzaro[46]	62%	84%	36%	5%	27%
Bas[47]	73%	82%	NA	NA	NA
Zeng[48]	59%	NA	38%	9%	21%
Lee[49]	72%	80%	57%	10%	15%
Suzuki[50]	70%	82%	NA	69%	NA
Vallbracht[51]	66%	82%	52%	13%	15%
De Rycke[52]	79%	81%	NA	NA	NA

RF, rheumatoid factor; RF+ and CCP+, percentage of patients positive for both RF and anti-CCP; RF^- and CCP+, percentage of patients negative for RF but positive for anti-CCP; RF+ and CCP^-, percentage of patients positive for RF and negative for anti-CCP. NA, not applicable.

A number of papers have suggested diagnostic algorithms incorporating anti-CCP antibodies resulting in improved sensitivity and specificity for diagnosis. In a study of 196 RA patients, the 56% sensitivity and 90% specificity of anti-CCP antibodies was improved when combined with rheumatoid factor seropositivity.[47]

Anti-CCP antibodies have been tested in ethnically diverse RA cohorts from North America, Europe, and Asia, and rates of anti-CCP detection are remarkably consistent. Additionally, these investigations used several different controls, including healthy individuals and populations of various arthritic and non-arthritic inflammatory diseases, and used various methods of data collection and analysis. Despite this, no control population has shown an equivalent rate of

anti-CCP positivity to that found in RA, and the specificity remains high even if controls with similar inflammatory disease processes are used.[17]

A good serological marker for RA should be highly specific for the disease and be able to distinguish RA from other arthritides that mimic RA.[58]

In the original studies of Schellekens et al,[44] in which anti-CCP was measured in cohorts of RA patients, in patients with other rheumatic diseases, in patients with infectious diseases and in healthy controls, it could already be concluded that anti-CCP antibodies (anti-CCP1 in this case) are very specific for RA. These results were subsequently confirmed by Bizzaro et al.,[46] Bas et al.,[59] and many others.

These earlier studies have been reviewed by van Boekel et al.[60] More recent studies confirmed this specificity also for the second generation CCP2 test. In a large multicenter trial 78% of RA patients, 15% of healthy controls and 50% of disease controls tested positive for IgMRF, while 79% of RA patients, none of the healthy controls and only 5% of disease controls were positive for anti-CCP2.[61] In another large cohort study anti-CCP2 was positive in 82% of (chronic) RA patients, 1% of healthy controls, and 2% of disease controls (80%, 1%, and 12%, respectively for IgM-RF).[15] A recent study by Pinheiro et al. with 150 RA patients independently confirms these results (80% sensitivity at 98% specificity).[62] CCP2 thus has a comparable sensitivity but a much higher specificity for RA than RF.

In a recent study by Lee and Schur, a somewhat lower specificity of only 90% for CCP2 is reported (66% sensitivity; RF 72% sensitivity and 80%

specificity).[49] Most of the false positives in this cohort were juvenile RA (JRA) patients, 29% of which were positive for anti-CCP. Previous reports[63,64] have shown that anti-CCP (CCP1 at that time) antibodies can be present in a subset of JRA patients, mostly in polyarticular, IgM-RF positive (which is rare in JRA),[65] erosive JRA patients. The JRA patients in the Lee and Schur cohort comprised adults (average age 31, range 21–50) with longstanding disease (average disease duration 21 years) and high prevalence of erosions (87%).[49] Some of these JRA patients might actually have adult RA with childhood-onset, which could explain the high frequency of anti-CCP antibodies in the JRA group of this cohort.

When the level of the anti-CCP titer is taken into account, specificity appears to be almost absolute. In a study by Bizzaro et al.[46] 7 out of 232 controls (3%) tested positive for anti-CCP1, three of them with high titers (1000 units; cut-off for CCP1 is 50 units). After reexamination, two of the three patients with high anti-CCP titer were diagnosed with RA. The third patient had died. None of the four patients that were weakly positive for anti-CCP had developed signs of RA.[46] Higher titers of anti-CCP are thus almost exclusively observed in RA patients. In conclusion due to its high specificity, anti-CCP makes a reliable diagnosis for RA possible.[58]

Potential predictive value of anti-CCP antibodies to detect individuals at-risk for RA

Ideally, screening healthy individuals at high risk of developing RA, for example those with a family history of RA, could allow for increased vigilance and the possibility of early intervention. A number of studies have documented

examined the appearance of anti-CCP antibodies *prior to* the onset of RA. A cohort of 83 RA patients had blood samples available in a blood bank predating their diagnosis. Anti-CCP antibodies were positive prior to diagnosis in 33.7% of the RA patients vs. 1.8% in controls taken from the same pool of subjects ($p < 0.0001$).[66] Median time between blood sampling and the development of disease was 2.5 years, with a maximum interval of 9 years. Rheumatoid factor was positive in 19.3% of donors who would eventually be diagnosed with RA, compared to 6% of control donors, which was not significant in logistic regression models. A second similar study identified 79 RA patients who had donated blood to a regional blood bank prior to their diagnosis.[67]

Forty percent of RA patients tested positive for anti-CCP antibodies prior to the onset of disease, compared with 0.6% in the control population. Anti-CCP antibodies were identified a median of 4.8 years before RA diagnosis, and one patient had anti-CCP antibodies 14 years prior to RA symptoms. Rheumatoid factor was positive in 27.8% of patients prior to diagnosis, and was positive in only 1.1% of controls. In a study using banked sera from the Nurses' Health Study, anti-CCP antibodies were detected up to 12 years prior to diagnosis, and were associated with an odds ratio of 5.1 for developing RA after adjusting for hormonal status and other confounding variables.[68]

Anti-CCP antibodies can appear years in advance of actual disease, and may eventually allow for identification of individuals who are likely to develop disease.[17]

Anti-CCP antibodies predict RA diagnosis in early arthritis

Early in the disease process, RA is often difficult to distinguish from other types of inflammatory arthritis and systemic inflammatory conditions, as their initial presentations may be similar. Several studies have examined the utility of anti-CCP antibody testing in distinguishing RA from other inflammatory diseases, by studying cohorts of patients who presented with non-specific early inflammatory arthritis.[17]

In one such study, 524 patients with early undifferentiated arthritis of <2 years duration had anti-CCP antibody testing at inception, and were followed longitudinally for 2 years.[69] After 2 years, 60% had self-limited inflammatory arthritis, 16% had persistent non-erosive arthritis, and 24% had persistent erosive arthritis. Anti-CCP positivity conferred an odds ratio of 4.58 for persistent vs. self-limited arthritis, as well as an odds ratio of 4.58 for erosive vs. non-erosive disease. Rheumatoid factor conferred an odds ratio of 2.99 for persistent vs. self-limited arthritis, and an odds ratio of 2.99 for erosive vs. non-erosive disease.

In another early arthritis study,[45] 318 patients with undifferentiated inflammatory arthritis of <2 years duration were followed for 3 years. RA was eventually diagnosed in 64/69 (93%) of those with a positive initial anti-CCP2 antibody test. In this study, anti-CCP antibodies conferred an odds ratio of 38.6 for the diagnosis of RA, compared to an odds ratio of 9.8 for rheumatoid factor. These studies, and the others, demonstrate the significant predictive value of anti-CCP antibodies in early arthritis for the eventual diagnosis of RA. The ability to identify patients who are at greatest risk for progressive and destructive arthritis

is especially useful, as these individuals will benefit most from early aggressive intervention.

Jansen and coworkers[53] tried to discriminate RA from undifferentiated polyarthritis, and found that the combined presence of IgM-RF and anti-CCP1 is able to predict which patients with early arthritis ultimately develop RA with a sensitivity of 55.4% and a specificity of close to 97%. Similar observations were made by van Gaalen et al.[55]

In a large cohort of 936 patients with recent onset arthritis, 318 patients could not be properly classified and were categorized as undifferentiated arthritis (UA). After 3 years of follow-up, 40% of these UA patients had developed RA. Of the UA patients that were negative for anti-CCP2 at baseline, 25% developed RA. In contrast, of the UA patients with a positive anti-CCP2 test at baseline 93% progressed to RA (odds ratio 37.8).[58]

The conclusion from all these studies is that anti-CCP antibodies are present early in disease, and that their presence is able to accurately predict the development of RA.[58]

Anti-CCP antibodies correlate with disease activity parameters

Patients with RA show considerable variability in disease activity, which can be difficult to predict at the onset of disease. Anti-CCP antibodies have proven useful in identifying those patients who are likely to have clinically significant disease activity. In 150 patients with long-standing RA, a strong correlation was found between greater disease activity and anti-CCP positivity.[62]

In another study, anti-CCP2 assays were done on sera from 242 RA patients who were followed for 3 years.[70] The patients were treated at the physician's discretion, and the physicians were blinded to the patient's anti-CCP status. Anti-CCP antibodies were positively correlated with higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen joint count, and worse physician global assessment ratings. Presence of rheumatoid factor was positively correlated with increased ESR and CRP, but there was no association with other disease activity markers.

In a similar study, anti-CCP status was correlated with disease activity parameters in 379 early RA patients.[71] Statistically significant correlations were seen between anti-CCP positivity and higher CRP, ESR, and disease activity measurements. Of note, current or previous cigarette smoking was also associated with a positive anti-CCP test. This is especially interesting, as there is an association between tobacco use and the development of RA, as well as increased RA disease activity.[72] In summary, anti-CCP antibodies identify patients with significantly greater disease activity more reliably than rheumatoid factor.

Anti-CCP antibodies predict disease damage

In addition to disease activity, irreversible damage from RA is an important outcome with significant impact on quality of life and functional capability. Predicting which patients will accrue damage is difficult, and disease activity parameters are not always accurate in predicting subsequent joint destruction. In a study addressing the progression of radiological damage in RA, anti-CCP1 antibodies were measured in 273 RA patients with <1 year of

symptoms.[73] The patients were followed for at least 6 years and had plain radiographs of the hands and feet performed every 6 months. X-rays were graded by a radiologist blinded to the clinical data. After 6 years, anti-CCP1 positive patients had significantly more radiographic damage than anti-CCP1 negative patients ($p<0.05$). Rheumatoid factor was also associated with increased radiological damage at 6 years ($p<0.0001$). Some 32% of patients in the study had both rheumatoid factor and anti-CCP antibodies, 33% had only anti-CCP, and 24% had only rheumatoid factor. Anti-CCP antibodies identified a large group of patients at increased risk of damage who would not have been identified using rheumatoid factor testing alone.

In another study, 104 early RA patients had anti-CCP antibodies and hand radiographs done at inception.[74] Anti-CCP antibodies were positive in 36/67 (54%) of those who had at least one erosion at inception, compared with 8/37 (22%) with non-erosive disease. Rheumatoid factor was positive in 39/67 (58%) with erosive disease, vs. 11/37 (30%) with non-erosive disease. Among seropositive patients, 22% had only anti-CCP antibodies. Thus, anti-CCP antibodies may be useful in identifying a group of RA patients who are more likely to develop damage, and who may not be identified by rheumatoid factor testing alone.

Change in anti-CCP titres with treatment

Some reports describe a decrease in titre of anti-CCP antibodies following successful treatment of RA. In a RA treatment trial, 35% of patients had a decrease in anti-CCP2 titres of >15%, while 19% had an increase of >15%; 46%

of patients had anti-CCP2 titres within 15% of the baseline values. All but 5 of 242 patients with a positive anti-CCP2 antibody test remained positive when tested serially over a 3-year period.[70] In a similar study, serial anti-CCP2 levels were measured in 43 patients with RA who were treated for at least 2 years.[75] Mean anti-CCP2 titres at inception were 107±9.5 U, which fell to a mean of 92 ± 9.8U (p=0.0001) after 24 months of treatment. Titres were more likely to decrease in patients showing a greater degree of clinical improvement. In summary, a decrease in anti-CCP titre can be seen with RA treatment, however, the decrease is usually modest and should not drive treatment decisions. Anti-CCP positive patients usually remain positive despite treatment.

Insights into pathogenesis

Citrullinated peptides have been found in synovial tissues from RA patients as well as non-RA controls, although the formation of antibodies against citrullinated proteins seems to be very specific for RA.[76]

Citrullination of synovial proteins has also been demonstrated in mouse models of inflammatory arthritis, however the mice do not form antibodies to citrullinated peptides.[77] Whether anti-CCP antibodies are involved in pathogenesis and contribute to ongoing immune activation or are a by-product of inflammation in the synovium is not known. In a Japanese RA cohort, a haplotype of the enzyme that converts arginine to citrulline was associated with RA,[78] but this association was not confirmed in an British RA cohort.[79]

A number of investigators have found an association between anti-CCP antibody production and the presence of certain MHC class II alleles containing

the 'shared epitope'.[80-83] The shared epitope refers to a conserved motif in the peptide binding cleft of the MHC molecule which is encoded by certain HLA class II alleles, and has been associated with risk of developing RA, as well as greater disease severity.[84] In a blood donor cohort, the presence of both anti-CCP antibodies and the shared epitope in asymptomatic donors was associated with an odds ratio of 66.8 for subsequent development of RA.[85] Anti-CCP antibodies or shared epitope alone were less predictive of the future onset of disease than the two combined. Furthermore, RA patients with both anti-CCP antibodies and shared epitope alleles had more destructive joint disease than RA patients with anti-CCP antibodies and no shared epitope alleles.[86]

In RA patients, shared epitope alleles are strongly associated with anti-CCP antibodies.[82,83] In mice transgenic for shared epitope MHC, conversion of arginine to citrulline on synthetic peptides allowed high-affinity binding of the peptide to the MHC.[85] This binding could result in immune cell activation, and subsequently a directed immune response against citrullinated peptides and production of anti-citrullinated peptide antibodies. The demonstration that citrullinated peptides bind to the shared epitope MHC supports the hypothesis that an arthritogenic antigen exists and plays a pathogenic role in RA. Anti-CCP antibodies may be a marker for this phenomenon. An interesting recent study has demonstrated a strong gene-environment interaction between cigarette smoking and anti-CCP antibody production in RA patients.[86] In this study, the likelihood of having anti-CCP antibodies was related to previous smoking in a dose-dependent manner for RA patients carrying the shared epitope MHC, which was not the case for patients without the shared epitope. Citrullinated peptides were

detected in the broncho-alveolar lavage fluid of the patients who smoked, and were not present in non-smokers, suggesting that smoking could cause citrullination of peptides in the lung, and that possibly these could promote an immune reaction to citrullinated peptides in the genetic background of the shared epitope MHC.

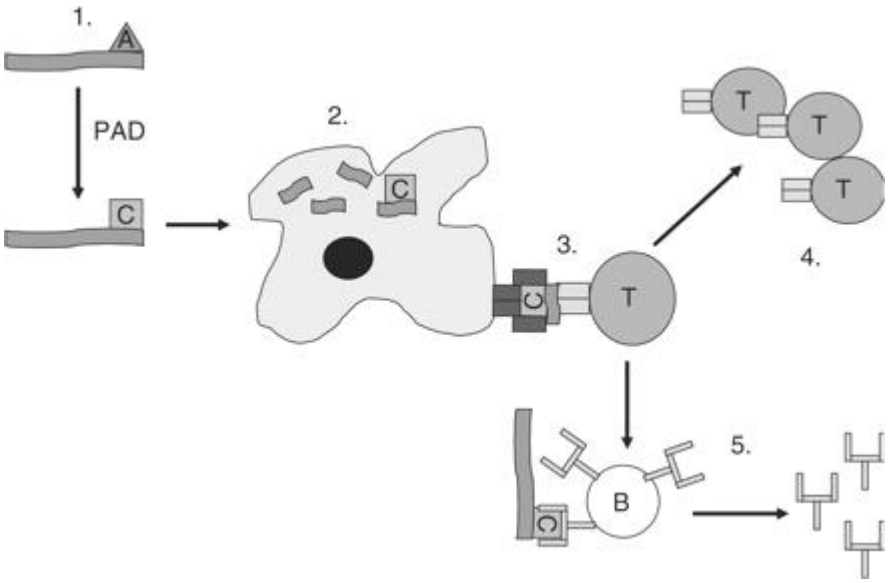


Figure 4. Potential mechanism for anti-CCP antibody formation in rheumatoid arthritis. (i) Arginine (A) on peptides is converted to citrulline (C) by the enzyme peptidyl arginine deiminase (PAD) in the setting of local inflammation. (ii) Peptides are processed by antigen-presenting cells. (iii) Antigen-presenting cells with shared epitope MHC molecules bind citrulline with high affinity, and could present citrullinated self antigens to T cells. (iv) T-cell activation by the antigen-presenting cell leads to clonal expansion of T cells and cell-mediated immunity against citrullinated antigens. (v) B cells reactive to citrullinated peptides are activated by T cells, causing production of anti-CCP antibodies.[17]

Anti-CCP antibodies are a highly specific marker for RA in several diverse patient groups. This specificity extends to patients with early disease, in whom a timely diagnosis is most needed. The low sensitivity of the test (40–50% in most published cohorts) indicates that a negative anti-CCP antibody test does not exclude disease, but its high specificity means that a positive result markedly increases the probability that the patient will have RA. Anti-CCP antibodies also identify a subset of patients who are likely to have substantial ongoing disease

activity, accrue more damage, and who will probably benefit most from early aggressive treatment. A significant number of these patients do not have rheumatoid factor, and may not otherwise have been expected to develop severe aggressive disease. Anti-CCP antibodies tend to remain stable or decline slightly with treatment, and have not been found frequently in non-RA inflammatory or arthritic diseases. The presence of anti-CCP antibodies in serum years before the onset of RA suggests the possibility of pre-clinical detection, and may provide information about early events in the pathogenesis of the disease.[17]

Approach Considerations

The optimal care of patients with rheumatoid arthritis consists of an integrated approach of pharmacologic and nonpharmacologic therapies. Many nonmedication therapies are available for this disease, including exercise, diet, massage, counseling, stress reduction, physical therapy, and surgery. The active participation of the patient and family in the design and implementation of the therapeutic program helps to boost morale and to ensure compliance, as does explaining the rationale for the therapies used.

Medication-based therapies comprise several classes of drugs, including NSAIDs, DMARDs, immunosuppressants, biologic response modifiers, and corticosteroids. Early therapy with DMARDs has become the standard of care, as it cannot only retard disease progression more efficiently than later treatment, but it may also induce more remissions.

In pregnant patients with rheumatoid arthritis, no special obstetric monitoring is indicated beyond what is performed for usual obstetric care.

However, some of the medications used in treating this condition can have adverse effects on the fetus and may need to be discontinued several months before conception is planned.

Surgical treatments for RA include synovectomy, tenosynovectomy, tendon realignment, reconstructive surgery or arthroplasty, and arthrodesis.

Prognosis

Outcome is compromised when the diagnosis and treatment are delayed. The clinical course of rheumatoid arthritis is generally one of exacerbations and remissions. Approximately 40% of patients with this disease become disabled after 10 years, but outcomes are highly variable.[87] Some patients experience a relatively self-limited disease, and others have a chronic progressive illness.

Improvements in the detection of early joint injury have provided a previously unappreciated view of the ubiquity and importance of early joint damage. Nonetheless, predicting the course of an individual case of rheumatoid arthritis at the outset remains difficult, although the HLA-DRB1*04/04 genotype, a high serum titer of autoantibodies (RF, anti-cyclic citrullinated peptide [CCP]), extra-articular manifestations, a large number of involved joints, age younger than 30 years, female sex, and systemic symptoms all correlate with an unfavorable prognosis in terms of joint damage and disability. Insidious onset is also an unfavorable sign.

A retrospective study used logistic regression to analyze clinical and laboratory assessments in patients with RA taking only methotrexate.[88] The

authors found that measures of C-reactive protein (CRP) and swollen joint count after 12 weeks of methotrexate administration were most associated with radiographic progression at week 52.

There is generally a much worse prognosis of RA among patients with positive RF results, but the absence of RF does not necessarily portend a good prognosis. Other laboratory markers of a poor prognosis include early radiologic evidence of bony injury, persistent anemia of chronic disease, elevated levels of the C1q component of complement, and the presence of anti-CCP antibodies.

Rheumatoid arthritis that remains persistently active for longer than 1 year is likely to lead to joint deformities and disability.[89] Periods of activity lasting only weeks or a few months followed by spontaneous remission portend a better prognosis.

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. RA also is associated with cardiovascular risk factors, both traditional and nontraditional.

The overall mortality rate in patients with RA is reportedly 2.5 times that of the general population. In those with severe articular and extra-articular disease, the mortality rate approaches that of patients with 3-vessel coronary disease or stage IV Hodgkin disease. Much of the excess mortality derives from

infection, vasculitis, and poor nutrition. With the exception of lymphoma, mortality from cancer is unchanged.

TNF and Mortality

The leading cause of excess mortality in RA is cardiovascular disease, followed by infection, respiratory disease, and malignancies. The effects of concurrent therapy, which is often immunosuppressive, may contribute to mortality in RA. However, studies suggest that control of inflammation may improve mortality.

A large national prospective cohort study over a mean of 4 years demonstrated that anti-TNF therapy was not associated with a significant increase or decrease in mortality and did not increase any additional risk or benefit on overall mortality risk when compared with standard nonbiologic DMARD therapy.[90] The results from another study confirmed that the risk of serious infection and malignancy is not increased in patients receiving anti-TNF therapy when the patients have early RA and have not been previously treated with DMARDS and/or methotrexate (MTX).[91]

Most data on disability rates derive from specialty units caring for referred patients with severe disease. Little information is available on patients cared for in primary care community settings. Estimates suggest that more than 50% of these patients remain fully employed, even after 10-15 years of disease, with one third having only intermittent low-grade disease and another one third experiencing spontaneous remission.

Chapter 4

Methodology

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 2010 to December 2010.

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 2010 to December 2010.

Place

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

Method of collection of data

Source of Data

Patients with history, suggestive of RA in the Department of Medicine and Department of Immunology and Rheumatology at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

A total of 100 patients with history, suggestive of RA were included in the study. The sample size was calculated by considering average of similar cases admitted to KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over the period of last three years.

Selection criteria

Inclusion Criteria

- All patients fulfilling American College of Rheumatology Criteria 1987 for classification under RA.[8]

Exclusion Criteria

- Gout and Pseudo gout.
- Osteoarthritis.
- Systemic lupus erythematosis.
- Lymes disease.
- Reactive arthritis.
- Sarcoidosis.
- Ankylosing spondylitis.
- Infective arthritis.

Procedure

The study was approved by the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum. Patients presenting with history,

suggestive of RA in the Department of Medicine and Department of Immunology and Rheumatology at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre Belgaum were evaluated based on selection criteria. The patients were selected by American College of Rheumatology Criteria for RA 1987.[8] The selected patients were briefed about the nature of the study and a written informed consent was obtained (Annexure–I).

Demographic data like gender and age were collected along with relevant history, symptoms and recorded on predesigned and pretested proforma (Annexure-II) followed by thorough clinical examination.

The RA was diagnosed based on the ACR criteria[8] that is;

- Morning stiffness more than one hour.
- Soft tissue swelling of more than or equal to three joint groups.
- Swelling of PIP, MCP, or wrist joints.
- Symmetrical swelling.
- Subcutaneous nodule.
- Positive rheumatoid factor
- Radiographic erosion.

For classification purposes, a patient shall be said to have rheumatoid arthritis if patient has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses were not excluded. Designation as classic, definite, or probable rheumatoid arthritis was not made.

Further they were subjected to investigations such as CBC with peripheral smear, platelet count, ESR, RA factor and X ray of hand. Further the Anti-CCP antibody test was done using ELISA method. Patients with anti-CCP titres more than 10 IU/dL were considered as positive. Positivity of anti CCP antibody was assessed in two subsets of RA patients that is, RA factor positive and RA factor negative patients.

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 (1,2). 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 (3) based on clinical assessment of joint counts and drawing a blood sample for ESR or CRP.

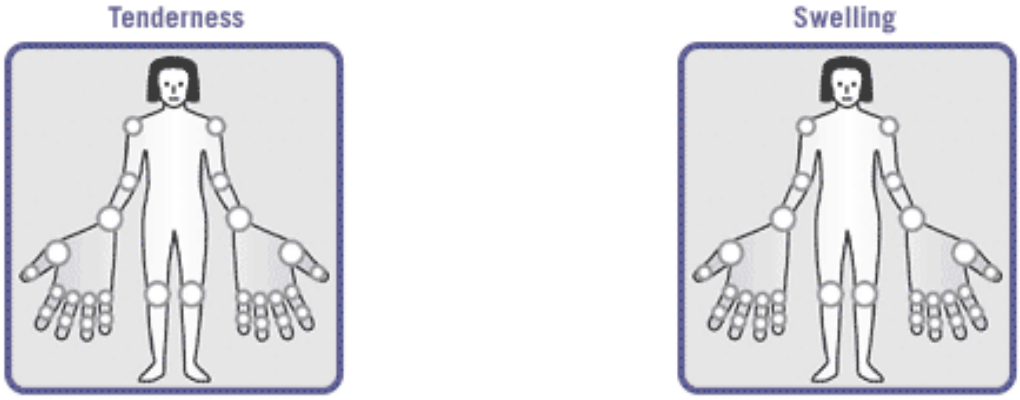


Figure 5. Tender and swollen joint counts

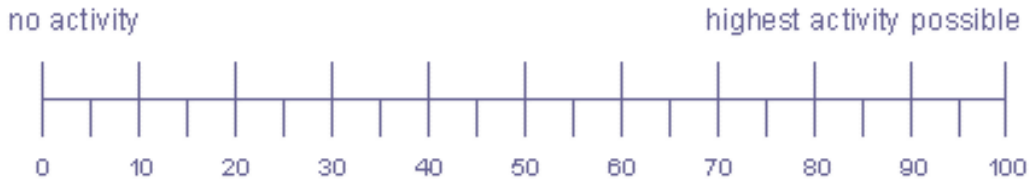


Figure 6. Visual analog scale

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.

Statistical analysis

Data obtained was tabulated on Microsoft Excel spreadsheet and expressed in terms of rates, ratios and percentages. The significance of Anti-CCP positivity in the diagnosis of RA was established. In proved cases, co-relation between Anti CCP and RF with severity of the disease were drawn. Anti-CCP positivity also studied in two subsets of rheumatoid arthritis patients that is, RA factor positive and RA factor negative using chi-square test, Pearson's correlation and t-test. A probability value (p value) of less than or equal to 0.5 was considered as statistically significant.

Chapter 5

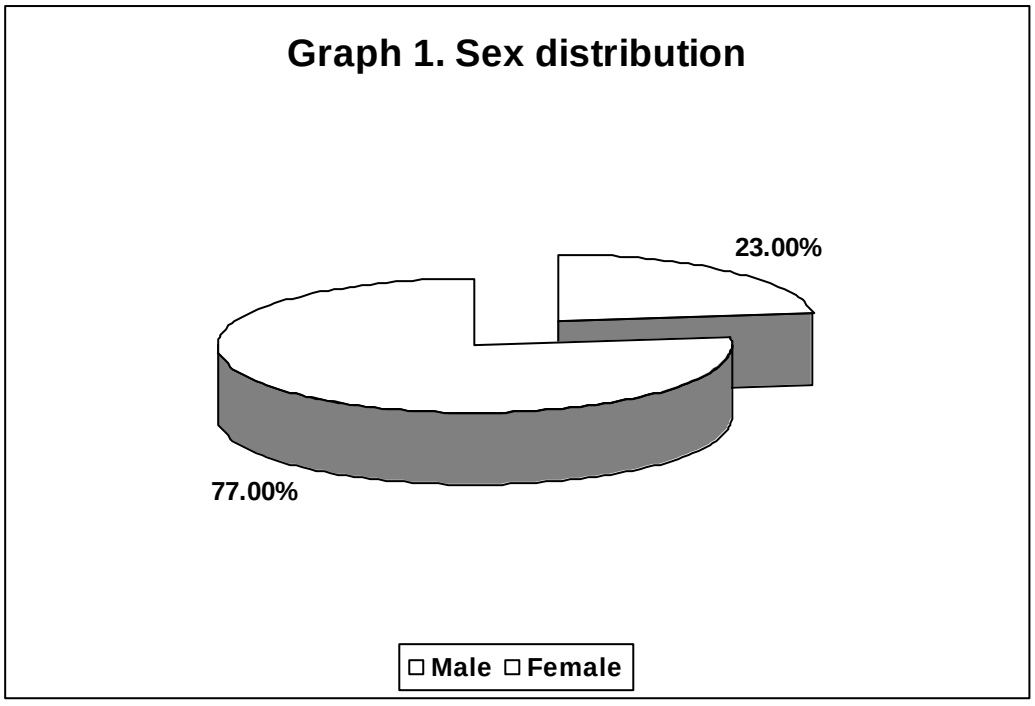
Results

RESULTS

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010 on 100 patients with history, suggestive of RA. Data obtained was tabulated on Microsoft Excel spreadsheet and analysed as below.

Table 1. Sex distribution

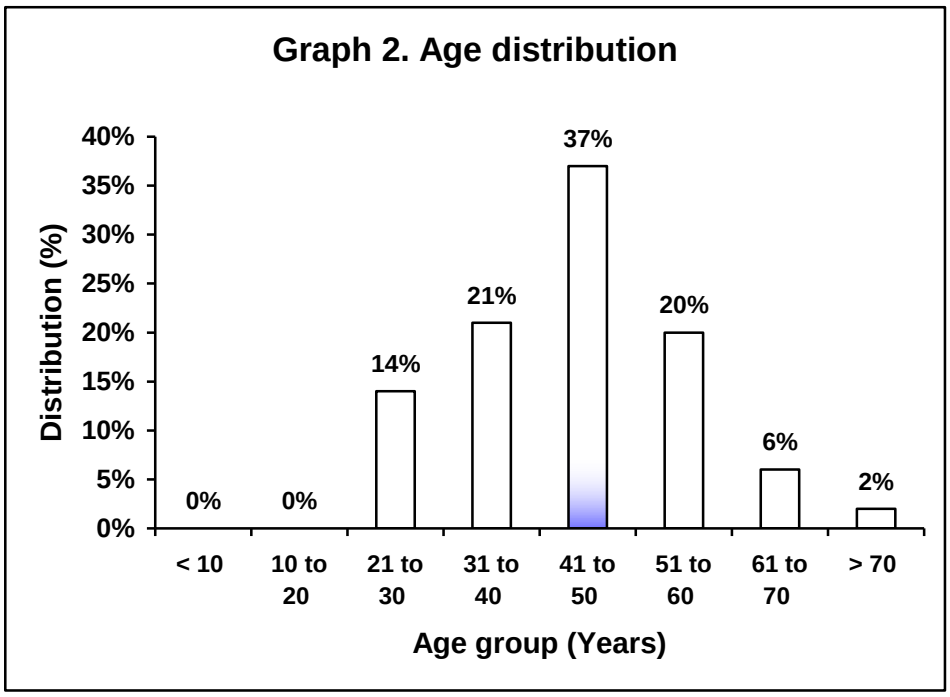
Sex	Distribution (n=100)	
	Number	**Percentage**
Male	23	23.00
Female	77	77.00
Total	**100**	**100.00**



Females outnumbered male (77% vs 23%) with male to female ratio of 1 : 3.34.

Table 2. Age distribution

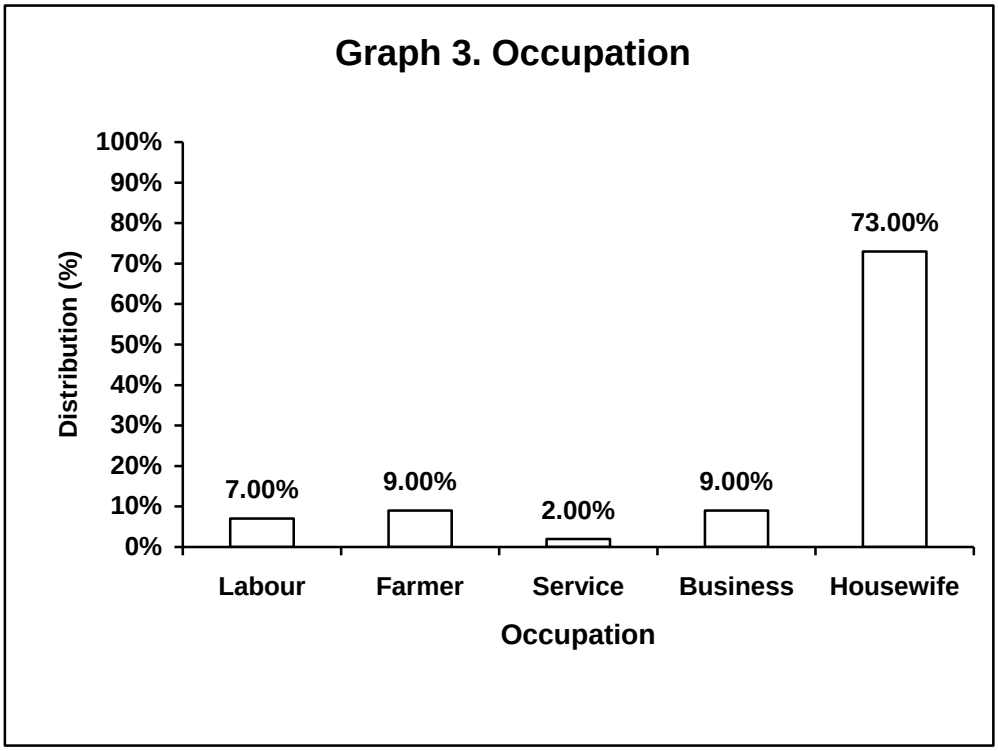
Age group (Years)	Distribution (n=100)	
	Number	**Percentage**
< 10	0	0.00
10 to 20	0	0.00
21 to 30	14	14.00
31 to 40	21	21.00
41 to 50	37	37.00
51 to 60	20	20.00
61 to 70	6	6.00
> 70	2	2.00
Total	**100**	**100.00**



The maximum incidence (78%) was seen between the ages of 30 to 60 years.

Table 3. Occupation

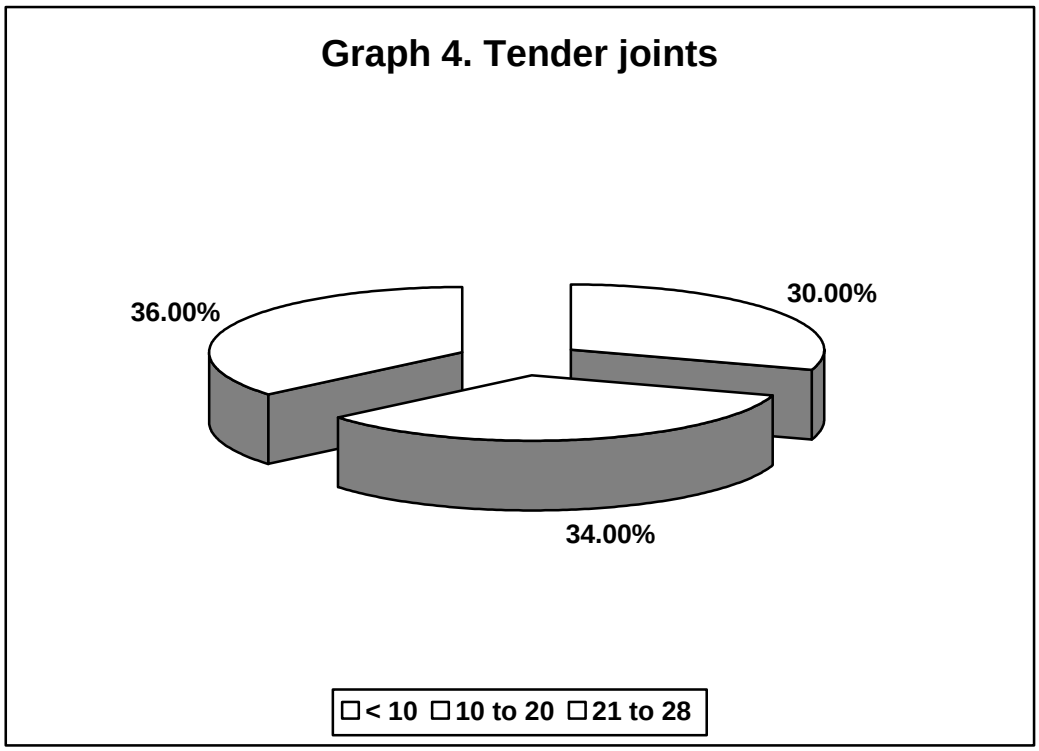
Occupation	Distribution (n=100)	
	Number	**Percentage**
Labour	7	7.00
Farmer	9	9.00
Service	2	2.00
Business	9	9.00
Housewife	73	73.00
Total	**100**	**100.00**



Majority of patients (73%) were found to be housewives .

Table 4. Tender joint

Number of joints	Distribution (n=100)	
	Number	**Percentage**
< 10	30	30.00
10 to 20	34	34.00
21 to 28	36	36.00
Total	**100**	**100.00**



With respect to tender joint count, patients with < 10 joints were affected in 30% of patients, 10 to 20 joints in 34 % and 21 to 28 joints in 36 % respectively.

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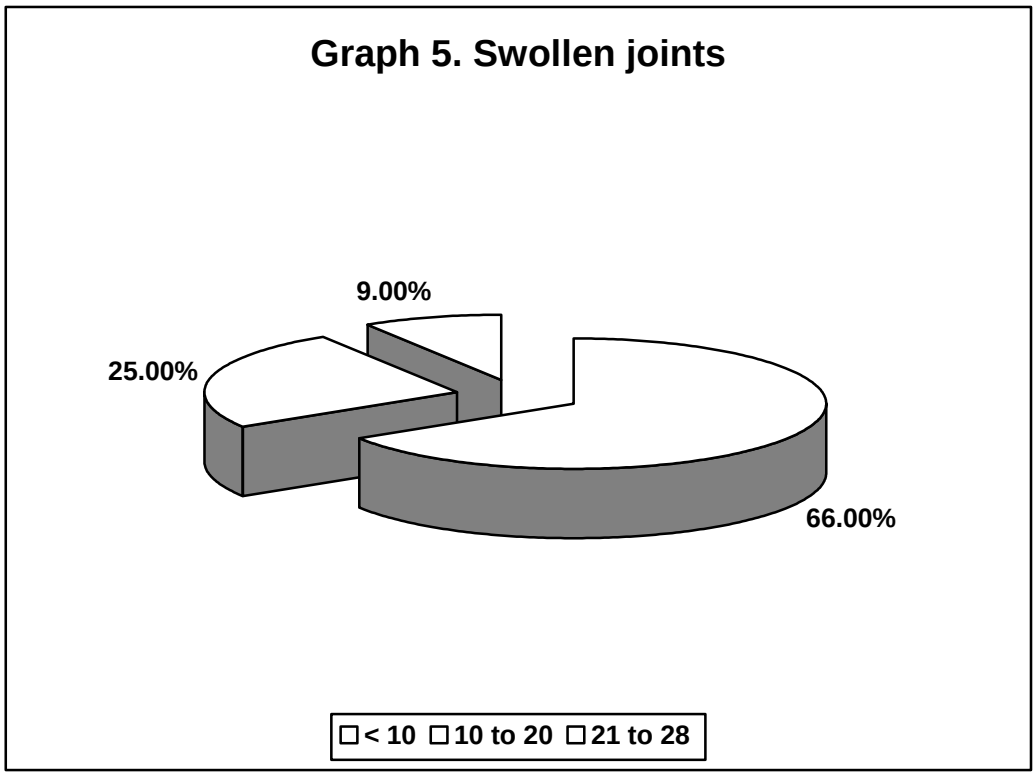
Table 5. Swollen joint

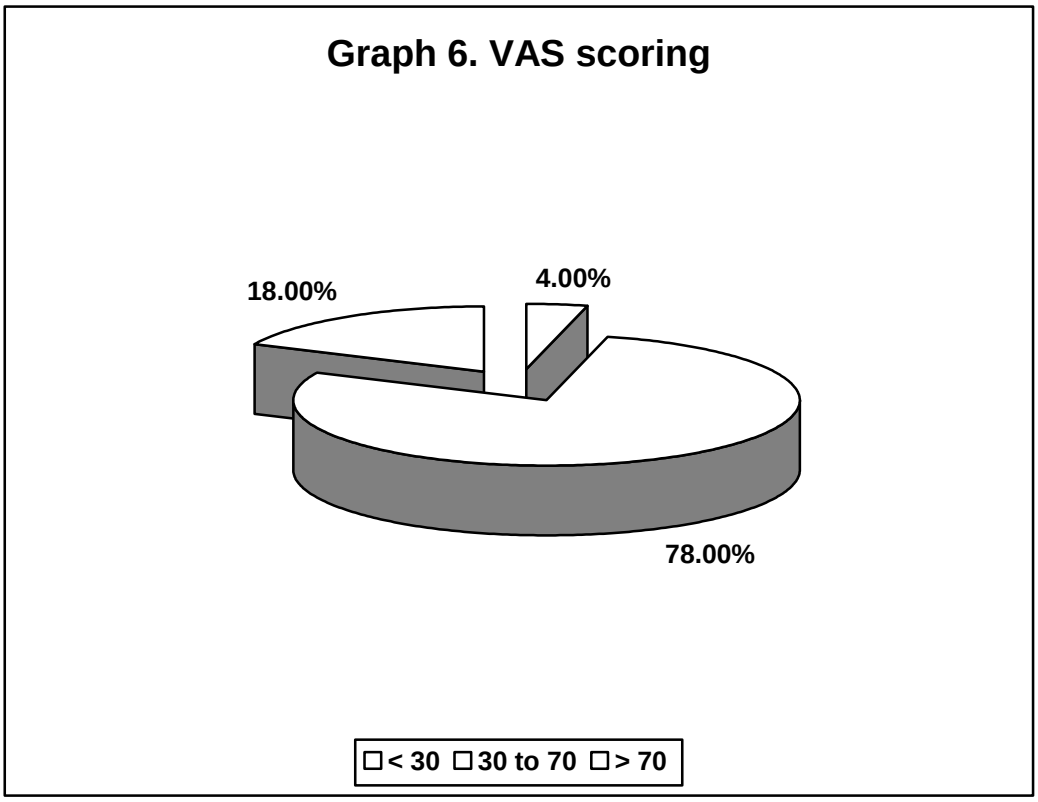
Swollen joints	Distribution (n=100)	
	Number	**Percentage**
< 10	66	66.00
10 to 20	25	25.00
21 to 28	9	9.00
Total	**100**	**100.00**



With respect to swollen joint, <10 joints were involved in 66 %, 10 to 20 joints in 25% and 21 to 28 joints 9 % respectively.

Table 6. VAS Scoring

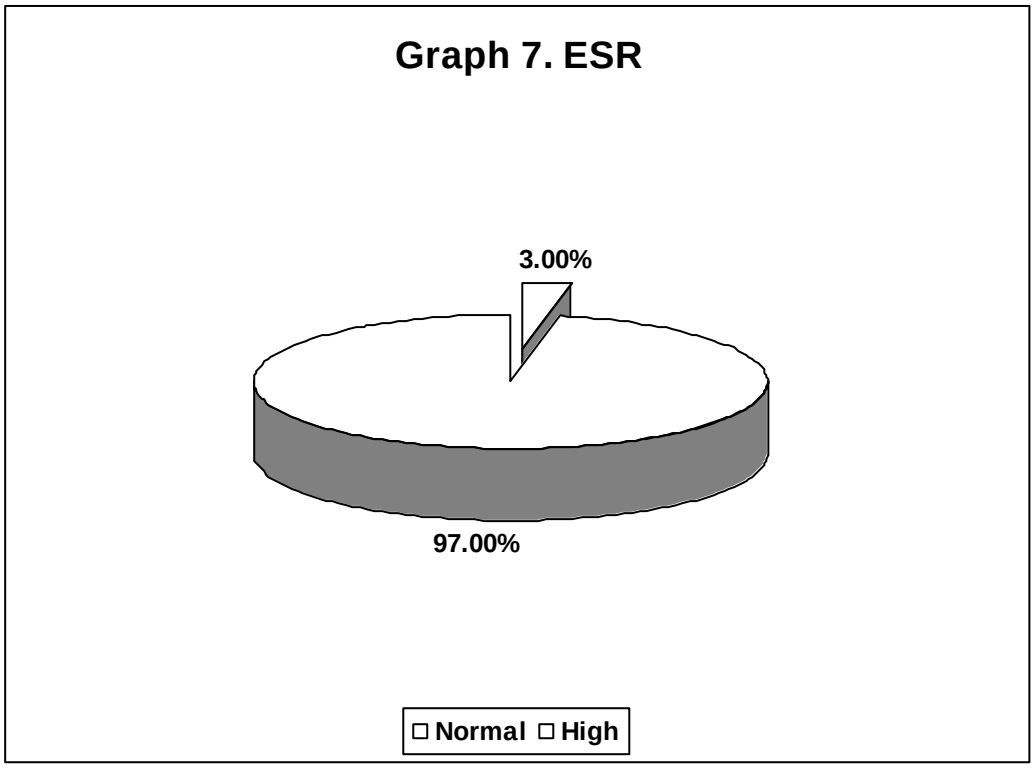
VAS Score	Distribution (n=100)	
	Number	**Percentage**
< 30	4	4.00
30 to 70	78	78.00
> 70	18	18.00
Total	**100**	**100.00**



With respect to VAS (visual analogue scale), patients had < 30 in 4 %, 30 to 70 in 78% and > 70 in 18 % of the cases.

Table 7. ESR

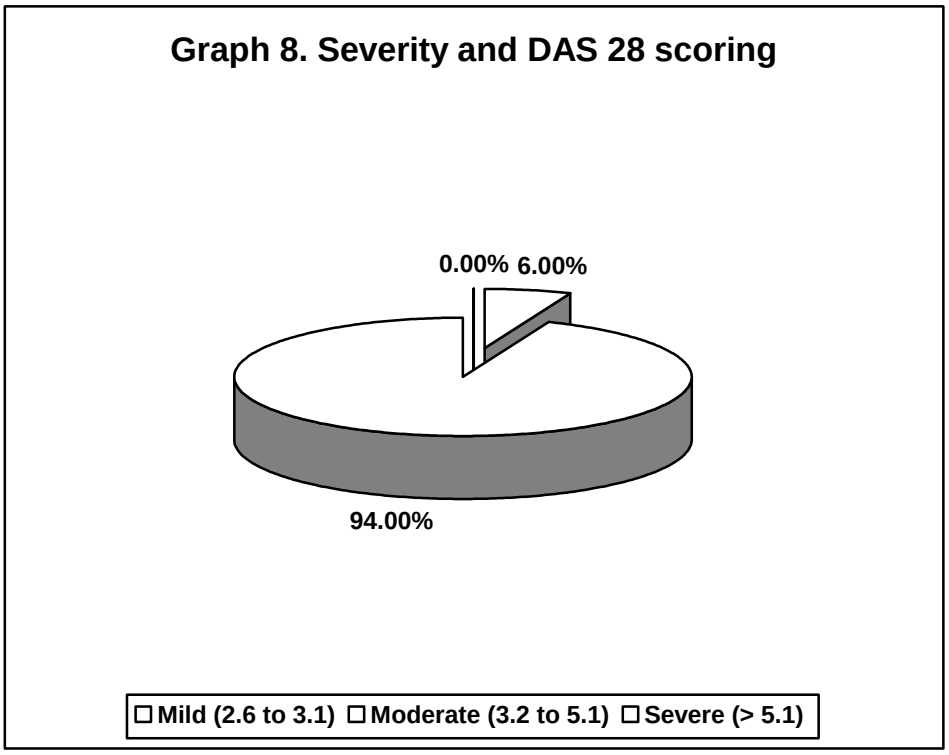
ESR	Distribution (n=100)	
	Number	**Percentage**
Normal	3	3.00
High	97	97.00
Total	**100**	**100.00**



The ESR is high in 97% of the patients in the present study

Table 8. Severity and DAS 28 Scoring

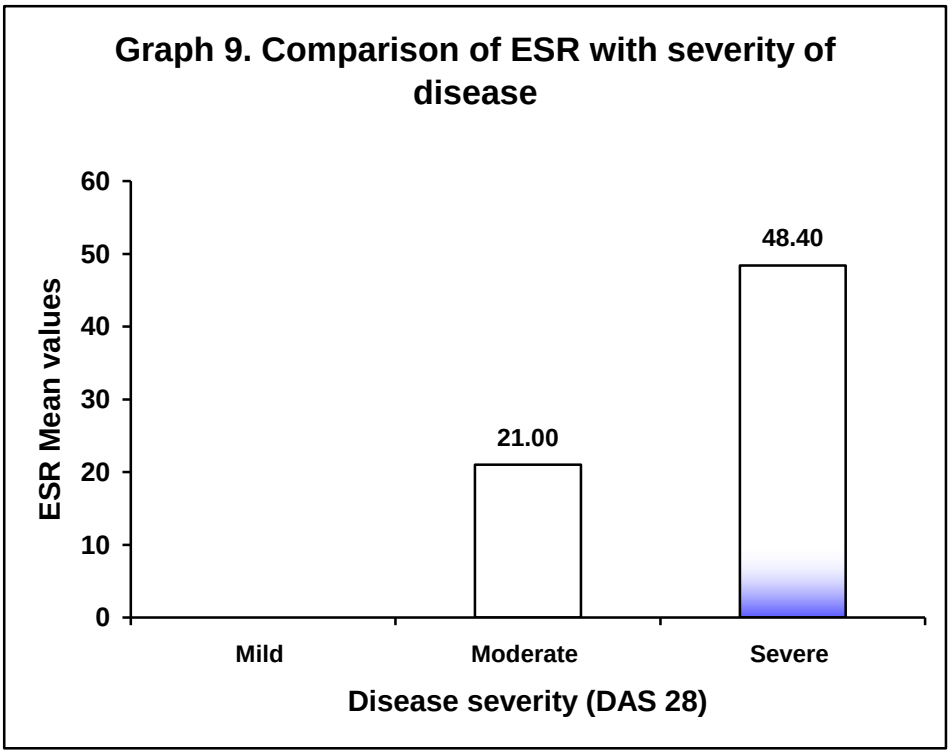
Severity (DAS 28 scores)	Distribution (n=100)	
	Number	**Percentage**
Mild (2.6 to 3.1)	0	0.00
Moderate (3.2 to 5.1)	6	6.00
Severe (> 5.1)	94	94.00
Total	**100**	**100.00**



94% of the patients were having severe disease while 6% had moderate disease.

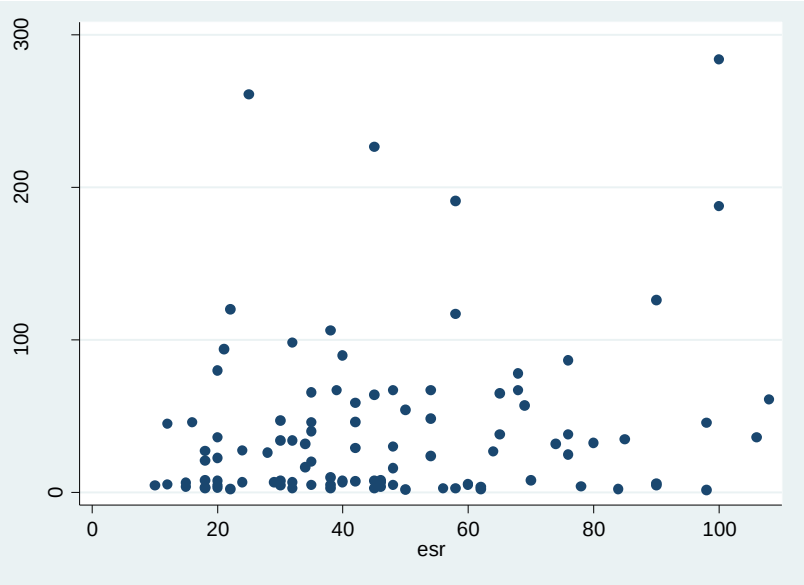
Table 9. Comparison of ESR with severity of disease

Severity (DAS28 Scores)	ESR	
	Mean	SD
Mild (2.6 to 3.1)	-	-
Moderate (3.2 to 5.1)	21.00	9.70
Severe (> 5.1)	48.40	24.20



The mean ESR score for the moderate DAS 28 category is 21 ± 9.7. For the severe DAS 28 category, the mean ESR score was 48.4 ± 24.2. A t-test was used to evaluate differences in ESR score by the DAS categories. The p-value was 0.002 denoting that there was a statistically significant difference in ESR score by the DAS categories.

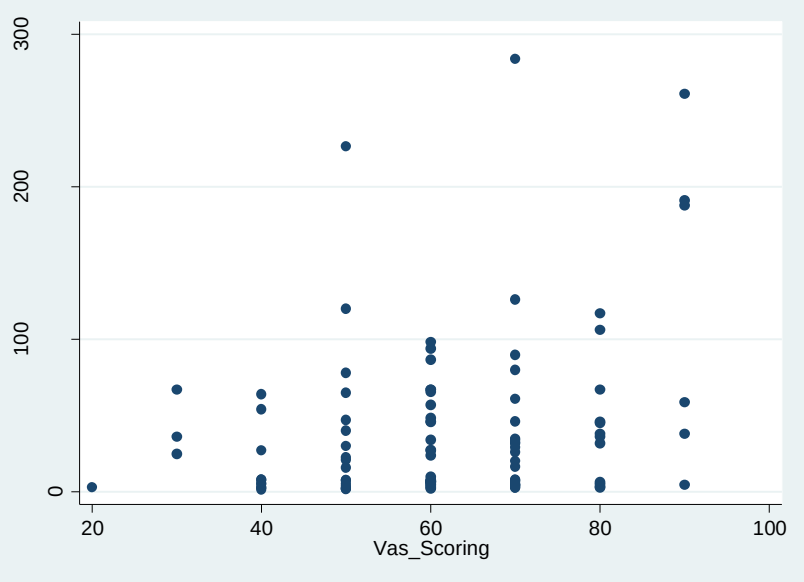
Graph 10. Correlation between CCP titters and ESR



Pearson's correlation co-efficient=0.207 **p=0.038**

The pearson's correlation between anti-CCP and ESR showed weak positive correlation.

Graph 11. Correlation between CCP titters and VAS scoring

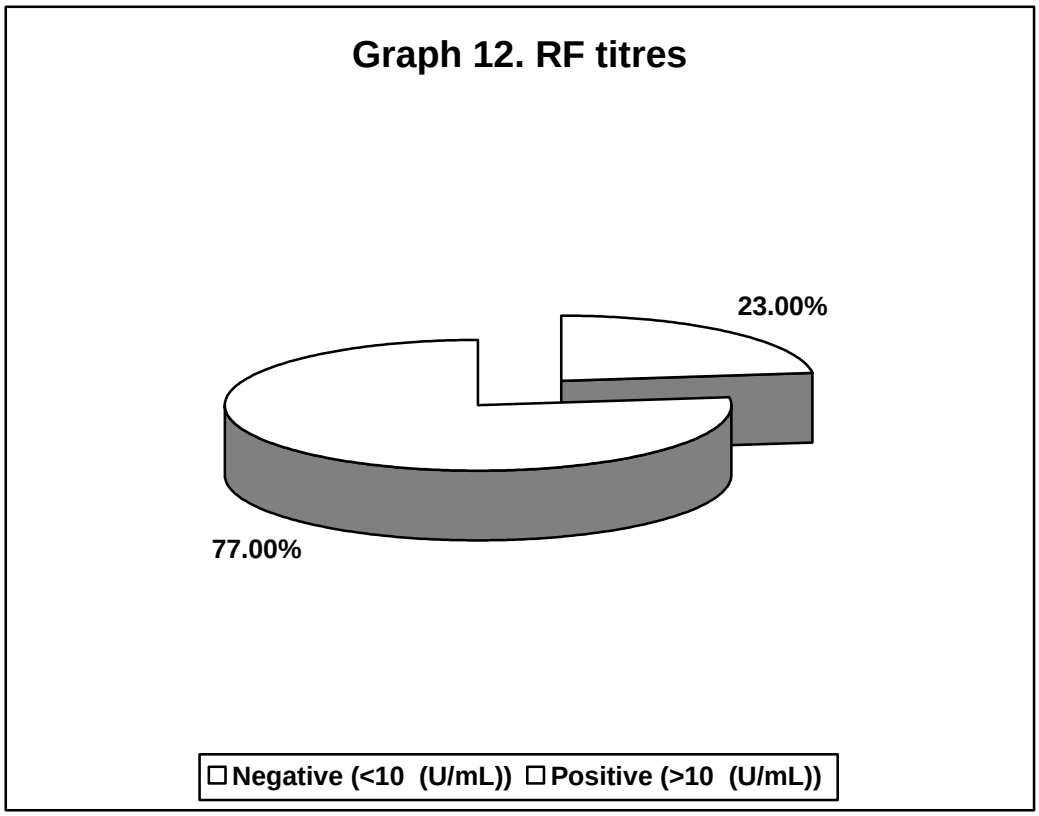


Pearson's correlation co-efficient=0.260 **p=0.009**

The VAS score in this study ranged from 20 to 100. The pearson's correlation between anti-CCP and VAS showed weak positive correlation.

Table 10. RF titres

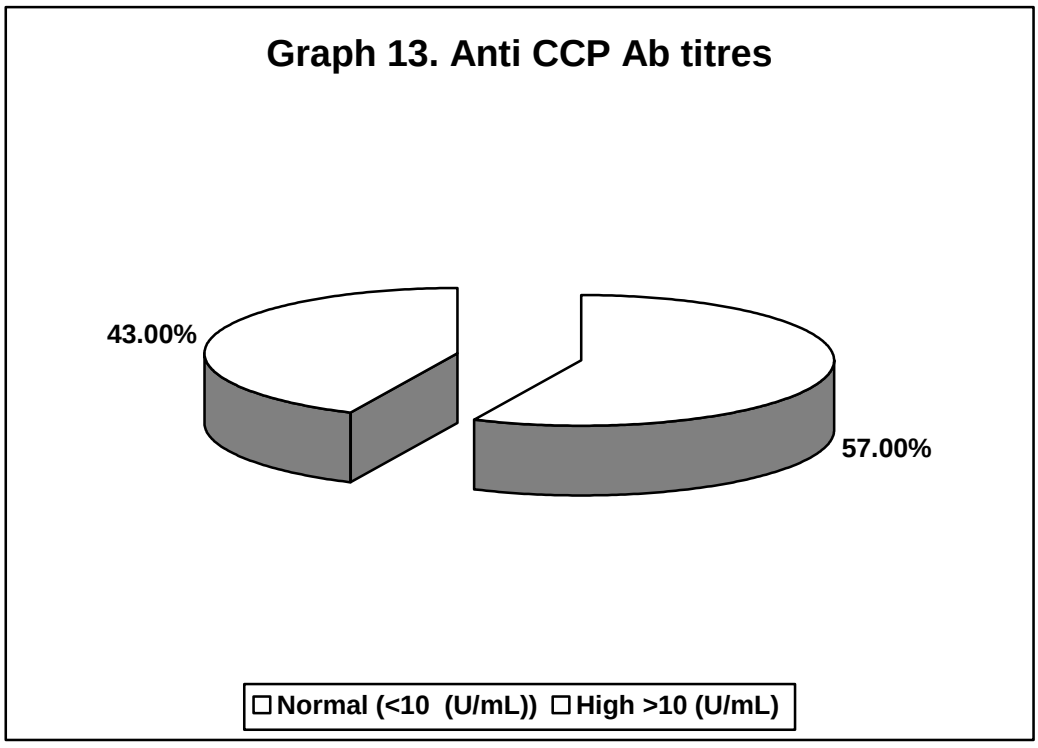
RA factor (U/mL)	Distribution (n=100)	
	Number	**Percentage**
Negative (<10)	23	23.00
Positive (> 10)	77	77.00
Total	**100**	**100.00**



RF is positive in 77% and negative in 23%..

Table 11. Anti CCP Ab titres

Anti CCP (U/mL)	Distribution (n=100)	
	Number	**Percentage**
Negative (< 10)	57	57.00
Positive (> 10)	43	43.00
Total	**100**	**100.00**

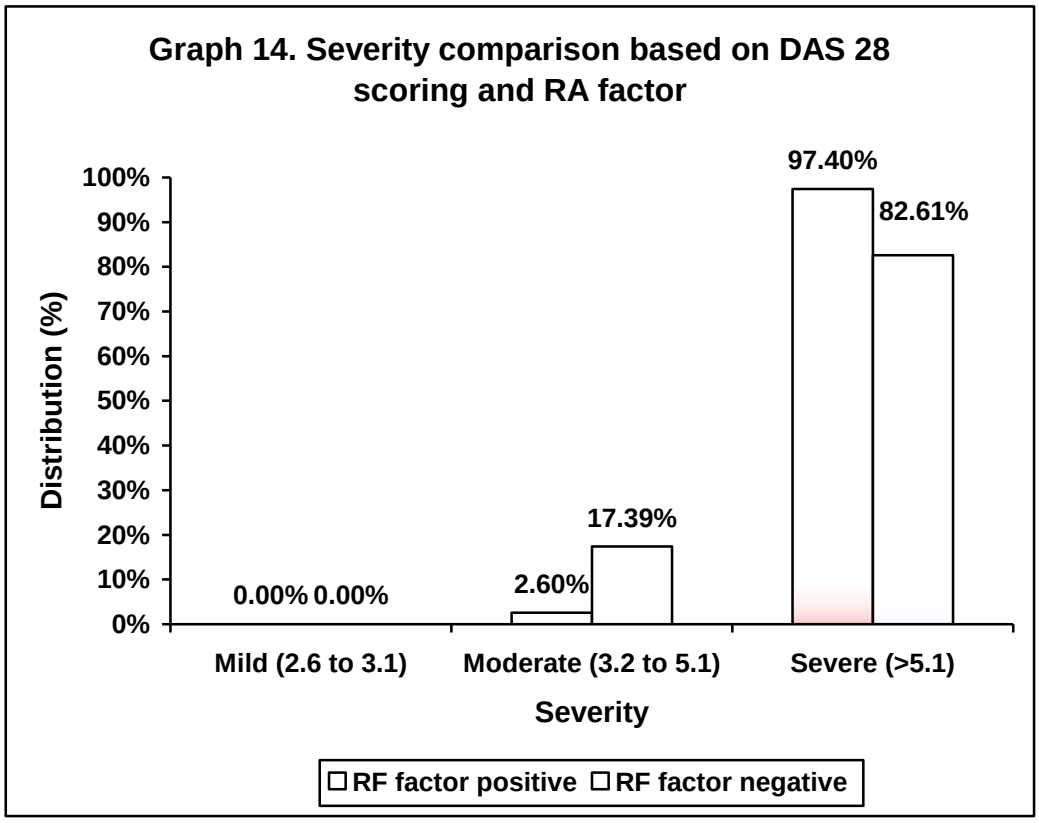


Anti CCP was found to be positive in only 43 % and negative in 57%.

Table 12. Comparison of severity based on DAS 28 scoring and RA factor

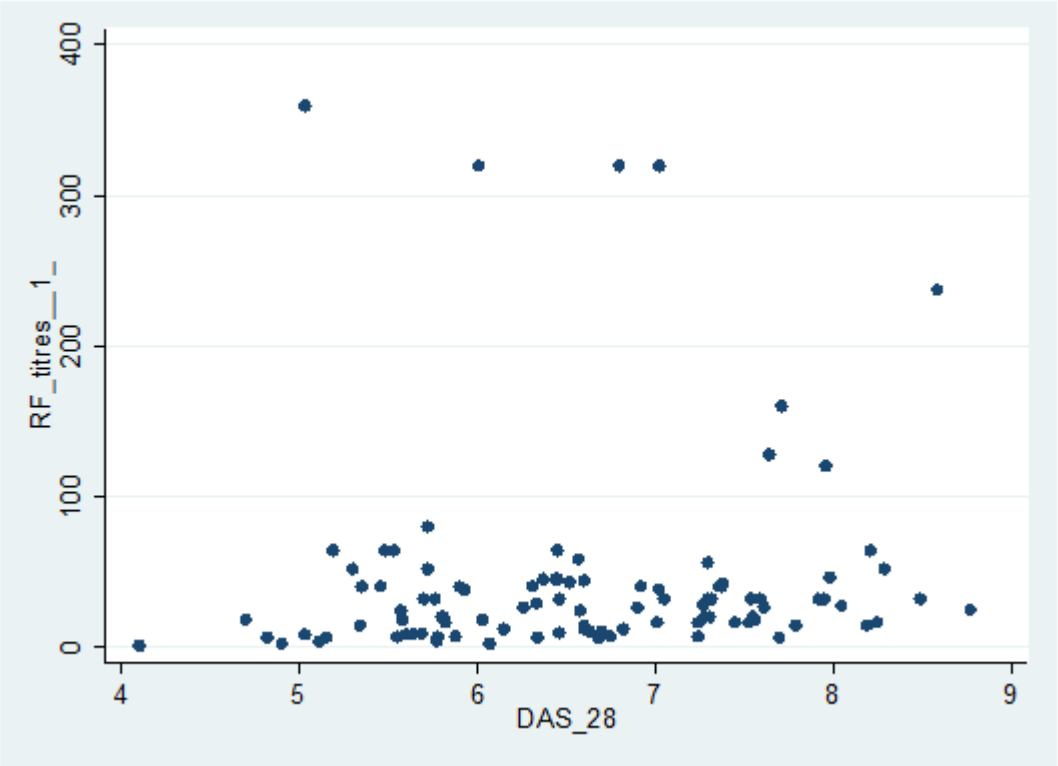
Severity (DAS28 Scores)	RF factor positive (n=77)		RF factor negative (n=23)	
	Number	**Percentage**	**Number**	**Percentage**
Mild (2.6 to 3.1)	0	0.00	0	0.00
Moderate (3.2 to 5.1)	2	2.60	4	17.39
Severe (> 5.1)	75	97.40	19	82.61
Total	**77**	**100.00**	**23**	**100.00**

x^2 (Yate's correction) = 4.500 p = 0.034 (significant)



. Among RF positive patients (n=77), 97.4% (75) of patients had severe disease while 2.6% (2) had moderate disease. Among RF negative patients 82.6% (19) of patients had severe disease while 17.39% (4) had moderate disease.

Graph. 15 Correlation of RF titres with DAS scoring

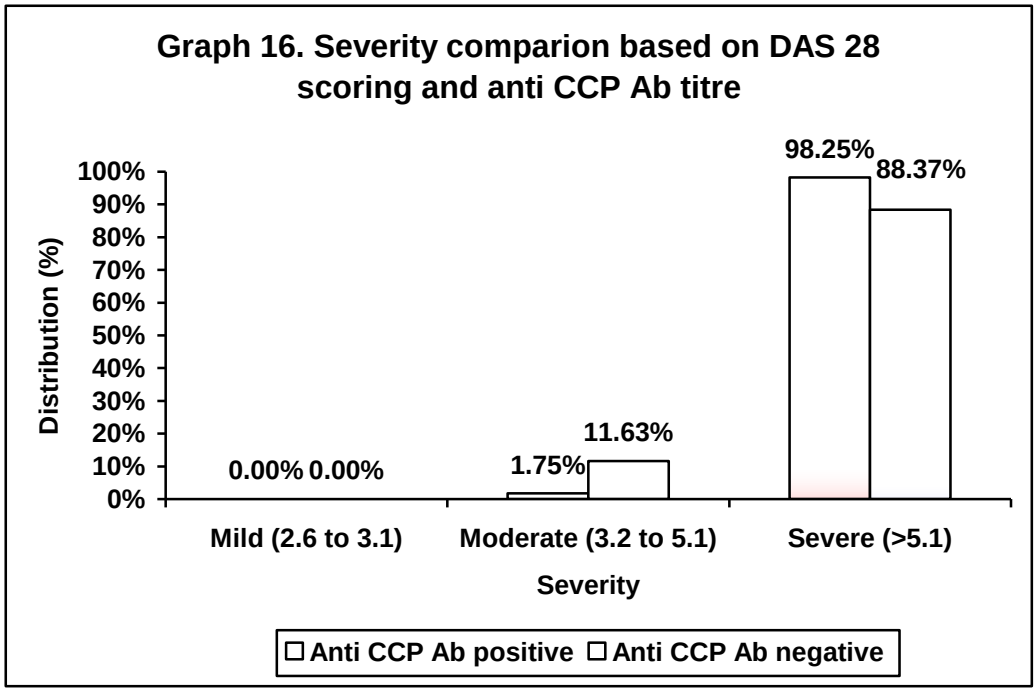


In our study the DAS score has been identified to be in the range of 4 to 9. The Pearson's correlation between RF titres and DAS is 0.08 with a p-value of 0.417. So, RF titres and DAS is only weakly associated.

Table 13. Comparison of severity based on DAS 28 scoring and anti CCP antibody titre

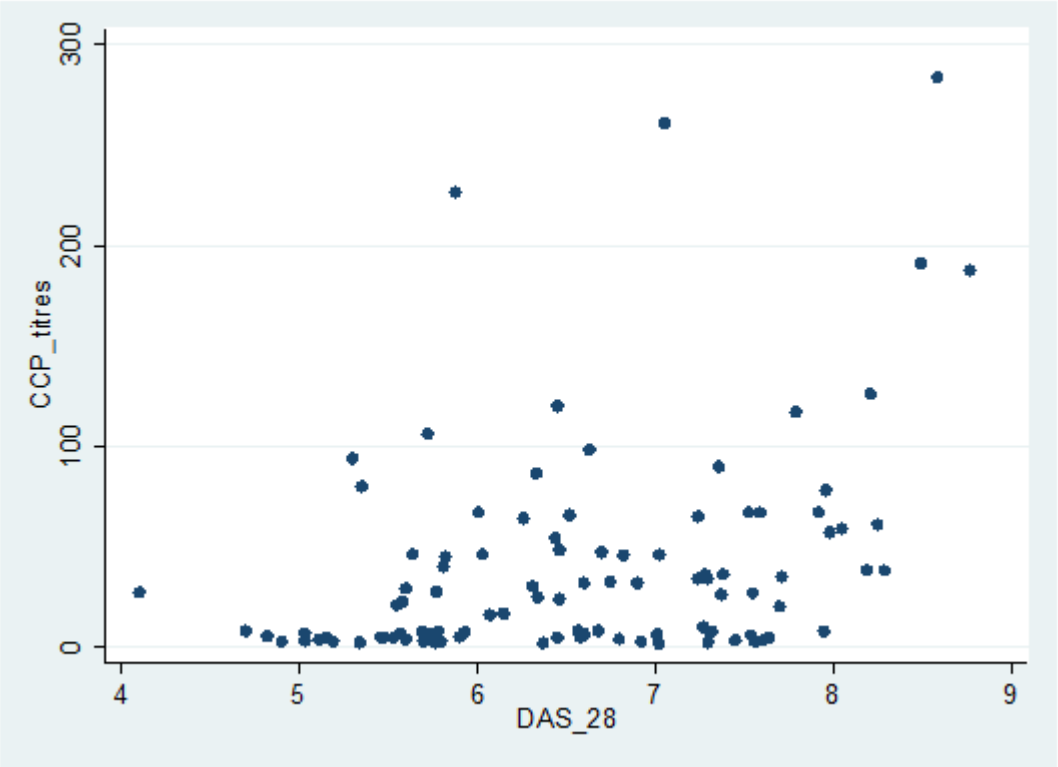
Severity (DAS 28 scores)	Anti CCP Ab Positive (n=57)		Anti CCP Ab negative (n=43)	
	Number	Percentage	Number	Percentage
Mild (2.6 to 3.1)	0	0.00	0	0.00
Moderate (3.2 to 5.1)	1	1.75	5	11.63
Severe (> 5.1)	56	98.25	38	88.37
Total	**57**	**100.00**	**43**	**100.00**

x^2 (Yate's correction) = 2.667 p = 0.102 (Not significant)



Among Anti CCP positive patients (n=57), 98.25% (56) of patients had severe disease while 1.75% (1) had moderate disease. Among Anti CCP negative patients 88.37% (38) of patients had severe disease while 11.63% (5) had moderate disease.

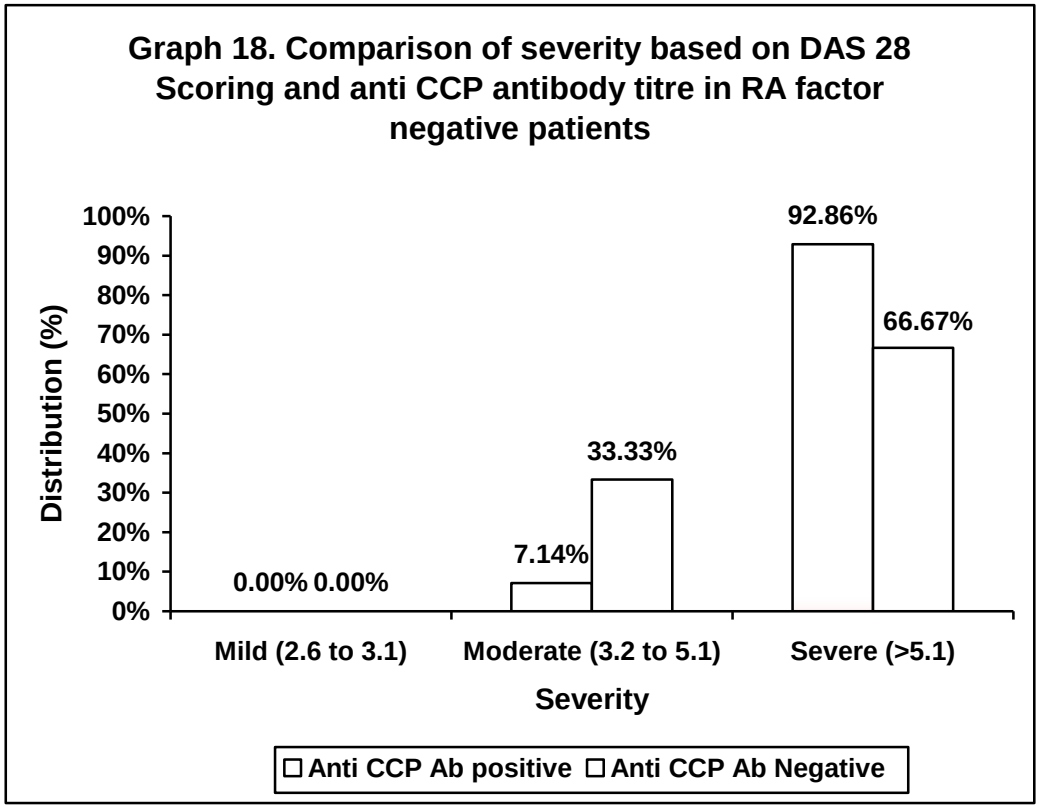
Graph 17. Correlation of CCP titres with DAS scoring



The Pearson's correlation between CCP titres and DAS is 0.359 with a p-value of 0.0003. So, anti CCP titres and DAS is moderately associated in the positive direction and this is statistically significant.

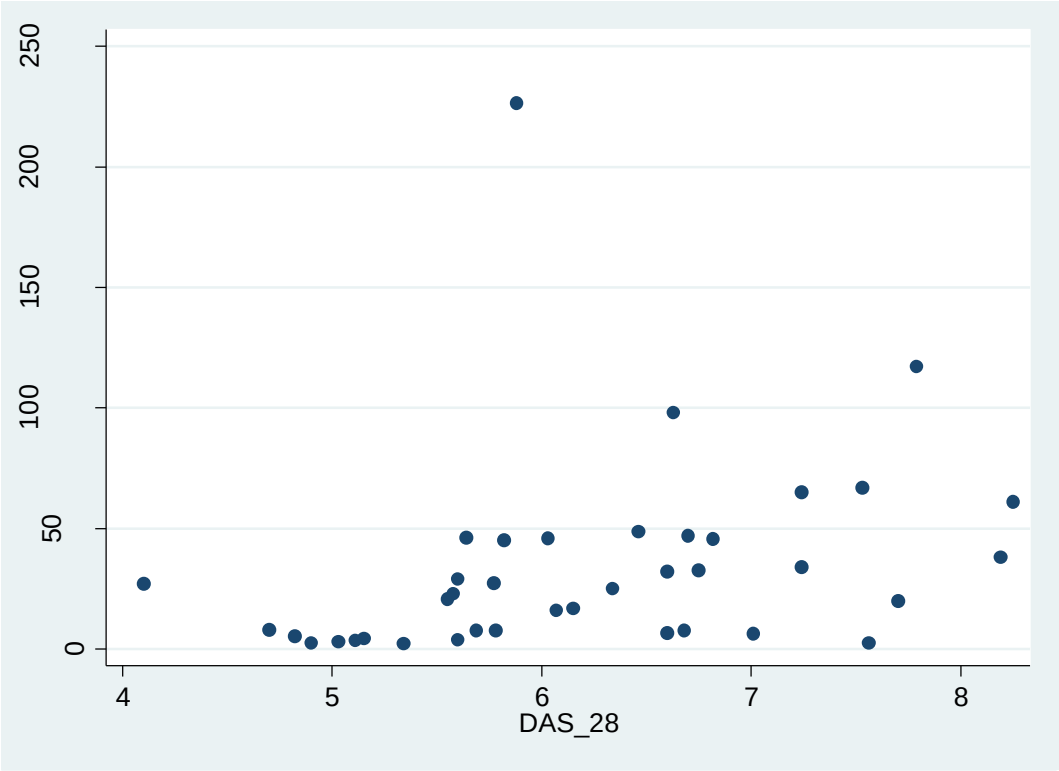
Table 14. Comparison of severity based on DAS 28 Scoring and anti CCP antibody titre in RA factor negative patients (n=23)

Severity (DAS28 Scores)	Anti CCP Ab Positive (n=14)		Anti CCP Ab negative (n=9)	
	Number	Percentage	Number	Percentage
Mild (2.6 to 3.1)	0	0.00	0	0.00
Moderate (3.2 to 5.1)	1	7.14	3	33.33
Severe (> 5.1)	13	92.86	6	66.67
Total	**14**	**100.00**	**9**	**100.00**



RF negative and Anti CCP positive patients (n=23), 92.86% (13) had severe disease and 7.14% (1) had moderate disease. RF negative and Anti CCP negative patients 66.67% (6) of patients had severe disease while 33.3% (3) had moderate disease.

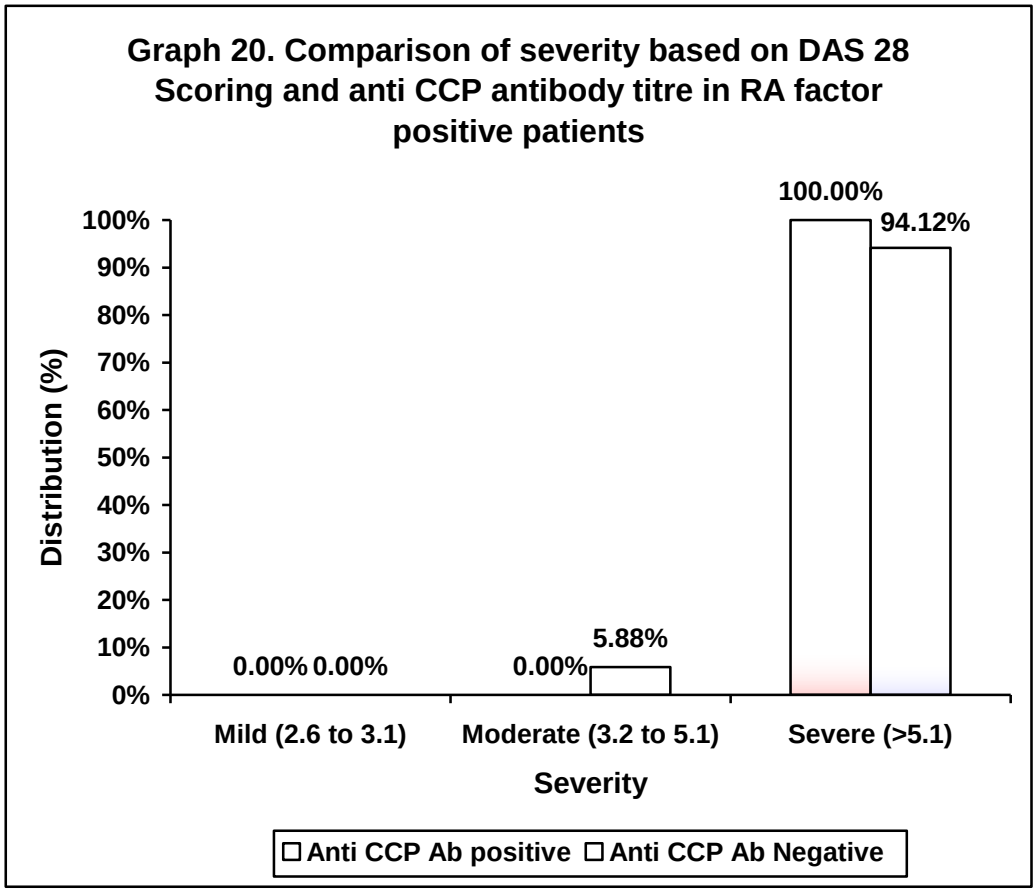
Graph 19 Correlation of CCP tires with DAS among RF negatives



The Pearson's correlation coefficient is 0.291 with p-value 0.073, that is there is no correlation between CCP titres and severity of disease in RF negative subset

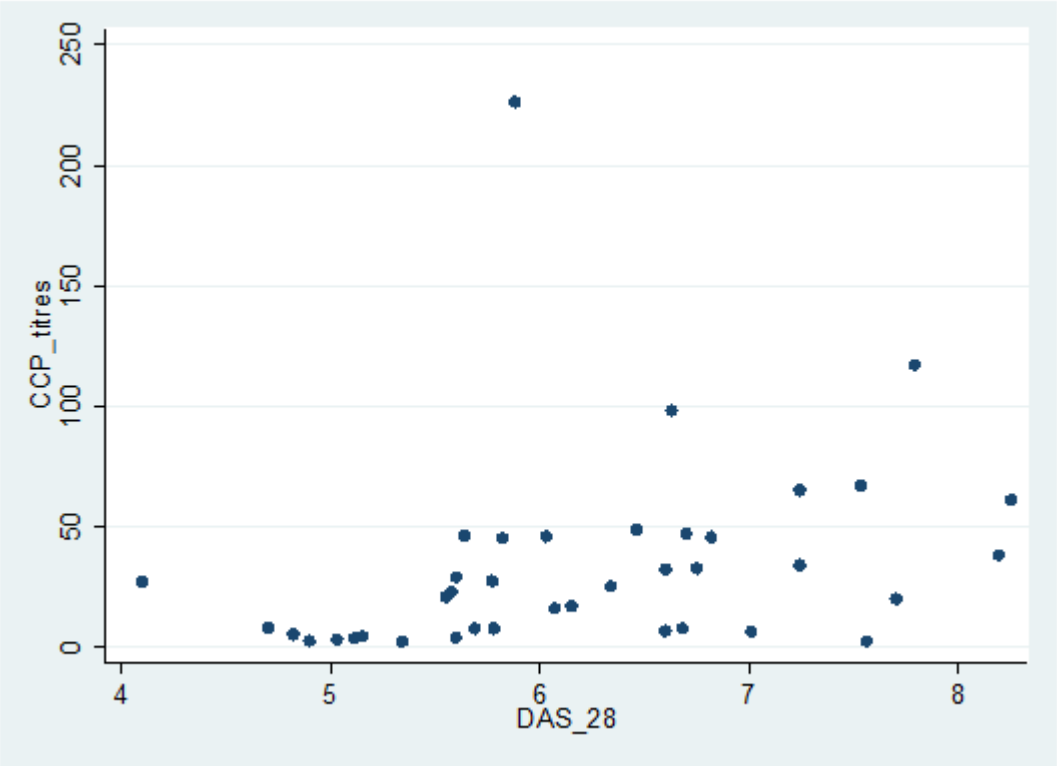
Table 15. Comparison of severity based on DAS 28 Scoring and anti CCP antibody titre in RA factor positive patients (n=77)

Severity (DAS28 Scores)	Anti CCP Ab Positive (n=43)		Anti CCP Ab negative (n=34)	
	Number	Percentage	Number	Percentage
Mild (2.6 to 3.1)	0	0.00	0	0.00
Moderate (3.2 to 5.1)	0	0.00	2	5.88
Severe (> 5.1)	43	100.00	32	94.12
Total	**43**	**100.00**	**34**	**100.00**



RF positive and Anti CCP positive patients (n=43), had 100% severe disease. RF positive and Anti CCP negative patients 94.12% (32) of patients had severe disease while 5.88% (2) had moderate disease.

Graph 21 Correlation of CCP tires with DAS among RF positive



The Pearson's correlation coefficient is 0.381 with p-value 0.0024, that is there is a positive correlation between anti-CCP titres and severity of disease in RF positive subset.

Chapter 6

Discussion

DISCUSSION

Rheumatoid arthritis (RA) is a common, systemic autoimmune disease affecting 0.5 to 1% of the population.[58] Worldwide, the annual incidence of Rheumatoid arthritis is approximately 3 cases per 10,000 populations, and the prevalence rate is approximately 1%, increasing with age and peaking at age 35 to 50 years. Rheumatoid arthritis affects all populations, although the disease is much more prevalent in some groups (5-6% in some Native American groups) and much less prevalent in others (black persons from the Caribbean region) In India, the prevalence of rheumatoid arthritis (0.75%) is similar to that in the West. In China, Indonesia, and the Philippines, in contrast, rheumatoid arthritis appears rare (prevalence below 0.4%), in both urban and rural settings.

Anti-CCP is a very useful test to order during the diagnostic evaluation of a person who may have rheumatoid arthritis. If present at a moderate to high level, it not only confirms the diagnosis but also may indicate that the patient is at increased risk for damage to the joints. Low levels of this antibody are less significant. In the past, doctors relied on another antibody, the rheumatoid factor (RF) to confirm a diagnosis.[58]

The present study was undertaken to find the prevalence of anti CCP antibodies in patients with rheumatoid arthritis, to assess the positivity of anti CCP antibody in subsets of RA factor positive and RA factor negative patients and to correlate anti CCP positivity with severity of rheumatoid arthritis. This one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the

period of January 2010 to December 2010 on 100 patients with history, suggestive of RA.

In the present study anti CCP was found to be positive in 43% and negative in 57% of the patients which was comparable to a study conducted in Nairobi by Ayunga et al[95] to determine the prevalence of anti CCP and RF in inflammatory arthritis, overall prevalence of Anti-CCP antibodies in the population was 47.4% in comparison to that of rheumatoid factor (RF) that was prevalent at 36.8% in patients with RA.

In our study, females outnumbered males (77% v/s 23%) with male to female ratio of 1 : 3.34. These findings also corroborate with literature which mentions that women are affected by RA approximately 3 times more often than men,[26,27] but sex differences diminish in older age groups.[26]

In our study, the incidence seen as per decade wise were as follows, 21 to 30 (14%), 31 to 40 (21%), 41 to 50 (37%), 51 to 60 (20%), 61 to 70 (6%) and > 70 (2%) with the maximum incidence was seen between the ages of 30 to 60 years. Overall the mean age was 44.74 ± 11.62 years. Our finding corroborate with literature which mentions that the maximum incidence is between 35 to 50 years. The incidence and prevalence of RA generally rises with increasing age until about age 70, then declines.[96]

In our study, majority of the patients were found to be housewives (73%) out of which 23% were involved in other occupation earlier but had stopped working as a result of the debility caused by the disease. Businessmen (9%)

Farmer (9%) and Laborers (7%) were the other common occupations seen in our study.

In our study, with respect to tender joint count, we found that patients with < 10 joints were affected in 30% of patients, 10 to 20 joints in 34 % and 21 to 28 joints in 36 % of patients.

In our study, with respect to swollen joint we found that < 10 joints were involved in 66 %, 10 to 20 joints in 25% and 21 to 28 joints 9 % respectively.

In our study, with respect to VAS (visual analogue scale) we found that patients had < 30 in 4 %, 30 to 70 in 78% and > 70 in 18 % of the cases. The Pearson's correlation between CCP titters and VAS scoring is 0.260 with p-value 0.009 which showed a weak positive correlation. Studies conducted by Serdaroğlu et al concluded that there was also no significant correlation between anti-CCP antibody and VAS.

In our study the ESR was high in 97% of the patients. The DAS28 score was also categorized by the standard definition, out of which, 94% of the patients were in the severe category, 6% in moderate and none in the mild. The mean ESR score for the moderate DAS category is 21% ± 9.7 and for the severe DAS category, the mean ESR score is 48.4% ± 24.2. A t-test was used to evaluate differences in ESR score by the DAS categories. The p-value is 0.002 denoting that there is a statistically significant difference in ESR score by the DAS28 categories.

The ESR level was associated with disease activity correlating with the findings mentioned in the literature.[70] 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,[8] in the diagnosis and follow-up of RA patients.

The Pearson's correlation between CCP titters and ESR is 0.207 with p-value 0.038 which is significant. Wolfe et al[97] suggested that ESR measures elements of chronicity and severity of RA in addition to the acute phase response. He concluded that ESR may measure aspects of general severity of RA better than CRP, even though it is a poorer measure of inflammation. These observations are supported by the findings of the met analysis by Ward et al.[98] Wolfe et al[97] also showed that the ESR can be elevated when RA is quiescent clinically and vice versa.

In our study, all those patients with RF titre < 10U/ml were taken as negative and titres >=10 U/ml were taken as positive. RF was found to be positive in 77% and negative in 23% of patients.

In our study, all those patients with anti CCP titre < 10 U/ml were taken as negative and anti CCP titres >=10 U/ml were taken as positive. Anti CCP was found to be positive in 43% and negative in 57% of the patients which was comparable to a study conducted in Nairobi by Ayunga et al95 to determine the prevalence of anti CCP and RF in inflammatory arthritis, overall prevalence of Anti-ccp antibodies in the population was 47.4% in comparison to that of rheumatoid factor (RF) that was prevalent at 36.8% in patients with RA.

In our study we found a correlation between RA factor positivity and severity of disease, as categorized by the standard definition. Among RF positive patients (n=77), 97.4% (75) of patients had severe disease while 2.6% (2) had moderate disease. Among RF negative patients 82.6% (19) of patients had severe disease while 17.39% (4) had moderate disease. The p value was determined using the chi square test (p=0.034) which was statistically significant thereby indicating a positive correlation. Palosuo T et al[99] and van Boekel MA[60] indicated that rheumatoid arthritis is more severe in patients with rheumatoid factor positivity.

We also tried to find a correlation of RF titres with DAS28 scoring. We found that the Pearson's correlation between RF titres and DAS28 is 0.08 with a p-value of 0.417. So, RF titres and DAS28 were weakly associated.

The sensitivity of anti-CCP in measuring RF is 55.7%. That is, among those who were RF positive, 55.7% were anti CCP positive. The specificity of anti-CCP in measuring RF is 35.9%, that is among those who were RF negative, 35.9% were also CCP negative.

In the original studies of Schellekens et al.,[41] in which anti-CCP was measured in cohorts of RA patients and in patients with other rheumatic, infectious diseases and in healthy controls concluded that anti-CCP antibodies are very specific for RA. Study reported that, using prevalent RA and non-RA sera, the anti-CCP ELISA proved to be extremely specific (98%), with a reasonable sensitivity (68%).

We also tried to find a correlation of anti-CCP titres with DAS28 scoring The Pearson's correlation between anti-CCP titres and DAS is 0.359 with a p-value of 0.0003. So, anti-CCP titres and DAS are moderately associated in the positive direction and this is statistically significant. There are several studies which conclude that anti-CCP antibodies identify patients with significantly greater disease activity more reliably than rheumatoid factor. A meta analysis conducted by Nishimura et al[100] also concluded that Anti-CCP antibodies are more specific than RF for diagnosing rheumatoid arthritis and may better predict erosive disease.

In our study, we also tried to find a correlation of anti CCP in RA negative and RA positive subsets.

In RF negative subset of patients (n=23), we found that anti CCP Ab positive in 14 (60.8%) patients and negative in 9 patients. In this subset, the Pearson's correlation coefficient is 0.291 with p-value 0.073, which means that there is a weak correlation between anti CCP tires with DAS 28 scoring. We could not find a statistically significant correlation between DAS 28 scoring and anti-CCP positivity in this subset of patients.

In RF negative subset, out of 19 patients that were found to have severe disease, 6 were anti-CCP negative whereas 13 had anti-CCP positive, which is a significant number in this subset, but not statistically significant. Studies mention that a positive anti-CCP in seronegative RA strongly supports the diagnosis of RA serologically, thereby benefiting this subset of patients with RA treatment.

In our study, with RA positive subset of patients (n=77), anti CCP positive in 43 patients and negative in 34 patients. Anti CCP positive titres were seen to have a significant positive correlation with severity of RA disease (p=0.001). We also found that the Pearson's correlation coefficient is 0.381 with p-value 0.0024 which suggest that anti-CCP have a significant correlation with DAS 28 scoring

A cross-sectional study[101] compared the rheumatoid factor (RF) and anti-CCP status in RA patients and a control group consisting of healthy subjects, and patients with SLE and scleroderma. The study suggests that testing for anti-CCP is only cost-effective in the RF-negative patient in whom there is a strong clinical suspicion of RA. Anti-CCP antibodies also identify a subset of patients who are likely to have substantial ongoing disease activity, accrue more damage, and who will probably benefit most from early aggressive treatment. A significant number of these patients do not have rheumatoid factor, and may not otherwise have been expected to develop severe aggressive disease.

The anti-CCP antibody evaluation will be useful along with RF in suspected cases of RA. Presence of anti-CCP antibody titer in RF negative patients will help in the management of RA.

Chapter 7

Conclusion

CONCLUSION

Overall in the present study, the prevalence of anti-CCP in patients diagnosed with RA was 43%.

In RA positive subset of patients (n=77), Anti-CCP is positive in 55.8% (43) of patients, and negative in 44.2% (34) of patients. Anti-CCP positive titres were seen to have a significant positive correlation with severity of RA disease (p=0.001).

In RA negative subset of patients (n=23), 60.8% (14) of patients were found to be anti-CCP positive and 39.1% (9) of patients were found to be anti-CCP negative, suggesting that testing for anti-CCP was effective in the RF-negative patient in whom there is a strong clinical suspicion of RA. Out of 19 patients with severe disease, 6 were anti-CCP negative whereas 13 had anti-CCP positive, which is a significant number in this subset, but not statistically significant.

Anti-CCP titres were found to have a positive correlation with the severity of the disease hence, anti-CCP should be used along with RF, especially in patients with RF negative.

Chapter 8

Summary

SUMMARY

Rheumatoid arthritis is a common, systemic autoimmune disease. 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. The cyclic citrullinated peptide (anti-CCP) antibodies meet the demands for a good and useful marker for early RA. Anti-cyclic-citrullinated-peptide antibodies hold promise for earlier and more accurate diagnosis of disease, improved prognostic information, and have been implicated in RA pathogenesis. In view of the above, the present study was undertaken to find the prevalence of anti CCP antibodies in patients with rheumatoid arthritis, to assess the positivity of anti CCP antibody in subsets of RA factor positive and negative patients and to correlate anti CCP positivity with severity of rheumatoid arthritis.

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010 on 100 patients with history, suggestive of RA and fulfilling ACR Criteria 1987. The severity of the disease was calculated using Disease Activity Score 28 (DAS 28) score.

In the present study females outnumbered male (77% vs 23%) with male to female ratio of 1 : 3.34. Maximum cases were seen between the ages of 30 to 60 years and the mean age was 44.74 ± 11.62 years. RF was positive in 77% and negative in 23% of all patients and anti CCP was found to be positive in only 43 % and negative in 57% of the patients. 94% of the patients were having severe

disease while 6% had moderate disease. The sensitivity of CCP in measuring RF was 55.7% and the specificity of CCP in measuring RF was 35.9%. Pearson's correlation between CCP titters and VAS scoring showed a weak positive correlation (Pearson's correlation co-efficient=0.260 p=0.009). The mean ESR score for the moderate DAS 28 category is 21 ± 9.7. For the severe DAS 28 category, the mean ESR score was 48.4 ± 24.2 suggesting significant correlation between ESR and disease severity. A weak positive correlation was seen between ESR and anti-CCP titre (Pearson's correlation 0.207, p=0.038). The Pearson's correlation between anti-CCP titres and DAS was 0.359 with a p-value of 0.0003 suggesting anti-CCP titres and DAS were moderately associated in the positive direction.

In RA positive subset of patients anti-CCP positive titres had significantly positive correlation with severity of RA disease. In RA negative subset (n=23) 60.8% of patients were found to be anti-CCP positive.

Anti-CCP titres were found to have a positive correlation with the severity of the disease hence, anti-CCP should be used along with RF, especially in patients with RF negative.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

TITLE OF TOPIC "ASSESSMENT OF ANTI CCP ANTIBODIES IN RHEUMATOID ARTHRITIS"- ONE YEAR CROSS SECTIONAL STUDY AT KLES Dr. PRABHAKAR KORE HOSPITAL & MRC, BELGAUM.

OBJECTIVE AND PURPOSE OF THE STUDY

This research is intended to study the study the prevalence of anti CCP antibodies in patients with rheumatoid arthritis. The principal investigator of the study is Dr. Toby Chandy under the guidance of Dr. Rekha Patil My co-operation will be of great help to patients with extensive pulmonary tuberculosis.

PROCEDURE

If you agree to be part of the research study u will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood sample and get a chest x ray done for the same study.

RISK AND BENEFITS

The only risk and possible discomfort you might get is while taking blood from my arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn. You may also face some radiation hazards while getting an x ray done.

ALTERNATIVES

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

VOLUNTARY PARTICIPATION/ WITHDRAWAL

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

PRIVACY AND CONFIDENTIALITY

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

INSTITUTION / SPONSOR'S POLICY

Does not apply to this research

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.

If you have any questions about my rights as a participant you may call Dr. V. D. Patil, Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number 0831-2471350.

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

Signature /Left Thumb print of the Participant or legally authorized representative.

Participant's Name/ Impression of the participant's — Signature/ Left Thumb

Witness's Name — Signature/ Left Thumb

Investigators name and Signature: …….

Date and Place: ……

Annexures

Annexure II

ANNEXURE II – PROFORMA

Patient Name: I.P number:

Age: Sex:

Address: Occupation:

Date of admission: Date of discharge:

SYMPTOMS:

- Fever Yes/No
- Weight loss Yes/No
- Fatigue Yes/No
- Joint pain Yes/No
- Swelling Yes/No
- Skin rash Yes/No
- Oral ulcer Yes/No
- loss of hair Yes/No
- Dry mouth Yes/No
- dry eyes Yes/No
- Muscle pain Yes/No
- Muscle weakness Yes/No
- Tingling/ numbness Yes/No
- Dysnoea Yes/No
- Raynaud’s phenomenon Yes/No
- Morning stiffness Yes/No
- Duration of stiffness Yes/No

PAST HISTORY:

FAMILY HISTORY :

General physical examination:

1) Height
2) Weight
3) Body mass index
4) Temperature
5) Pulse
6) Respiratory rate
7) Blood pressure
8) Pallor
9) Cyanosis
10) Pedal edema
11) Lymphadenopathy

Systemic Examination

1) CVS
2) Respiratory system
3) Abdomen
4) CNS
5) Extra articular disease

ARA CRITERIA FOR RA:

	Ever? '-' or '+'	If '+' Mo/Yr.
Morning stiffness >1hr		
Soft tissue swelling of ≥3 joint groups		
Swelling of PIP, MCP, or Wrist Joints		
Symmetrical swelling		
Subcutaneous Nodule		
Positive Rheumatoid factor		
Highest rheumatoid factor		
Radiographic Erosion		

EXTRA- ARTICULAR DISEASE

	Ever? '-' or '+'	Onset Mo/Yr.
Pulmonary fibrosis		
Pulmonary nodules		
Clinical pericarditis		
Felty's syndrome		
Lymphadnopathy		
Carpel tunnel		
Tarsal tunnel		
Vasculitis		
Scleritis		
Neuropathy		
Raynaud's phenomenon		
Dry Eeys		
Dry Mouth		

Investigation

6) Hemogram
7) Biochemical profile
    a. Urea
    b. SGPT, Serum albumin, Total Protein
    c. CRP
8) Urine (RE)
9) ESR (WG) _____mm fall in 1st hour
10) RF (ELISA)_____IU/ltr
11) Anti CCP (ELISA)
12) X-ray hand

Other relevant investigations:

Diagnosis:

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

Anti-CCP	-	Anticyclic Citrullinated Peptide Antibody
B	-	Business
CCP	-	Citrullinated Peptide Antibody
DAS 28	-	Disease Activity Score
ESR	-	Erythrocyte sedimentation rate
F	-	Farmer
F	-	Female
H	-	Housewife
L	-	Labour
M	-	Male
N	-	Negative
P	-	Positive
RF	-	Rheumatoid factor
S	-	Service
VAS	-	Visual analog score

ANNEXURE III - MASTER CHART

Serial Number	In Patient Number	Age (Years)	Sex	Occupation	Tender Joints	Swollen Joints	VAS Score	ESR	RF	RF titres	Anti CCP	CCP titres	DAS 28
1	10622	65	F	H	20	13	70	90	P	128	N	4.3	7.64
2	10644	28	F	H	20	8	40	98	P	320	N	1.5	7.02
3	10649	35	F	H	28	9	60	64	P	20	P	26.7	7.55
4	10645	55	F	H	20	14	60	90	P	32	N	5.8	7.54
5	10658	60	F	H	28	16	70	90	P	64	P	126	8.21
6	9204	28	F	H	24	14	70	40	P	40	P	89.7	7.36
7	10200	33	M	S	26	10	60	68	P	16	P	67	7.53
8	10665	42	F	H	26	8	50	30	N	10	P	47	6.70
9	10199	65	M	L	8	4	30	20	P	20	P	36	7.28
10	9332	69	F	H	28	23	80	18	P	40	N	3.2	7.45
11	9268	40	F	H	27	24	50	68	P	120	P	78	7.96
12	8619	45	F	H	20	13	60	20	P	64	N	4.5	6.45
13	8398	39	F	H	8	0	50	45	P	32	N	7.6	7.95
14	9622	30	F	H	28	14	80	54	P	32	P	67	7.92
15	9791	50	F	H	22	2	90	30	P	64	N	4.5	5.53
16	9787	48	F	H	20	16	70	85	P	160	P	34.6	7.71
17	9788	52	F	H	18	2	70	78	P	320	N	3.7	6.80
18	7441	33	M	F	20	10	70	38	P	40	N	2.5	6.92
19	10107	50	M	H	26	22	80	58	P	14	P	117	7.79
20	9778	56	M	H	24	12	90	25	P	32	P	261	7.05
21	10193	26	M	L	24	9	50	22	P	45	P	120	6.45
22	10233	55	F	H	13	6	60	24	N	4	P	27.3	5.77
23	10231	46	F	H	6	4	60	35	P	40	N	4.6	5.46
24	10259	25	F	H	7	7	50	46	N	8	N	3.6	5.60
25	10380	56	F	H	18	8	60	32	N	10	P	98	6.63
26	10384	50	F	H	12	9	50	20	P	18	P	22.7	5.58
27	10373	33	F	B	9	8	50	22	P	14	N	2.1	5.34
28	10459	42	F	H	13	6	70	34	P	12	P	16.7	6.15
29	10458	24	F	H	7	4	70	42	N	8	P	29	5.60
30	10446	44	M	S	14	8	30	76	N	6	P	25	6.34
31	10444	49	M	H	5	4	40	56	P	64	N	2.5	5.19
32	10120	52	M	B	26	2	60	16	P	18	P	46	6.03
33	10471	42	F	H	18	2	60	98	P	12	P	45.7	6.82
34	10188	35	F	H	8	2	80	74	P	26	P	32	6.90
35	10522	45	F	H	26	6	70	45	P	32	N	2.4	5.70
36	10516	35	F	H	26	4	80	35	P	38	P	46	7.02

ANNEXURE III - MASTER CHART

Serial Number	In Patient Number	Age (Years)	Sex	Occupation	Tender Joints	Swollen Joints	VAS Score	ESR	RF	RF titres	Anti CCP	CCP titres	DAS 28
37	10511	32	F	H	28	15	60	32	P	56	P	34	7.30
38	10572	58	F	H	26	10	70	62	P	26	N	3.4	7.61
39	10533	50	F	H	17	6	80	106	P	42	P	36.1	7.38
40	10537	35	F	H	8	5	40	48	P	64	N	4.6	5.48
41	10533	50	F	H	10	2	50	62	P	32	N	2.3	5.76
42	10518	50	F	H	28	0	80	12	P	16	P	45	5.82
43	10185	58	M	B	20	10	60	84	P	32	N	2.2	7.30
44	10634	55	F	H	28	8	70	40	P	32	N	7.6	7.32
45	10594	54	F	H	20	6	60	35	P	43	P	65.7	6.52
46	10048	48	F	H	18	4	50	50	P	45	N	2	6.37
47	10517	25	F	H	16	8	40	45	P	26	P	64	6.26
48	10560	54	F	H	28	18	80	65	P	14	P	38	8.19
49	10651	50	F	H	18	9	70	34	P	12	P	32	6.60
50	10162	34	F	F	28	26	90	58	P	32	P	191	8.49
51	10145	50	F	H	24	20	80	15	P	16	N	6.4	7.01
52	10179	38	F	F	13	13	30	39	P	320	P	67	6.01
53	10275	38	F	H	9	3	40	18	P	18	N	8	4.70
54	10346	45	F	F	10	8	60	32	P	20	N	2.5	5.80
55	10352	45	F	H	23	11	50	65	P	16	P	65	7.24
56	10363	51	F	H	12	2	60	21	P	52	P	94	5.30
57	10386	41	F	H	4	3	60	40	P	360	N	6.7	5.03
58	10119	60	F	H	14	8	80	38	P	40	N	4.8	5.90
59	10436	45	F	H	10	4	40	18	N	2	N	2.5	4.90
60	10174	47	F	H	10	10	20	20	N	8	N	2.8	5.03
61	107040	51	F	H	6	6	80	38	P	80	P	106	5.72
62	10597	26	F	H	8	6	70	20	P	40	P	80	5.35
63	10681	30	F	H	4	2	40	18	N	1	P	27	4.10
64	10050	55	M	L	24	8	60	24	P	14	N	6.7	6.60
65	10493	30	F	H	22	12	80	58	P	18	N	2.5	7.56
66	10497	26	F	H	24	20	70	108	P	16	P	61	8.25
67	10549	24	F	H	8	10	60	30	N	9	N	7.7	5.69
68	10871	23	F	H	10	8	70	10	N	6	N	4.3	5.15
69	10738	73	M	L	8	8	50	12	N	6	N	5.2	4.82
70	10780	40	F	H	10	10	70	80	N	6.7	P	32.6	6.75
71	10763	32	M	L	22	20	60	38	P	27	N	9.8	7.27
72	10777	37	F	H	9	8	60	42	P	38	N	7.2	5.93

ANNEXURE III - MASTER CHART

Serial Number	In Patient Number	Age (Years)	Sex	Occupation	Tender Joints	Swollen Joints	VAS Score	ESR	RF	RF titres	Anti CCP	CCP titres	DAS 28
73	10778	42	F	B	9	9	50	45	N	6.8	P	226.4	5.88
74	10596	45	F	F	27	24	90	100	P	24.7	P	187.6	8.77
75	10625	40	M	B	12	10	60	54	N	9.2	P	48.5	6.46
76	10701	43	F	H	8	8	60	15	N	3.4	N	3.4	5.11
77	10797	64	M	F	28	27	60	48	P	32	P	67	7.59
78	9991	47	F	H	28	26	70	100	P	237	P	284	8.59
79	10435	58	F	H	14	14	40	70	N	5.7	N	7.8	6.68
80	10592	44	F	H	12	10	50	18	N	6.5	P	20.6	5.55
81	10547	30	F	H	14	10	50	20	N	6.5	N	7.6	5.78
82	10811	61	F	H	7	4	70	42	N	8.3	P	46.2	5.64
83	369863	50	F	H	22	20	70	30	N	6.6	P	34	7.24
84	10762	53	M	F	10	10	50	48	N	2	P	16	6.07
85	10656	42	F	H	26	24	70	35	N	6	P	20	7.70
86	11579	48	F	H	6	6	70	46	P	52	N	6.7	5.72
87	10246	42	F	H	12	10	60	54	P	32	P	24	6.46
88	1670039	67	F	H	26	20	90	42	P	27	P	58.7	8.05
89	1686337	48	F	H	17	13	60	69	P	46	P	57	7.98
90	10597	54	F	H	24	22	70	28	P	40	P	26	7.37
91	10564	50	F	H	12	8	70	60	P	24	N	4.8	6.58
92	10116	34	F	B	24	20	90	76	p	52	P	38	8.29
93	10424	42	M	B	14	14	40	50	P	45	P	54	6.44
94	10459	74	M	B	26	18	60	32	P	20	N	6.7	7.31
95	10666	42	M	L	10	6	60	76	P	29	P	86.7	6.33
96	10696	57	M	B	12	6	50	35	P	20	P	40	5.81
97	10711	40	M	F	15	13	40	60	P	44	N	5.4	6.60
98	10122	44	M	L	13	10	50	48	P	40	P	30	6.31
99	10729	32	M	F	12	12	70	46	P	58	N	7.8	6.57
100	10026	39	F	H	8	8	60	29	P	24	N	6.7	5.57