RHEUMATOID ARTHRITIS – AETIOLOGICAL FACTORS AND VITAMIN D STATUS

Thesis submitted to the University of Calicut in partial fulfillment of the Rules and Regulations for the award of

Doctor of Philosophy (PhD)
in Rheumatology

By

Dr.SHIJI P.V.

Assistant Professor of Medicine

Govt.Medical College, Calicut

DEPARTMENT OF GENERAL MEDICINE
GOVERNMENT MEDICAL COLLEGE, KOZHIKODE
KERALA, INDIA

2018

ENDORSEMENT BY THE PRINCIPAL / HEAD OF THE INSITUTION

This is to certify that the thesis entitled "**Rheumatoid Arthritis – Aetiological factors and Vitamin D status"** is a bonafide research work done by **Dr.Shiji P.V.** in partial fulfillment of rules and regulations of Calicut University for the award of **PhD DEGREE IN RHEUMATOLOGY.**

Dr.V.R.Rajendran
Principal / Head of the Institution
Government Medical College,
Kozhikode – 673008

Date :
Place :

DEPARTMENT OF GENERAL MEDICINE

GOVT.MEDICAL COLLEGE, KOZHIKODE

CERTIFICATE

This is to certify that the thesis entitled "**Rheumatoid Arthritis – Aetiological factors and Vitamin D status"** is a bonafide research work done by **Dr.Shiji P.V.** in partial fulfillment of rules and regulations of Calicut University for the award of **PhD DEGREE IN RHEUMATOLOGY.**

Dr.N.K.THULASEEDHARAN,MD
Professor & Head
Department of General Medicine
Government Medical College,
Kozhikode - 673008

DEPARTMENT OF GENERAL MEDICINE

GOVT.MEDICAL COLLEGE, KOZHIKODE

CERTIFICATE

This is to certify that the thesis entitled **"Rheumatoid Arthritis – Aetiological factors and Vitamin D status"** is a bonafide research work done by **Dr.Shiji P.V.** under my guidance and supervision in partial fulfillment of rules and regulations of Calicut University for the award of PhD DEGREE IN RHEUMATOLOGY. It is the result of original and independent work carried out by her under my direct guidance and supervision. The thesis needs no corrections has suggested by adjudicators.

Dr.P.K.SASIDHARAN, MD;FRCP
Professor of Medicine,
Former Head of the Department
Department of Medicine
Govt.Medical College, Calicut - 8

DEPARTMENT OF GENERAL MEDICINE

GOVT.MEDICAL COLLEGE, KOZHIKODE

CERTIFICATE

This is to certify that the thesis entitled **"Rheumatoid Arthritis – Aetiological factors and Vitamin D status"** is a bonafide research work done by **Dr.Shiji P.V.** under my guidance and supervision in partial fulfillment of rules and regulations of Calicut University for the award of PhD DEGREE IN RHEUMATOLOGY. It is the result of original and independent work carried out by her under my direct guidance and supervision. This work has not been submitted for the award of any Degree, Diploma or similar titles in any other University.

Dr.P.K.SASIDHARAN, MD;FRCP
Professor of Medicine,
Former Head of the Department
Department of Medicine
Govt.Medical College, Calicut - 8

GOVT. MEDICAL COLLEGE, KOZHIKODE
INSTITUTIONAL ETHICS COMMITTEE

Chairman:
Adv.D.V.Narayanan, LLB
Advocate, Calicut Bar
9447776977

Secretary:
Dr.N.C.Cherian LLB, PGDMLE
Consultant in Med. Law & Ethics
9847108965

GMCKKD/RP2011/EC/JULY/02 Dtd. 20/07/2011

APPROVAL OF RESEARCH PROJECT

The Institutional Ethics Committee, Govt. Medical College, Kozhikode has evaluated the protocol of the research project titled "RHEUMATOID ARTHRITIS AETIOLOGICAL STUDY AND VITAMIN D STATUS" submitted by Dr.SHIJI.P.V, Assistant Professor, Dept. Of General Medicine, Government Medical College, Kozhikode.

The Committee has approved the same.

SECRETARY

CHAIRMAN

Place : Calicut.
Date : 20/07/2011

DECLARATION

I hereby declare that this dissertation/thesis entitled **"Rheumatoid Arthritis – Aetiological factors and Vitamin D status"** has been prepared by me under the guidance and supervision of Dr.P.K.Sasidharan, Professor and Former Head of the Department, Department of Medicine, Government Medical College, Kozhikode and is submitted to Calicut University in partial fulfillment of rules and regulations for PhD Degree in Rheumatology. This has not been submitted previously to any other university or institution. The conclusions drawn are entirely my own.

Dr.Shiji P.V.
Assistant Professor of Medicine
Govt.Medical College, Kozhikode

Date:
Place: Kozhikode

ACKNOWLEDGEMENT

I am greatly indebted to ***Dr.N.K.Thulaseedharan****, Professor & Head, Department of Medicine, Govt Medical College, Kozhikode for his valuable help and suggestions in completing this study.*

I am extremely grateful to my guide and my beloved teacher ***Dr.P.K.Sasidharan,*** *Professor and Former Head of the Department, Department of Medicine for his valuable suggestions and guidance during my entire thesis work and PhD training.*

I sincerely express my gratitude to ***Dr.Ajitha B.****K whose statistical expertise has been immensely useful in the analysis of my thesis.*

I am extremely thankful to all ***my teachers, colleagues and my friends*** *for the moral support and valuable suggestions towards the study.*

I am thankful to ***my father Dr.P.V.Bhaargavan and my mother Mrs.P.Vijayakumari, my husband Mr.S.V.Rajesh and my kids*** *whose prayers are always with me throughout my life.*

I thankfully remember ***all my patients*** *and their relatives who trusted me and were central to materializing this study without which the study would have been far from reality.*

Finally I bow in reverence to ***the Almighty*** *for having given me the opportunity to undertake this work and the strength and ability for successfully completing it.*

Dr. Shiji P.V.

CONTENTS

Page No.

LIST OF TABLES

LIST OF FIGURES

Introduction

Rheumatoid arthritis(RA) is a chronic inflammatory disease of unknown cause which mainly affects the synovium**.** It is one of the most common inflammatory joint disease .There may be involvement of multiple organs and extra articular systems in rheumatoid arthritis[1]. It can be considered as a spectrum of diseases that begins many years before the onset of clinical symptoms. There is believed to be a complex interplay between genetic and environmental factors in the development of RA[2]. Diagnosis of RA is mainly by history and physical examination results in conjunction with laboratory data. Radiographic data seldom helps in diagnosis as it is usually a late manifestation of RA.Patients of RA who are chronic smokers and who have high titre of rheumatoid factors have high incidence of extra articular manifestations.

Vitamin D deficiency is common in general population. Its deficiency has been linked to many diseases. Several studies have assessed the association of vitamin D deficiency in rheumatoid arthritis and have reached at different conclusions. While some studies could prove a link between severity of RA and severity of vitamin D deficiency, others could not find any link[3]. The present study looks in to the identifiable etiological factors in rheumatoid arthritis and also the association between severity of rheumatoid arthritis and vitamin D deficiency[4.]

Aim of the study

.

The present study was therefore undertaken with the following objectives

- To study the complete clinical profile of newly diagnosed patients with rheumatoid arthritis attending outpatient sections and wards for a period of 6years from 2011-2017
- To evaluate the known risk factors in the development of rheumatoid arthritis
- To look for possible association between the presence of vitamin D deficiency and severity of rheumatoid arthritis as assessed by DAS score

Review of literature

EPIDEMIOLOGY:

The prevalence of rheumatoid arthritis is 1 % in general population.the overall minimum prevalence of RA is 1.16% in women and 0.44%in men in UK. It has been estimated that the prevalence of rheumatoid arthritis in India is 0.75% which is higher when compared to China and Indonesia[5].

ETIOLOGY OF RHEUMATOID ARTHRITIS

Evidence for the role of genetic factors in the development of RA: All throughout the history there has been reports of RA affecting several generations of a given family. This has led to many studies and these studies compared the number of cases of RA in relatives of patients with disease with number of cases in general population. In these studies it was shown that relatives of patients with RA are at increased risk of getting the disease compared to general population. A study done by Thomas Friesel et al from Sweden showed that even though family history is an important risk factor,the presence of a positive family history has no relation to the clinical parameters or response to treatment.[6] Jiang et al in arthritis rheumatology concluded that family history of RA remains an important identifiable risk factor for development of RA and also proposed the need for further etiological studies for sero positive and sero negative RA[7]. There have been several studies on twins which had thrown more light on the genes that contributed to the risk of RA [8]

Identical twins were more likely to develop the disease than non identical twins. Heritability estimates of RA in different studies showed that it could be between 53 and 68 per cent suggesting that genetic factors could account for half of the disease susceptibility in these populations. Studies have been undertaken to identify the genes involved in RA. A recent genetic study have identified more than 100 genetic areas associated with RA.[8] Accordingly the largest risk factor for RA was identified to be HLA Class 2 region which encodes for HLADRD1 molecule. The largest genetic association with RA outside HLA region lies in the protein tyrosine phosphorylase non receptor 22 (PTPN 22).Mutations with PTPN 22 is also associated with other autoimmune conditions[9].

Environmental factors:

Even though there are a lot of studies linking RA to genetics it is also clear that it does not account for all of an individual's susceptibility to disease. Many patients do not have a family history at all and in them definitely environmental factors are playing a role. The identification of these environmental factors is important as necessary preventive strategies based on the avoidance of these risk factors would be helpful. It is likely that environmental factors trigger the autoimmunity in genetically predisposed individuals. A number of environmental risk factors have been implicated in the development of RA[10].

Smoking:

Smoking and infections are found to be the main environmental factors for the development of RA. Smoking is one of the most important environmental risk factor implicated in the development of RA.[11]A study conducted in the Swedish epidemiological investigation of RA showed that individuals who smoke and carry SE (HLA Shared Epitope)alleles are more prone to develop sero positive RA[12].

A study by Klareslog et al have shown that there are citrullinated proteins in the bronchioalveolar lavage of smokers that bring in the possibility of increased citrullination of proteins in the lung by smokers and this in the presence of HLA DRD1is believed to lead to the development of autoimmune reactions[13]. Heliövaara M et al described as early as in 1993 that smoking leads to severe RA with extra articular manifestations[14].

Infections:

Another important factor implicated in the etiology of rheumatoid arthritis is infections. The main infectious etiologies implicated include Epstein-Barr virus *(EBV),* Mycobacterium tuberculosis, Escherichia coli, Proteus mirabilis, retroviruses and parvovirus B19 [15.] This association with an infectious aetiology could be a part of molecular mimicry or the development of large quantity of antibodies to an infectious agent. But till date

no single infectious agent or environmental factor has been implicated in the development of RA[16].

Estimates of heritability suggest that genetic factors are responsible for only 50% of the risk of developing RA[17]. The rest 50% could be explained by genetic and environmental interactions. Environmental factors important in RA may act years before clinical disease becomes apparent. The RA associated auto antibodies, rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) may be present more than 10 years before the onset of clinical disease. This suggests that important environmental factors are acting years before disease onset.[18]

PATHOGENESIS

The synovial membrane in patients with RA is characterised by hyperplasia, increased vascularity and infiltrate of inflammatory cells primarily CD4 +T cells. In genetic studies rheumatoid arthritis is strongly linked to major histocompatibility class II antigens. The main function of HLA class II molecules is to present antigen peptides to CD4+Tcells which suggests that rheumatoid arthritis is caused by unidentified arthritogenic antigen. The antigen could either be an exogenous viral protein or an endogenous protein.[19]

Cellular mediators of inflammatory joint damage:

Antigen activated CD4 + T cells stimulate monocytes,macrophages and synovial fibroblasts to produce cytokines,interleukein 1 ,interleukin 6,TNF alpha and to secrete matrix metalloproteinases through cell surface signalling by means of CD 69,CD118 as well as through release of soluble mediators such as interferon gamma ,interleukin -17, interleukin- 1 etc.Activated Tcells also stimulate B cells through cell surface contact.[20]

The precise pathological role of rheumatoid factor is unknown but it may involve the activation of complement through the formation of immune complexes. The inflammatory process is located in the synovium and can affect many joints at the same time. The inflamed synovial tissue becomes invasive causing erosion of the bone around the joint. The inflammatory process involves subchondral bone and periarticular soft tissue often resulting in bursitis, ligamentitis, tenosynovitis. The structural damage that occurs is irreversible. Once it has occurred it creates favourable conditions for the development of osteoarthritis even if primary inflammation has subsided[21].

Rheumatoid factor:

It is an auto antibody. It is an immunoglobulin with IgG reactivity. The usual tests for RA detect only the IgM subtype. But RA factor can also be IgA or IgM. It is present in 75-80% of patients with RA. In the initial stages many patients my be rheumatoid factor negative but in due course of the illness many

of them will become positive. But rheumatoid factor is not specific for RA and it can be positive in SLE, idiopathic pulmonary fibrosis, psoriatic arthritis, chronic infections and chronic inflammation of any aetiology.[22]

Anti cyclic citrullinated peptide antibody:

The auto antibodies against citrullinated peptides in RA were described as early as 1970s.These are directed against citrullinated peptides and proteins. It has a sensitivity between 69and 77% and specificity between 87 and 93%.During inflammation arginine aminoacid residues may be converted to citrulline residues which can be detected as antigens by the immune system.[22] Anti CCP antibody appears early in disease and also predicts severe disease and irreversible damage.

Symptoms

The incidence of RA increases between 25 and 55yrs and then plateaus until 75 yrs of age. The most common earliest symptom is inflammatory joint pain which usually starts in small joints of hand. It usually starts as poly arthritis of small joints of hand thus distinguishing it from other inflammatory arthritis which usually cause mono or oligo arthritis. It also has a chronic and progressive course of more than 6 weeks and usually lasting months to years. Other reactive arthritis have a duration of less than six weeks. The articular involvement in RA is typically additive and finally becomes symmetrical. This helps to distinguish it from seronegative arthropathies[23].

In the initial stages RA shows preference for metacarpophalangeal joints and proximal interphalangeal joints. Towards the later stages it affects all the joints with the exception of thoracic and lumbosacral spine. Distal interphalangeal joints are rarely involved in RA. Flexor tendon tenosynovitis leading to trigger fingers is a frequent finding in RA. The initial inflammation is followed by progressive destruction of joints leading to irreversible damage. Subluxation of metacarpo phalangeal joint with subluxation of proximal phalanx to volar side will lead to ulnar deviation .Hyperextension of the proximal interphalangeal joint with flexion of distal interphalangeal joint will cause swan neck deformity while flexion of proximal interphalangeal joint with hyperextension of distal interphalangeal joint will lead to botounnaire deformity and subluxation of first MCP joint with hyper extension of the first interphalangeal joint will cause Z line deformity. Inflammation about the ulnar styloid and tenosynoitis of extensor carpiulnaris with subluxation of distal ulna will cause piano key movement of ulnar styloid. Chronic inflammation of ankle and mid tarsal regions may lead to flat feet. In established disease large joints maybe involved. Cervical spines are most commonly involved in RA and the Atlanto axial involvement can lead to compressive myelopathy. RA rarely affects thoracic and lumbar spines. Radiological abnormalities of temperomandibular joints is common inRA.[24]

Extraarticular manifestations of rheumatoid arthritis: These are more common in smokers and males. Almost all organ systems like

skin,lung,GIT,CNS ,kidneys can be involved in RA.It is more common in patients with active disease and rheumatoid factor positivity.

Skin manifestations:

The most common skin manifestations are rheumatoid nodules but vasculitis ascociated manifestations like splinter haemorrhages,leg ulcers etc are also seen although less common.

Ocular manifestations:

The most common ocular manifestations include keratoconjuctivits sicca ascociated with secondary sjogrens syndrome.Episcleritis and scleritis my be seen in less than 1 % of patients.[25.]

Pulmonary

Pleuritis is the most common pulmonary manifestation.Exudative pleural effusions are also common. Presence of dry cough and interstitial lung disease may suggest the development of ILD. ILD is most commonly seen in cigarette smokers and patients with higher disease activity, solitary or multiple pulmonary nodules may also be seen.[26]

Cardiac

Pericardium is most commonly involved. But clinically manifesting pericarditis occurs in less than 10% of patients.Cardiomyopathy can occur in RA due to necrotising or granulomatous myocarditis, coronary artery disease,

or diastolic dysfunction. Rarely rheumatoid nodules may be seen in heart muscle.[27]

Vasculitis:

This can be seen in longstanding severe RA.But there has been a decrease in incidence recently. The presence of petechiae,purpurae,digital infarct,gangrene,livedoreticularis etc may suggest vasculitis.[28]

Hematological abnormalities:

The most common hematological abnormality is normo chromic normocytic anemia.The degree of anemia correlate with titres of CRP and ESR[29].Iron deficiency anemia,haemolytic anemia and anemia due to bonemarrow aplasia are also seen in RA.The other abnormalities noted is thrombocytosis and sometimes mild leukocytosis.There is found to be an increased incidence of lymphoproliferative diseases like non hodgkins lymphoma.

Systemic manifestations:

Constitutional symptoms are rare in RA, if they are present a search for chronic infections is mandatory. The most common constitutional symptoms include low grade fever, weight loss, fatigue, malaise and depression In severe forms of RA in the initial stages may be associated with fever weight loss and

other systemic symptoms. Rheumatoid nodules may be seen in some of the patients.

LABORATRY INVESTIGATIONS IN RA

The diagnosis of rheumatoid arthritis is mainly clinical. But certain investigations may help us in arriving at a diagnosis of RA. There may be hypochromic microcytic anaemia or anaemia of chronic disease.ESR may be very high in active rheumatoid arthritis. Investigations are mostly to look for alternative causes for the clinical picture. To differentiate RA from other connective tissue diseases ANA and ANA profile may be helpful. Two important investigations are rheumatoid factor and anti citrullinated cyclical peptide antibody which were discussed earlier.

Radiological investigations:

Like in any chronic inflammation radiography is rarely helpful in diagnosing rheumatoid arthritis. It can be useful in assessing the severity of the disease. Ultrasound and MRI are found to be superior to x-ray imaging. Ultrasound is mainly used for superficial and inflamed joints.MRI is considered to be the best radiological investigation for RA. In early disease MRI of hand joints is done and many MR imaging based disease activity scores are based on findings in wrist and hand joints[30]. In conventional radiography the most frequently involved joints and inflamed joints are assessed serially. Conventional radiology even though it has limitations in identifying early RA,

is still used as a research tool [31].The radiological findings include soft tissue swelling followed by juxta articular and generalised osteoporosis followed by joint space narrowing and marginal erosions.

DIAGNOSIS OF RHEUMATOID ARTHRITIS:

The 1987 Ameircan College of Rheumatology revised criteria for classifying rheumatoid arthritis was criticised a lot for it's lack of sensitivity[32]. So a new classification criteria was put forward by ACR /EULAR(American College of Rheumatology/European League Against Rheumatism). Which is used for early diagnosis and classification of rheumatoid arthritis. Accordinng to 2010 ACR EULAR classification for RA,definite RA is said to be present if there is synovitis in atleast one joint with absence of an alternative diagnosis for synovitis and if a total score of 6 can be obtained from individual score in four domains as mentioned below. The highest score achieved in a given domain is used for this calculation. These domains and their values are:

●Number and site of involved joints

•2 to 10 large joints (from among shoulders, elbows, hips, knees, and ankles) = 1 point

•1 to 3 small joints (from among the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists) = 2 points

•4 to 10 small joints = 3 points

•Greater than 10 joints (including at least 1 small joint) = 5 points

●Serological abnormality (rheumatoid factor or anti-citrullinated peptide/ protein antibody)

•Low positive (above the upper limit of normal [ULN]) = 2 points

•High positive (greater than three times the ULN) = 3 points

•Elevated acute phase response (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) above the ULN = 1 point

•Symptom duration at least six weeks = 1 point

In addition to those with the criteria above, which are best suited to patients with newly presenting disease, the following patients are classified as having RA:

- Patients with erosive disease typical of RA with a history compatible with prior fulfillment of the criteria above
- Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who have previously fulfilled the criteria above based upon retrospectively available data [33,34]

DISEASE ACTIVITY SCORES:

Disease Activity Score (DAS) is an assessment used by clinicians to measure rheumatoid arthritis (RA) disease activity, to determine whether the signs and symptoms have reduced or stopped, and if treatment needs to be adjusted. The DAS (disease activity score)includes the Ritchie Articular Index (RAI); a 44-joint swollen joint count ,erythrocyte sedimentation rate (ESR), and a general health assessment on a visual analog scale[34.1 35]

But it is difficult ot assess all the forty four joints during OP visits. Hence DAS28 came in to vogue which assessed only 28 joints. The DAS is most easily calculated using a programmed calculator or a computer. Online and downloadable calculators are freely available at http://www.das-score.nl.It showed a high predictive ability in distinguishing active RA from disease in remission.DAS 28correlated well with disease activity using a health assessment questionnaire(HAQ).A DAS 28 score of >5.2 indicate severe RA,3.2-5.2 indicate moderate disease activity and less than 3.2 indicate mild disease activity. DAS28 of 2.6 corresponds with being in remission according to the ARA criteria. A change of 1.2 (2 times the measurement error) in DAS28 is considered a meaningful change because changes that large are unlikely to be the result of random measurement error (P value 0.05). The EULAR response criteria classify patients as good, moderate, or non-responders, using the change inDAS28 and the level of DAS28 reached [**34.2 36**]

RAPID ASSESSMENT OF DISEASEACTIVITY IN RHEUMATOLOGY (RADAR):

It is a self administered questionnaire of disease symptoms in RA. The RADAR contains 6 items, global disease activity in the past 6 months; current disease activity in terms of joint tenderness and swelling; arthritis pain; duration of morning stiffness; functional class; tender joint Scale.

RADAR scores can range from 0 to 100 or 0 to 10 for comparison purposes. A total score is not provided. Good response is a 25%change or a score change by 3 points.

RHEUMATOID ARTHRITIS DISEASEACTIVITY INDEX (RADAI):

It is a measure for disease activity assessed by patient. It is a 5-item questionnaire which asks the patient about global disease activity in the past 6 months, current disease activity in terms of swollen and tender joints, arthritis pain, the duration of morning stiffness, and tender joints to be rated in a list of joints.

Vitamin D metabolism:

Vitamin D is a fat soluble vitamin obtained partially from food (vegetarian and non vegetarian diet) and partially from endogenous synthesis on exposure of skin to ultraviolet B light. It is known from historical times about the role of Vitamin D in bone growth and mineralisation. Recent

evidence has witnessed the emergence of importance of Vitamin D in other aspects of homeostasis and pathogenesis of diseases[37]

Vitamin D, synthesised in the skin or absorbed from the diet, enters into the circulation and hydroxylated at 25th position from the liver by 25 hydroxylase enzyme to form 25-hydroxycholecalciferol. 25-hydroxy D3 is the major circulating and storage form of vitamin D. Approximately 88% of the 25-hydroxyD3 circulate bound to vitamin D binding protein, 0.03% is free and the rest is bound to albumin. Its half life is about 2 to 3 weeks. Further hydroxylation occurs mainly in the kidneys with the help of 1 alpha hydroxylase enzyme to form 1,25dihydroxycholecalciferol. It is the rate limiting step in vitaminD metabolism. This step is activated by calcium / vitamin D deficiency and PTH and inhibited by 1,25- dihydroxy vitamin D. 1,25-dihydroxy vitamin D is also called calcitriol because of 3 hydroxyl bond at 1 , 3 and 25 position. Its half-life is 6 to 8 hours[38]. 1 alpha hydroxylase enzyme is also present in other tissues such as osteoclasts, skin, colon, brain, and macrophages, which may be the cause for it's beneficial effects at various extra–skeletal sites. Calcitriol binds to cytoplasmic Vitamin D receptor

Actions of calcitriol :Calcitriol enhance the absorption of calcium and phosphate from the intestine and tubular reabsorption of calcium and phosphate from the kidney. It also stimulates bone osteoblasts to release RANKL(Receptor Activator of Nuclear Factor κ B Ligand) that stimulate osteoclasts, which release calcium from bone .

Vitamin D deficiency:

People develop vitamin D deficiency mainly due to poor intake of vitamin D containing foods. Most of the population do not take balanced diet and therefore do not get vitamin D through food[38] . Reduced exposure to sunlight may be another cause for vitamin D deficiency as a result of urbanisation and life style changes. Even when exposure to sunlight is adequate there may be decreased cutaneous synthesis of vitamin D because of the increased melanin content in the skin which interfere with ultraviolet ray mediated vitamin D synthesis. There could also be the possibility that decreased intake of vegetables and fruits may cause hypomagnesaemia which may cause reduced parathyroid hormone secretion and reduced 1 alpha hydroxylation of vitamin D hence reduced active form of vitamin D[38].

Diagnosis of Vitamin D deficiency :

Vitamin D deficiency is confirmed by measuring serum 25(OH)D3 level, and not by measurement of 1,25(OH)2D. Serum 25(OH) vitamin D3is a prohormone whose half life is 3 weeks making it the best indicator of vitamin D status. A cut off value of 30ng/ml is usually considered as an optimal vitamin D level based on the fact that this level of vitamin D suppresses parathyroid hormone synthesis(major stimulus for PTH secretion is low level of serum ionised calcium). But this cannot explain many situations where serum PTH are normal in spite of very low 25(OH)vitamin D levels and

vice versa. This could be due to Magnesium deficiency which might lead to reduced Parathyroid hormone (PTH) secretion and the consequent reduction of 1 hydroxylation of vitamin D,since PTH is needed for this step.. Also in puberty PTH levels are high[39]. This is to drive 1,25(OH)2D production and calcium absorption during periods of increased calcium demands during the growing stages. Another method of assessing the optimal value for vitamin d level is that level of serum 25(OH)vitamin D level where there is no incremental response in the level of 1,25(0H)2 vitamin D level after giving vitamin D3. More recently, the criterion for optimal vitamin D status has moved away from being defined as the 25(OH) D concentration needed to achieve skeletal health to that which demonstrates optimal benefits on nonskeletal health outcomes[39].

Role of Vitamin D in various diseases :

The discovery that activated dendritic cells can produce vitamin D suggests that vitamin D could have immunoregulatory properties. Vitamin D as already mentioned could also decrease TH1(T Helper cell) driven autoimmunity. One of the causes for low levels of vitamin D is decreased sunlight exposure and this could be the reason for latitude prevalence of autoimmune diseases[40].

Recently we are witnessing a lot of change in the understanding of health benefits of vitamin D. The Skeletal roles of vitamin D are well known.

But the non skeletal manifestations are becoming more manifest these days. It is these non skeletal manifestations that are gaining more and more attention. Vitamin D plays a role in many types of cancers, hypertension, autoimmune diseases, Diabetes Mellitus.

Vitamin D and Tuberculosis:

Vitamin D has got numerous functions in infections. Incidentally the deficiency of Vitamin D in Tuberculosis and its link to nutritional deficiency was first reported from our insitution[38]. The historical link between vitamin D and innate immune function stemmed initially from the use of cod liver oil as treatment for tuberculosis.

Proposed mechanism of interaction between Vitamin D and tuberculosis:

Mycobacterium tuberculosis antigens stimulate the toll like receptors on monocytes and macrophages causing an up regulation of vitamin D receptors[41]. Binding of 1,25(OH)2 D3 activates vitamin D receptors(VDRs) and induces cathelicidin mediated killing of Mycobacteria. Vitamin D inhibits lipopolysacharide(LPS)-induced p38 activation and cytokine production in monocytes/macrophages. This effect is enhanced by cytokine interferon gamma. Thus patients with deficiency of vitamin D will be less able to support monocyte induction of antibacterial activity. So they are at increased risk of infection. Even then whether adjuvant vitamin D therapy can be used in

tuberculosis is a question that remains unanswered. Further studies have to be done on this aspect[42] .

Vitamin D in diabetes mellitus[43]:

Vitamin D deficiency predisposes individuals to type 1 and type 2 diabetes as the receptors for its activated form—1α,25- dihydroxyvitamin D3(VDR)—have been identified in both beta cells and immune cells. Vitamin D deficiency leads to the impaired secretion of insulin—but not other islet hormones—in both animal models and humans, and this induces glucose intolerance while replenishment with vitamin D rectifies the abnormalities. This is probably due to direct effect of vitamin D deficiency on the beta cell. Several studies have shown that cod liver oil taken during the initial period of life reduced the incidence of type 1 diabetes mellitus.[44] Also the incidence of childhood diabetes was more common in patients with rickets. Many trials have shown that hypovitaminosis D leads to alterations in insulin secretion which is due to direct action of vitamin D rather than its effect on calcium metabolism. According to the NHANES(National Health And Nutrition Expansion Survey)data, serum 25-OHD concentration (after multivariate adjustment) was inversely associated with diabetes prevalence in a dose dependent pattern in non-Hispanic whites and Mexican americans[45]

Vitamin D deficiency and cardiovascular disease:

Vitamin D receptors are distributed in vascular smooth muscle, endothelium, and cardiomyocytes. Many recent trials suggests that vitamin D deficiency may adversely affect the cardiovascular system.Vitamin D deficiency was implicated in several types of vascular disease including peripheral artery disease (PAD), atherosclerosis, myocardial infarction, and ischemic stroke. Vitamin D in vitro suppresses renin expression. So absence of vitamin D receptor activation leads to chronic up-regulation of rennin-angiotensin system. Through interaction with the vitamin D receptor on the cardiac myocyte, 1, 25(OH) 2D regulates calcium influx into the cell, controls the amount of free cytosolic calcium available, thus modifying contractility of the heart, and controls cell growth and proliferation. This might be the pathophysiology in the link between vitamin D and heart failure . Immune system activation has been associated with atherosclerotic and valvular calcification, and plays a role in plaque instability and rupture. Therefore the immunoregulatory effects of vitamin D may play a role in atherosclerosis. But the current evidence does not support screening of patients with cardiovascular disease for vitamin D deficiency[46]. Vitamin D deficiency can also lead to hypertension and hence accelerate the atherosclerosis[39].

Vitamin D and Breast cancer[47]

Vitamin D has been found to have anticancer effects. Vitamin D deficiency has a role to play in breast cancer according to recent literature. Breast epithelial cells have been found to have same epithelial cells as kidneys. They can manufacture vitamin D from precursors. Vitamin D may help in inhibiting proliferation of cancer cells and also promote differentiation of these cells. The antiproliferating and pro-differentiating effect of vitamin D has been found to have inverse relationship between serum levels of 25(OH) vitamin D and the development of breast cancer, recurrence and mortality rate.

Vitamin D and Rheumatoid arthritis:

Vitamin D deficiency may be associated with an increased risk for the development of RA. Greater intake of vitamin D was found to be inversely associated with risk of RA. Several studies have evaluated the association between vitamin D levels and RA activity[48]. Vitamin D is known to induce immunologic tolerance. Vitamin D inhibits Bcell proliferation,blocks B cell differenciation and immunoglobulin secretion.It also suppresses T cell proliferation and causes shift from TH1 cells to TH2 cells.TH2 cells facilitate induction of T lymphocyte cells.This leads to decreased production of inflammatory cytokines. Vitamin D has immunomodulatory properties.. Vitamin D decrease antigen presentation, inhibits the pro inflammatory T helper cells, induces regulatory T cells. 1,25(OH)2D3 suppresses proliferation

and immunoglobulin production. 1,25(OH)2 D3 also suppresses differentiation of B-cell precursors into plasma cells. These data support a role for vitamin D deficiency in the development and progression of autoimmune inflammatory conditions like rheumatoid arthritis. But vitamin D may be negatively affected in acute response, that is, its levels may decrease in the setting of inflammation, such as in active RA. Supplementation with vitamin D has been proposed as a means to induce immune tolerance and thus prevent the development of autoimmune diseases[48]

There has been multiple trials showing that when compared to healthy controls patients with RA have low vitamin D levels. Recently a study conducted by Dr.Qiong Hong et al showed that patients with RA had significantly low levels of vitamin D when compared to controls and that vitamin D levels were negatively associated with the level of inflammatory markers like IL-17[49]. The influence of vitamin D on inflammatory cytokines may be the reason for increased disease activity seen in vitamin D deficient individuals. In a study published in JAPI by Rajeev et al it was found that patients with severe RA had significantly low levels of vitamin D and those patients with moderate disease activity had vitamin D insufficiency[50]. In a study by Gopinath et al from Vellore it was found that supplementation of 500 units 1, 25 OH 2 vitamin D 3 daily to new patients with early RA who have not been started on disease modifying anti rheumatoid drugs resulted in

significantly higher pain relief at the end of 3 months[51]. This again shows that vitamin D has an effect on disease severity in RA.

The present study was aimed at finding the key environmental factors that could play an etiological role in development of rheumatoid arthritis, and the most common clinical symptoms of rheumatoid arthritis and also to estimate the relationship between vitamin D level and disease activity in RA.

Materials & Methods

Study design

Prospective study

Period : 6 yrs from sept 2011-aug 2017

Centre : Rheumatology OP, Medicine OP, Department of Medicine wards

Sample size – 60 patients

Inclusion criteria:

All newly diagnosed patients with rheumatoid arthritis whose age is more than 18yrs diagnosed according to the new ACR-EULAR criteria.Age and sex matched controls were chosen from among patients realtives for assessing vitamin D levels and it was compared with that of patients.

Exclusion criteria:

- Patients with history suggestive of polyarthritis due to other causes including mixed connective tissue disorders
- Patients already on vitamin D supplementation.
- Patients with vitamin D deficiency due to other co morbid conditions like renal or liver diseases ,malabsorption or drug intake .
- Patients who have not given consent for the study.

Data collection:

After noting the preliminary data of the patient a complete history was taken which included the mode of onset, preceding history of infection, pattern of joint involvement, duration of symptoms, extra articular manifestations, past history, family history and personal history. The diagnosis of rheumatoid arthritis was made clinically and using the ACR-EULAR criteria. The criteria rates the patients on a scale of 0-10 points with points assigned in for separate domains of signs and symptoms, joint involvement,serology,duration of symptoms, and acute phase reactants. Patients who tally 6 or more points were considered to have definite RA.

A complete general examination as well as detailed systemic examination was done in all the patients.A locomotr system examination was done to know the pattern of joint involvement and the presence of signs of inflammation.

Complete blood count, haemoglobin, ESR, urine routine, liver and renal function tests as well as fasting blood sugar were done in all the patients. Serum rheumatoid factor was done in all the patients. Anti CCP antibody was done in patients when indicated.

To assess the incidence and severity of vitaminD deficiency 25(OH) vitaminD levels were done by electrocheluminescent assay technique using vitamin D kits. To know the disease activity of patients and to correlate it with

vitamin D deficiency the disease activity score(DAS28) was calculated online in all patiemts according to the formula DAS28(4) = 0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR) + 0.014*GH .DAS28(4)

Statistical analysis: The data was analyzed using SPSS software and conclusions were reached. The statistical significance of different variables were assessed using chi square test.

Variables studied:

There were sociodemographic variables like age,sex,smoking history, pattern of diet etc.Clinical variables like duration of disease, clinical manifestations, pattern of joint involvement, extra articular manifestations and also serum 25(OH)vitamin D level and comparison with disease activity measured using DAS 28 score.

Statistical analysis:

Interpretation of results were done by another person who did not know the final results of previous studies. The significance of the mode of onset,sex difference ,effect of smoking, the presence of extraarticular manifestations and the severity of disease as well as its relation to vitamin D level was studied using appropriate statistical tests. Here we used SPSS package for statistical analysis.

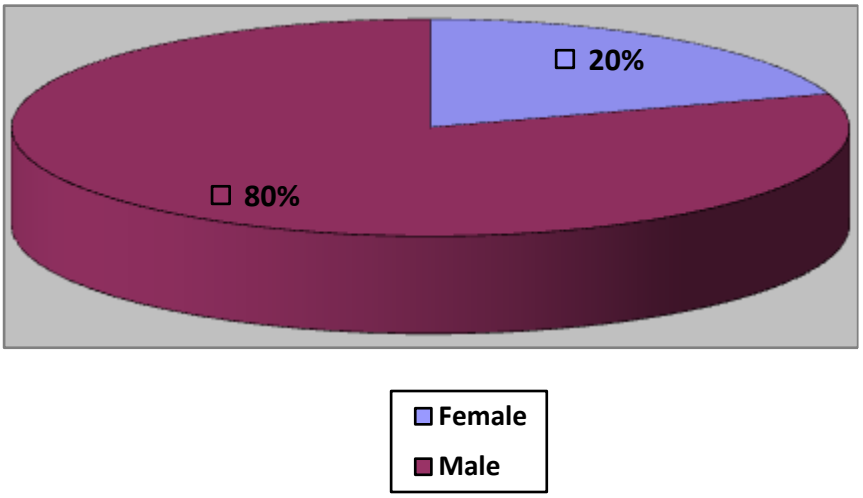
Observations:

Gender distribution:

There were a total of 60 cases (48 females and 12 males) and same number of age and sex matched controls were taken (Fig 5.1).The controls were healthy bystanders of the patients who did not have diabetes hypertension or other comorbidities. The male : female ratio is 1:4.

Fig :5. 1

Gender Distribution

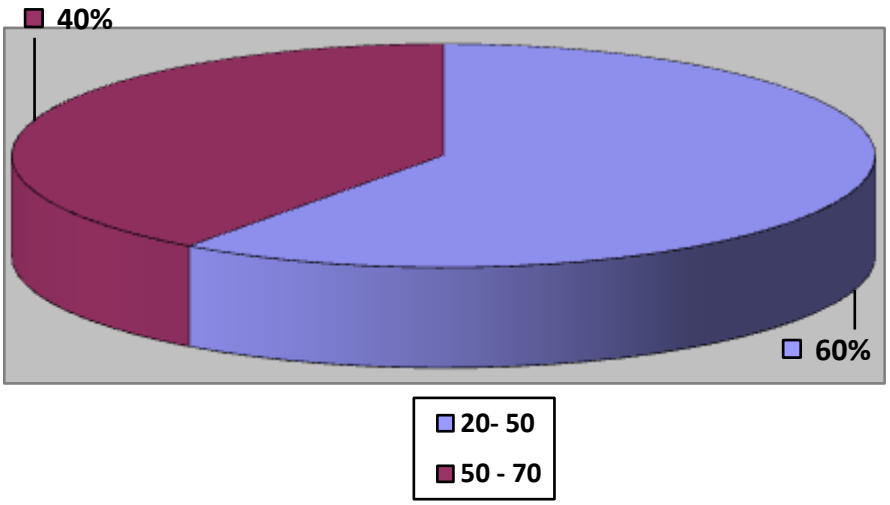


Age distribution:

The mean age of the cases was 48.38 yrs and that of controls were 48.35 yrs the difference being not statistically significant. The majority of cases were in the 20-50 age group60%(36) and the rest(24patients) were in 50 to 70 age group(fig 5:2).

Fig :5. 2

Age Distribution



Family History:

No family history of consanguinity was seen in any of the patients. Also there were no first and second degree relatives of patients with RA.

Dietetic history:

The dietary pattern of the patients and controls were studied to know the link between any particular dietary pattern and the rheumatoid arthritis. All the patients were taking a mixed diet. None of them were taking a pure vegetarian diet and none of them were having food faddism.

Addictions:

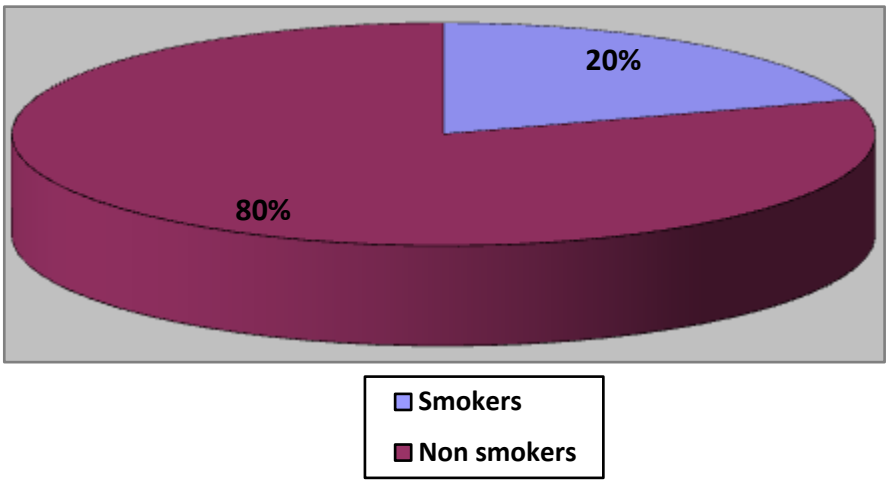
Smoking has been seen to increase the incidence of rheumatoid arthritis. But in our study group majority 80%(48 out of 60 pts)were females who were non smokers. All the 12 males were smokers.(Table 5.1 & Fig 5:3)

Table 5.1 : Smoking Vs RA

	Duration of smoking	
Severity of RA	**< = 20 years**	**> 20years**
mild	4	0
moderate	4	0
severe	1	3

Fig :5. 3

Addictions



All the 12 males with RA (100%) were smokers. Of them 3 who had duration of smoking >20 pack yrs had severe RA(Fig 5.4)

Fig :5. 4

Smokers with duration less than 20pack yrs only 1 had severe RA

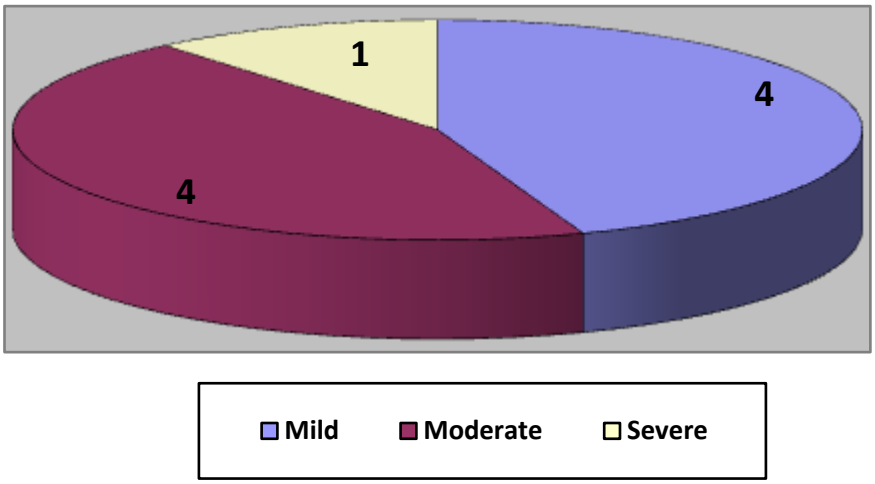
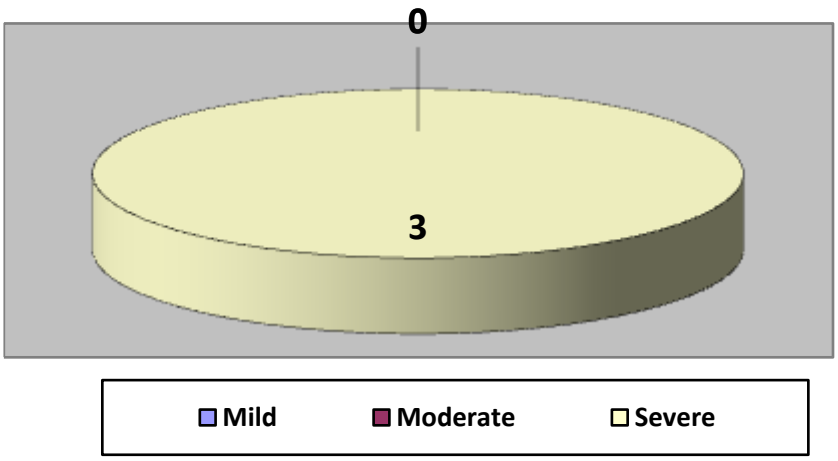


Fig :5. 5

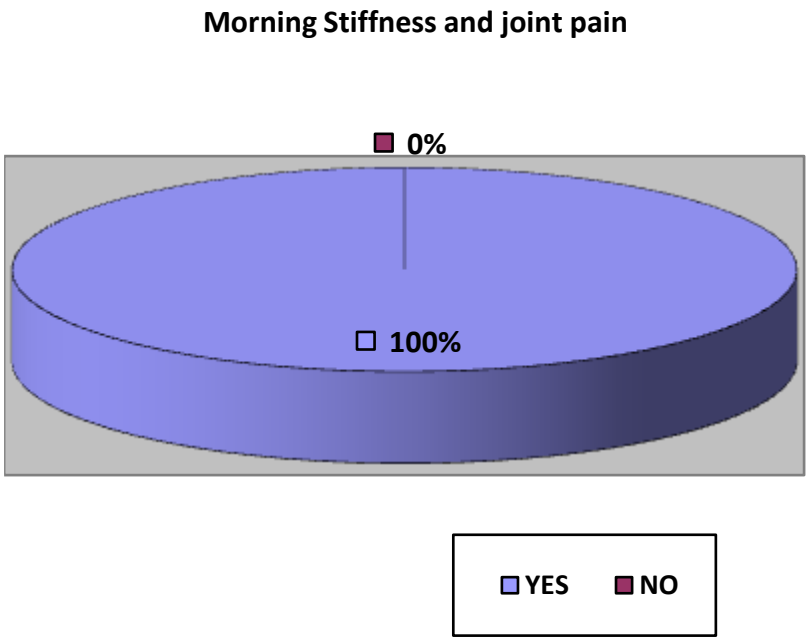
All smokers with duration >20 pack yrs had severe RA.



Clinical presentation

In our present study the major clinical feature was pain in the joints which was seen in all of patients and morning stiffness which was also seen in all the patients.(Fig 5.6)

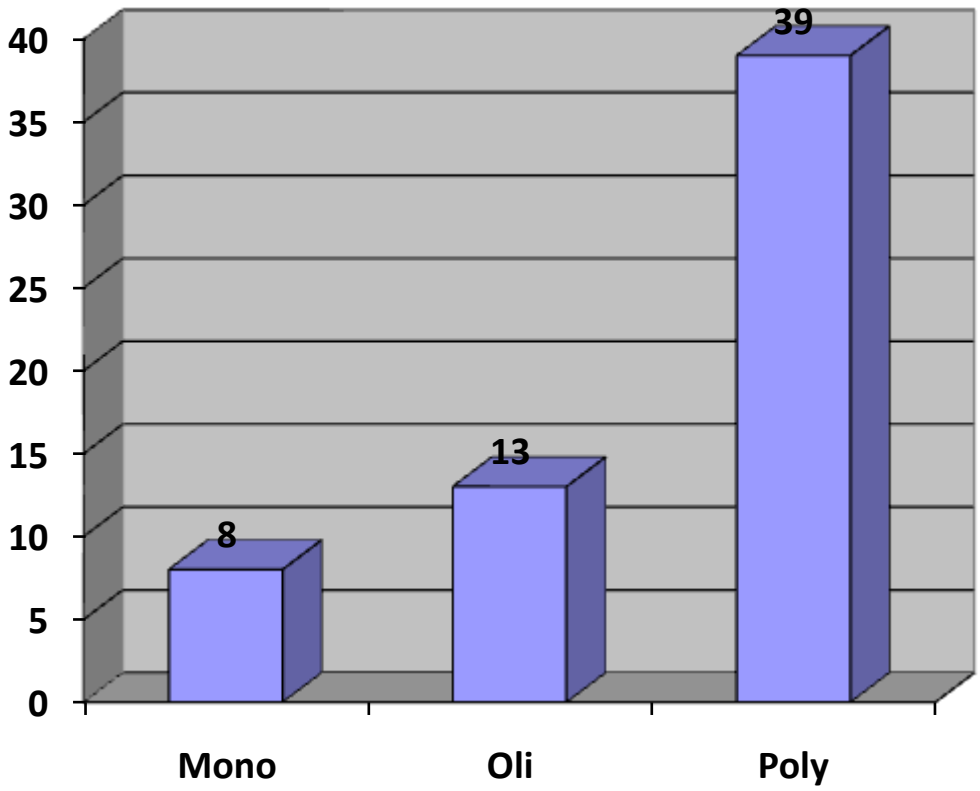
Fig : 5.6



39 Of the 60 patients (65%) presented as polyarthritis.13 patients(21.7%) presented as oligoarthritis and it was striking that 8 patients(13.3%)presented as monoarthritis.(Fig 5.7)

Fig : 5.7

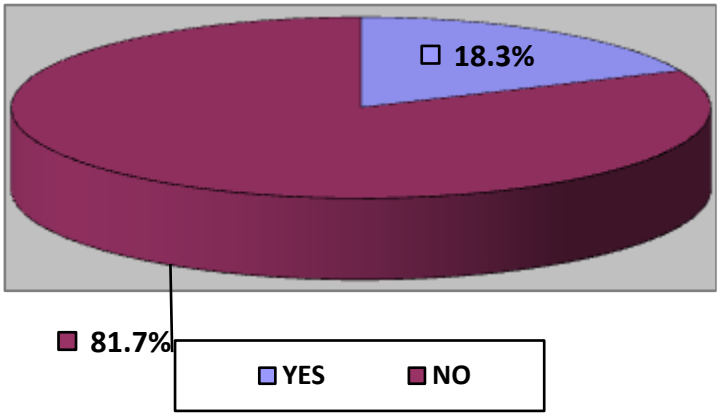
Mode of presentation



On general examination rheumatoid nodules were present in 11of the patients(18.3%).

Fig : 5.8

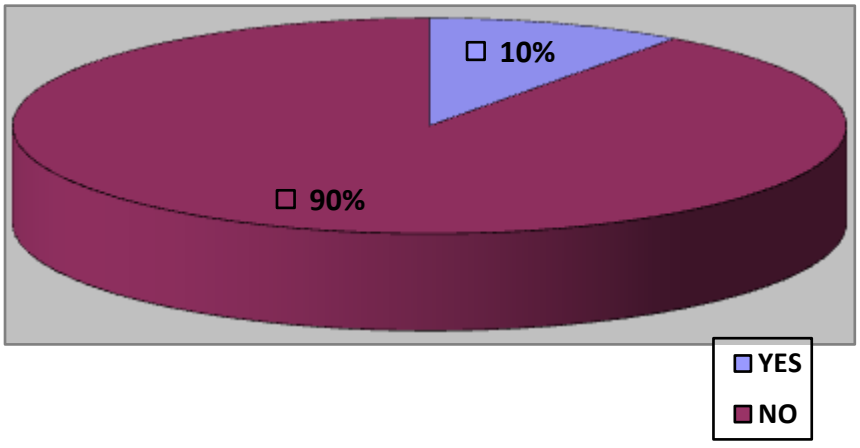
Presence of rheumatoid nodule



Sicca complex in the form of dry eyes were seen in 6 patients(10%).

Fig : 5.9

Dry Eyes



:

The commonest joint involved was proximal interphalyngeal and metacarpophalyngeal joint(82%). The joint deformities noted were boutonnaire deformity in 10%ie 6 patients, ulnar deviation in 12cases(20%). . The lower limb deformities were plantar subluxation of metatarsal heads in 3 patients(5%) of the patients and hallux valgus in 4cases(8%).

Table : 5.2

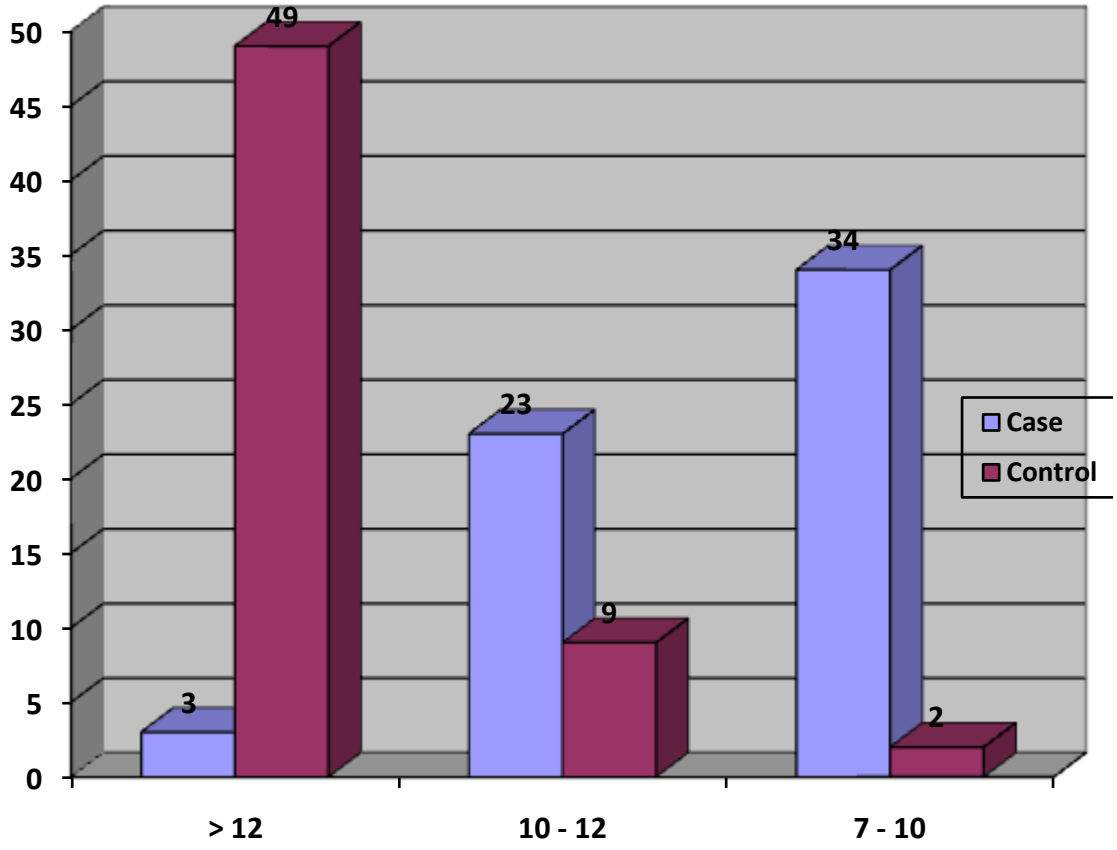
Clinical profile of patients with RA

Clinical profile	**% of patients**
Joint pain	100%
Joint stiffness	100%
Joint swelling	100%
Rheumatoid nodule	18,33%
Dry eyes	11%

Haemoglobin values:

The mean hemoglobin level was 9.88gm% in cases and12.14gm% in controls, the difference being statistically significant with a p value of 0.001. The anemia was further evaluated and 38 patients were having hypochromic microcytic anemia and rest was normochromic normocytic anemia. Among the patients 56.7%(34 number) had a very low haemoglobin below 10gm% where as 81.7% (49) controls had a normal haemoglobin above 12gm%(Fig 5.10).

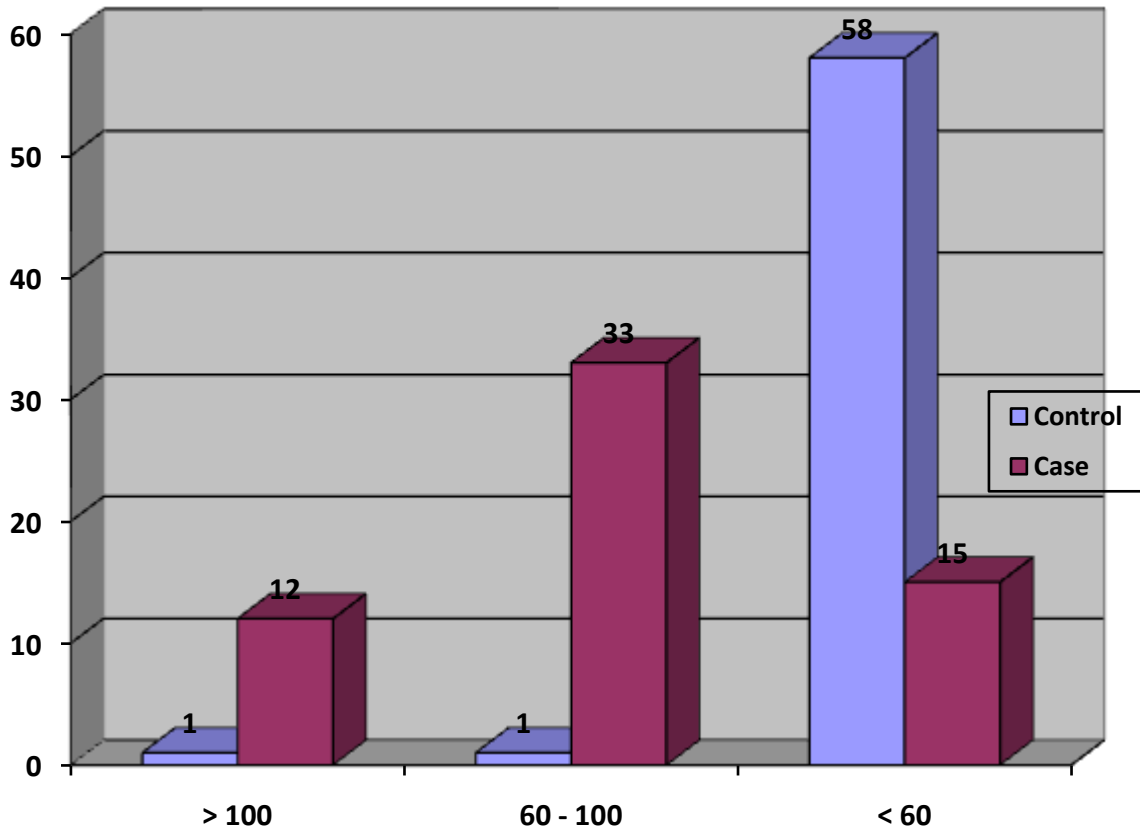
Fig: 5.10
Hb level



ESR values:

The mean ESR was 81.70mm/hr in cases and 29.70mm/hr in controls the difference being statistically significant with a p value of <0.0001. A very high ESR of >100mm/hr was seen in 12 patients and only 1 control. An ESR between 60 and 100 mm/hr was seen in 33 patients and1 control, while a low ESR of less than 60mm/hr was seen in 15 patients and 58 controls.

Fig. 5.11
ESR in in mm/hr

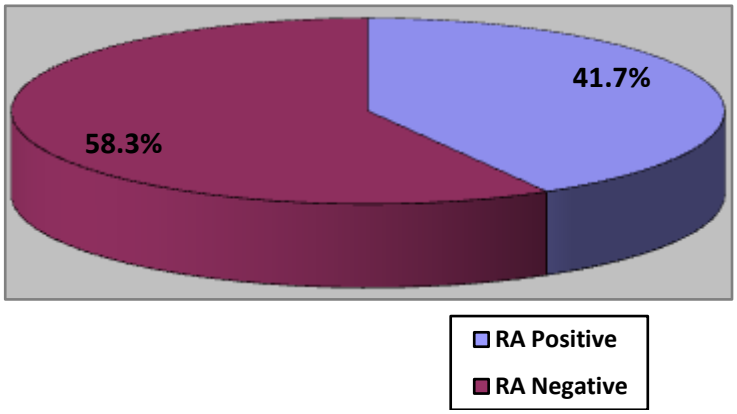


Rheumatoid factor:

The serum rheumatoid factor was positive in 41.7% (25 out of 60)patients. But it had no correlation with severity as assessed by DAS score. All the 12 males who were smokers had a positive rheumatoid factor (Fig. 5.12)

Fig. 5.12

Percentage of patients with Rheumatoid factor positivity



Anti CCP (cyclical citrullinated peptide):

Anti CCP ab was done only in patients who were negative for rheumatoid factor.Out of 35 patients in who it was done anti CCP antibody was positive in 20 patients .

Radiological findings:

The commonest radiological abnormality noted was soft tissue swelling 82%(48 patients) followed by periarticular osteopenia in 44 cases (74%) .

Table : 5.3

Radiological findings:

Radiological findings	**% of patients**
Soft tissue swelling	**82%**
Periarticular osteopenia	**44%**

DAS score:

The severity of the rheumatoid arthritis was assessed using DAS 28 score. Das score of >5.2 was seen in 9 patients(16%) indicating severe rheumatoid arthritis and DAS score of 3.2 -5.1 was seen in 51patients(85%).

Table : 5.4

DAS score

Das score	No. of patients
> 5.2	**9**
3.2 – 5.1	**51**

Vitamin D level:

Serum 25 (OH)vitamin D level was done in all patients and controls. The mean vitamin D level was 15.8ng/dl in cases and 21.54ng/dl in controls the difference of which was statistically significant (P value < 0.0001). This Shows that patients with RA has significantly low vitamin D levels when compared with age and sex matched controls.(table5.3).

Table 5.5

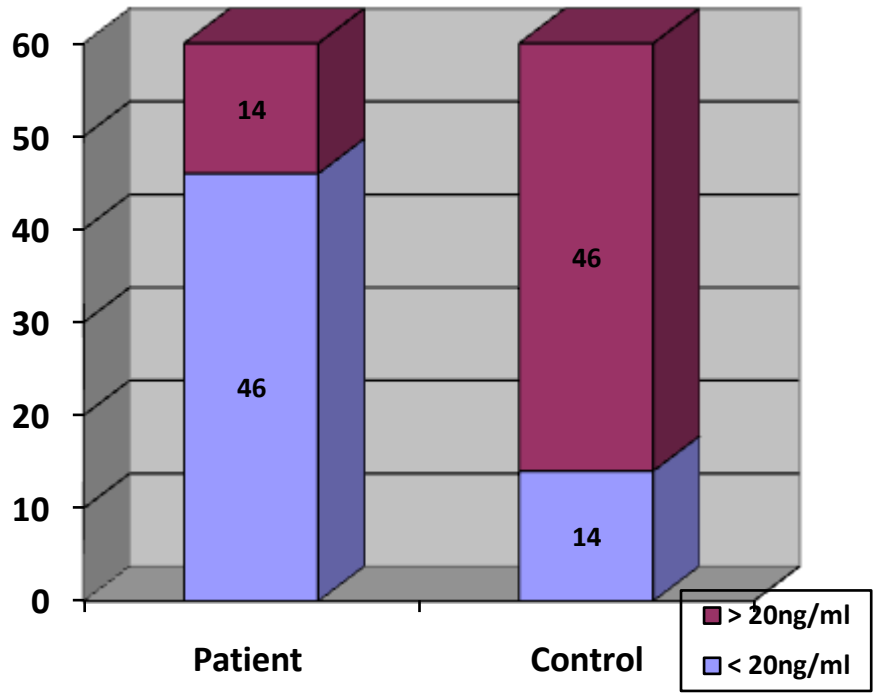
Comparison of average Vitamin D level in cases and controls

Average Vit D level in patients	Average Vit D level in controls
15.8ng/dl	21.54ng/dl

Among the patients 46 (76.7%) had serum vitamin D level below 20ng/ml(severe vitamin D deficiency). But only 16 controls(26.7%) had vitamin D level below 20ng/ml. The differences being statistically significant. It is notable that 44 controls (73.3%) also had only moderate Vitamn D deficiency (20-30ng/ml)while majority of the patients had severe vitamin deficiency. But none of the controls had vitamin D level >30 ng/ml(Fig.5.13)

Fig. 5.13

Comparison between the Vitamin D levels of patients and controls



Of the 9 patients who had severe rheumatoid arthritis with a DAS score of >5.2, all of them had severe vitamin D deficiency of <10ng/dl indicating that

severe vitamin D deficiency is seen in patients with severe rheumatoid arthritis and it is statistically significant (P=<.0001) (Table-5.6).

Table5.6

Serum Vitamin D level and association with severity

DAS score	Serum Vit D level (ng/ml)		
	< 20	**20 - 30**	**> 30**
3.2 – 5.1	38	11	2
> 5.2	8	1	0

Fig. 5.14 : Serum Vitamin D level and association with severity

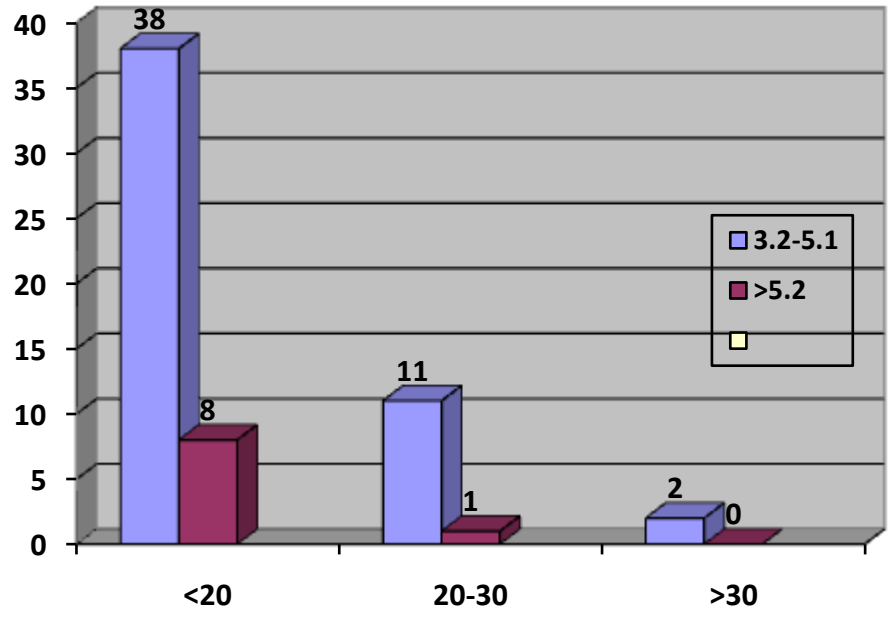


Table 5.7

Comparison of different variables between cases and controls:

Group Statistics

	Case	N	Mean	Std. Deviation	P value
Age	**Case**	60	48.38	10.55	
	Control	60	48.55	9.53	0.93
CBC	**Case**	60	9.88	1.31	
	Control	60	12.14	.66	<0.0001*
Vit D level	**Case**	60	15.8	6.58	
	Control	60	21.54	2.62	<0.0001*
ESR	**Case**	60	81.70	25.91	
	Control	60	29.70	14.21	<0.0001*

Discussion:

In the present study which included 60 patients majority were females. It is a frequently noted finding that most autoimmune diseases are more commonly seen in females. The most important cause for this is thought to be the sex hormonal influences. It is believed that cross talk between toll like receptors (TLR4) and T cell immunoglobulin signalling determines the severity of inflammation and it is found that it is more in females and that could be one reason why autoimmune diseases are more common in females[52].

Most of the patients were in the 20 to 50 age group. This is in accordance with most of the studies on clinical profile of rheumatoid arthritis. The study by Pradnya M Diggikar et al and many others show similar age wise distribution of cases of rheumatoid arthritis. Ester E Pensegra who studied 260 philippino patients also found that mean age of the patients were about 44 yrs[53].

In the present study there were no cases with a positive family history. This shows that environmental factors must be playing a major role in the development of RA. Some studies done before had shown that the risk of developing rheumatoid arthritis is four times higher in first degree relatives of affected patients compared to those who do not have affected first degree relatives[54]. In a study of 303 first degree relatives of RA patients Smolik et al found that first degree relatives of rheumatoid patients had more chances of joint symptoms than those having no family history[55]. This could suggest that there is a possible genetic influences on the development of rheumatoid arthritis.The results of the present study are in contrast to most of the previous

studies which have proven a strong familial history in RA patients. Even such familial occurrence could be due to sharing the same diet, lifestyle and environment.

Diet is not a well studied topic in rheumatoid arthritis. The effect of fasting followed by a one year vegetarian diet trial was done by J Kjeldsen-Kraghet al and it was found that there was a significant improvement in number of tender joints, Ritchie's articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, erythrocyte sedimentation rate, C-reactive protein, white blood cell count, and a health assessment questionnaire score[56.] In the present study all the patients were taking a mixed diet while two controls were pure vegetarians but no significant relation could be found between specific diet and the onset of symptoms. But a detailed study on diet was not attempted in the patients and that is an important shortcoming of the study.Hence no definite conclusion between diet, vitaminD level and disease activity could be reached.

All the males ie (20%)(12)were smokers .Of them three who had duration of smoking>20 yrs had severe RA. 11 males who were smokers also had positive rheumatoid factor. Severe smoking is associated with more severe RA [57]. Of the 12 males all the three males who had a smoking history of more than 20 yrs had more severe RA. Stroll p et al after a population based case control study on incident cases propsed that smokers among both sexes had high incidence of sero positive RA [58.]Hellovara et al after studying a cohort of

adult Finns propsed that smoking may trigger the production of rheumatoid factor and subsequent development of RA[59].

The most important clinical feature was pain in joints which was seen in 100% of patients followed by morning stiffness which was also seen in 100% of patients. This is similar to most of the other studies. 65% (39) of the patients presented as polyarthritis which is the most described presentation of rheumatoid arthritis . Oligoarthritis was seen in 27% patients.. Grassi et al reported that the commonest triad of symptoms includes pain in the joint, joint swelling and motion impairment[60.] But it was striking that 8(13.3%) patients presented as monoarthritis. Suresh et al describes monoarthritis as a mode of presentation in rheumatoid arthritis[61]. In such cases a complete history along with relevant investigations are needed to make a diagnosis. Hand joints were the most common joints involved in rheumatoid arthritis. Pradnya M et al reports proximal interphalangeal joimts and metacarpophalangeal joint as the most common joints involved in rheumatoid arthritis[23]. Jacoby et al also reported that in their study on 100 patients, the most commonly involved joints were metacarpophalangeal joints , wrist joint, and proximal interphalangeal joints[62].

In the present study 11(18.4%)of the patients had rheumatoid nodules and it was the most common extraarticular manifestation. Manoel Barros Bertolob Mario do et al also reported that the incidence of rheumatoid nodules as19.4%[63 .] In Turkey a single centre study done by calguer et al found

rheumatoid nodule as the most common extraarticular manifestation[64.]. Sicca complex was seen in 6% of our patients which is much less than that reported by Drosso et al which is 49%[65]. .Extra articular manifestations are less common in the study population.

Anemia with a haemoglobin level of <10gm%was seen in majority of the cases 34 (56.7%) patients when compared to controls (2 patients/3.3%). The most common type of anemia was hypochromic microcytic anemia followed by normocytic normochromic anemia. None of the patients had macrocytic anemia even though almost all of them were on methotrexate.There has been many studies on the hemetological abnormalities in RA and it has be found that anemia is the most common.The most common cause of anemia is anemia of chronic disease followed by iron deficiency anemia,and less common causes like haemolytic anemia and anemia of chronic disease[66].Here a detailed study of anemia was not done except for a peripheral smear.

Elevated ESR which is a marker of inflammation was seen in almost all the patients. . A very high ESR of >100mm/hr was seen in 12 patients and only 1 control. An ESR between 60 and 100 mm/hr was seen in 33 patients and1 control, while a low ESR of less than 60mm/hr was seen in 15 patients and 58 controls.

Majority of the controls (58 out of 60)were having a low ESR od <60mm/hr.ESR is an age old marker of inflammation whose estimation is

cheap and easily available. An elevated ESR strongly correlates with active disease as indicated by the relationship between ESR and DAS score. Even though there are more and more newer inflammatory markers and many trials have shown a poor correlation between ESR and disease activity ESR may still be used as an inflammatory marker in resource poor settings[67].

Rheumatoid factor is one of the most important investigatory finding in rheumatoid arthritis. It was positive in 35 (58.3%) patients. All the 12 males who were smokers had a positive rheumatoid factor. Akil et al have reported that 80% of patients with rheumatoid arthritis are seropositive for rheumatoid factor[68] but our study reports are similar to reports by Veeparen et al who states that positive RF rates are 65%, 62%, and 60% in English, Malaysian and Kuwaiti patients, respectively.[69]

X-ray of the involved joints were taken in all the patients and it was noted that the commonest radiological abnormality noted was soft tissue swelling 82%(48 patients) followed by periarticular osteopenia in 44 cases (74%) .All the patients were in the initial stages of RA and none of them had duration more than 2 years. X-ray cannot detect early RA. But more advanced imaging methods like MRI and ultrasound could not be used in patients due to financial limitations. Joint erosions are one of the late markers of RA. As such radilogical imaging has no role in diagnosis of RA, because mostly it is a clinical diagnosis[70].

Serum 25 dihydroxy vitamin D level was done in all patients and in age and sex matched controls. Vitamin D deficiency was defined as 25(OH)vitamin D level below 20 ng/ml, vitamin D insufficiency was defined as 25 (OH) vitamin D level 20-30 ng/ml and vitamin D sufficiency was defined as 25 (OH) vitamin D level 30-100 ng/ ml[71]. It was found that 45 cases (76%) had vitamin D level below 20ng/ml whereas only 9 (16%)of the controls had a serum vitamin D level below 20ng/ml, the difference being statistically significant. Majority of the controls 73.3 %(44) also had vitamin D level in the moderate deficiency range of 20-30ng/ml while only 16 (26.7%)) had vitamin D level below 20ng/ml . Neither the control nor the the cases had vitamin D level >30ng/ml.This is similar to the findings by P.K.Saisdaran et al which also found that there was widely prevalent vitamin D deficiency in Indian population[38]. Vitmain D is a fat soluble vitamin. It is obtained from diet and is also synthesised by the action of UV rays on the skin. Vitmin D has an effect on immunity due to its action on dendrtic cells and T helper cells[72]. It is believed to play a role in many autoimmune diseases due to its immunomodulatory properties. Vitamin D deificeincy is seen in majority of people in developing countries like India appears to be due to lack of balanced diet rather than decreased exposure to sunlight[38].

85%(51) patients had moderately severe RA based on DAS 28 score (3.2-5.1). and 15%(9) patients had very severe RA with a DAS score of >5.2. 74.5%(38)patients with moderately severe RA had severe vitamin D deficiency

(<20ng/ml). But it was striking that all the 9 patients who had very severe RA also had very severe vitamin D deficiency of <10ng/ml which is statistically significant. Rajeev Sharma et al reports that patients with high disease activity had significantly lower vitamin D levels in comparison to patients with low or moderate disease activity[73]. This result is comparable to our study where also it is found that even though vitamin D deficiency is common in general population.Patients with high disease activity had more severe vitamin D deficiency than patients with moderate disease activity. Low levels of vitamin D have been implicated in the etiology of RA. Also it was found that mean serum vitamin D levels in the patient population was significantly less when compared to controls.In contrast to the present study Rossini et al in a study published in 2010 found that vitamin D deficiency was equally common in both patients and controls[74].But most of the studies have found a negative correlation between vitamin D deficiency and severe RA[75].

Conclusions

- Rheumatoid arthritis is predominantly seen in females
- Environmanetal factors are more important than genetic factors in causing the disease, positive family history was absent in the study population
- Smoking could play an etiological role in development of disease and chronic smokers have severe rheumatoid arthritis.
- Rheumatoid factor need not be positive in all the patients and its positivity does not correlate with the severity of the disease
- ESR level correlates with disease severity
- Vitamin D levels are significantly lower in patients with RA as compared to the controls.
- Severe Vitamin D deficiency is associated with high disease activity
- Vitamin D deficiency is common in general population also
- The most common symptoms is pain and joint stiffness
- The most common joint involved is hand joints
- The most common extra articular manifestation is rheumatoid nodule.
- Anemia is the most common hematological manifestation

Limitations

- The sample size was small to arrive at statistically significant conclusions.

- The diet which plays a major aetiological role in rheumatoid arthritis as well as vitamin D deficiency was not studied in detail.

- The various parameters which affect serum vitamin D level was not studied in detail.

References

1. Majithia V, Geraci SA,"Rheumatoid arthritis: diagnosis and management". (2007). *Am. J. Med.* 120 (11): 936–9.
2. Smolen JS[1], Aletaha D[2], McInnes IB[3]. Rheumatoid arthritis.Lancet. 2016 Oct 22;388(10055):2023-2038.
3. Rossini M et al, Regional differences of vitamin D deficiency in rheumatoid arthritis patients in Italy ,2013 Jul 23; reumatismo.65(3):113-20
4. Scott DL, Wolfe F, Huizinga TW "Rheumatoid arthritis". (Sep 25, 2010). *Lancet*. 376 (9746): 1094–108.
5. Malaviya AN[1], Kapoor SK, Singh RR, Kumar A, Pande, .Prevalence of rheumatoid arthritis in the adult Indian population, Rheumatol Int. 1993;13(4):131-4.
6. Frisell T et al,Does a family history of RA influence the clinical presentation and treatment response in RA?, 2016 *Annals of the rheumatic diseases 75(6):1120-5*
7. Jiang X[1], Frisell T, Askling J, Karlson EW, Klareskog L, Alfredsson L, Källberg H. To what extent is the familial risk of rheumatoid arthritis explained by established rheumatoid arthritis risk factors , Arthritis Rheumatol. 2015 Feb;67(2):352-62.
8. Järvinen P[1], Koskenvuo M, Koskimies S, Kotaniemi K, Aho K. Rheumatoid arthritis in identical twins: a clinical and immunogenetic study of eight concordant pairs derived from a nationwide twin panelScand J Rheumatol. 1991;20(3):159-64..

9. Vander Woude D, Alemayehu WG, Verduijn W, de Vries RR, Houwing-Duistermaat JJ, Huizinga TW, et al. Gene–environment interaction influences the reactivity of autoantibodies to citrullinated antigens in rheumatoid arthritis. Nat Genet. 2010;42(10):814–816.
10. Ruiz-Esquide V[1], Sanmartí R, Tobacco and other environmental risk factors in rheumatoid arthritis.Reumatol Clin. 2012 Nov-Dec;8(6):342-50.
11. Kathleen Chang et al,Smoking and Rheumatoid ArthritisInt J Mol Sci. 2014 Dec; 15(12): 22279–22295.
12. Jonas k. Eriksson, Martin Neovius, Sofia Ernestam, Staffan Lindblad, Julia F. Simard, and Johan Asklin,, American College of Rheumatology. Incidence of Rheumatoid Arthritis in Sweden: A Nationwide Population-Based Assessment of Incidence, Its Determinants, and Treatment Penetration ,Arthritis Care & Research Vol. 65, No. 6, June 2013, pp 870 – 878
13. . Klareskog L[1,] Catrina AI, Paget S Rheumatoid arthritis. 2009 Feb 21;373(9664):659-72.
14. Heliövaara M[1], Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis,J Rheumatol. 1993 Nov;20(11):1830-5..
15. Inman RD[1]. Infectious etiology of rheumatoid arthritis,Rheum Dis Clin North Am. 1991 Nov;17(4):859-70..
16. Wilder RL[1,] Crofford LJ Do infectious agents cause rheumatoid arthritis?. Clin Orthop Relat Res. 1991 Apr;(265):36-41.

17. Soumya Raychaudhuri et al, Recent advances in the genetics of rheumatoid arthritis Curr Opin Rheumatol. 2010 Mar; 22(2): 109– 18.
18. Plenge RM,. Rheumatoid arthritis genetics: 2009 update. Curr Rheumatol Rep2009;11:351-6.
19. Weyand CM[1], Goronzy JJ. Pathogenesis of rheumatoid arthritis, Med Clin North Am. 1997 Jan;81(1):29-55..
20. Iain B. McInnes, F.R.C.P., Ph.D., and Georg Schett, M.D,The Pathogenesis of Rheumatoid Arthritis . N Engl J Med 2011; 365:2205-2219
21. Hair MJ,et al. Features of the synovium of individuals at risk of developing rheumatoid arthritis: implications for understanding preclinical rheumatoid arthritis.de Arthritis Rheumatol. 2014;66(3):513.
22. Menard HA, Lapointe E, Rochdi MD, Zhou ZJ. Insights into rheumatoid arthritis derived from the Sa immune system. Arthritis Res2000;2:429–32.
23. Pradnya M Diggikar et al ,A Study on Clinical Profile of Patients Presenting with Rheumatoid Arthritis in a Tertiary Care Hospital of Pune City J Med Res. 2016; 6(2): 146-150
24. Akil M, Amos RS. ABC of rheumatology: Rheumatoid arthritis clinical features and diagnosis. BMJ 1995; 310 587- 90.
25. A E Voskuyl, M A Van de Laar, H J Moens, and J K Van der Korst

xtra-articular manifestations of rheumatoid arthritis: risk factors for serious gastrointestinal events. Ann Rheum Dis. 1993 November; 52(11): 771–775.

26. Marigliano B, Soriano A, Margiotta D, et al., Lung involvement in connective tissue diseases: a comprehensive review and a focus on rheumatoid arthritis. Autoimmun Rev 2013; 12: 1076–1084.
27. Wynne J, Braunwald E.,The cardiomyopathies ,Braunwald's Heart disease. 7th. Philadelphia: Saunders;2005. ; p. 1659-96.
28. Helllmann M, Jung N, Owczarczyk K, et al. Successful treatment of rheumatoid vasculitis-associated cutaneous ulcers using rituximab in two patients with rheumatoid arthritis. Rheumatology (Oxford) 2008; 47:929.
29. Reugdenhil G, Wognum AW, van Eijk HG, Swaak AJ. Anaemia in rheumatoid arthritis: the role of iron, vitamin B12, and folic acid deficiency, and erythropoietin responsiveness. Ann Rheum Dis 1990; 49:93.
30. York Kiat Tan, Imaging in rheumatoid arthritis,journal of clinical rheumatology, August 2011Volume 25, Issue 4, Pages 569–584
31. f Sommer OJ, Kladosek A, Weiler V et-al. Rheumatoid arthritis: a practical guide to state-of-the-art imaging, image interpretation, and clinical implications. Radiographics. 25 (2): 381-98.
32. Behzad Heidari, Rheumatoid Arthritis: Early diagnosis and treatment outcomes,Caspian J Intern Med. 2011 Winter; 2(1): 161–170.

33. Birch JT Jr, Bhattacharya S. Emerging trends in diagnosis and treatment of rheumatoid arthritis. Prim Care.2010;37:779–92.
34. Gossec L, Combescure C, Rincheval N, et al. Relative Clinical influence of Clinical, Laboratory, and Radiological Investigations in Early Arthritis on the Diagnosis of Rheumatoid Arthritis. Data from the French Early Arthritis Cohort ESPOIR. J Rheumatol. 2010;37:2486–92
35. Jaap Fransen,1 Gerold Stucki,2 and Piet L. C. M. van Riel1,Rheumatoid Arthritis MeasuresDisease Activity Score (DAS), Disease Activity Score-28 (DAS28), RapidAssessment of Disease Activity in Rheumatology (RADAR), and RheumatoidArthritis Disease Activity Index (RADAI), Arthritis & Rheumatism (Arthritis Care & Research)Vol. 49, No. 5S, October 15, 2003, pp S214 –S224
36. G Wells et al,Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate, Ann Rheum Dis. 2009 Jun; 68(6): 954–960.
37. Lee P, Vitamin D metabolism and deficiency in critical illness, Best Pract Res Clin Endocrinol Metab. 2011 Oct;25(5):769-81.
38. Sasidharan PK, Rajeev E, Vijayakumari V. Tuberculosis and vitamin D deficiency. J Assoc Physicians India 2002; 50:554-8.

39. Gagan Velayudhan, Sasidharan PK, Vitamin D status in Hypertension , American International Journal of Research in Formal, Applied & Natural Sciences, ISSN (Print): 2328-3777, ISSN (Online): 2328-3785, ISSN (CD-ROM): 2328-3793
40. Cantorna MT, Mahon BD: Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med229 :1136– 1142,2004
41. Nursyam EW, Amin Z, Rumende CM: The effect of vitamin D as supplementary treatment in patients with moderately advanced tuberculous lesion. Acta Med Indones38 :3– 5,2006
42. Martineau AR, Wilkinson RJ, Wilkinson KA et al: A single dose of vitamin D enhances immunity to mycobacteria.Am J Respir Crit Care Med176 :208– 213,2007
43. Chiu KC, Chu A, Go VL, Saad MF: Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr79 :820– 825,2004.
44. Hyppönen E, Läärä E, Reunanen A, Järvelin M-J, Virtanen SM: Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. Lancet358:1500– 1503,2001.
45. National Center for Health Statistics. National Health and Nutrition Examination Survey,2001–2006. Available from: http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.html. Accessed February 25, 2011.

46. Bucher HC, Cook RJ, Guyatt GH, Lang JD, Cook DJ, Hatala R, Hunt DL: Effects of dietary calcium supplementation on blood pressure: A meta-analysis of randomized controlled trials. JAMA275 :1016–1022,1996 .
47. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nature Reviews Cancer. 2007;7(9):684-700.
48. Andjelkovic1, J. Vojinovic3, N. Pejnovic2, BRIEF PAPER ON Disease modifying and immunomodulatory effects of high dose 1 (OH) D3 in rheumatoid arthritis patients ,J.Clinical and Experimental Rheumatology 1999; 17: 453-456.
49. Hong Q[1], Xu J[2], Xu S[3], Lian L[3], Zhang M[3], Ding C[4] Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis, Rheumatology (Oxford). 2014 Nov;53(11):1994-2001.
50. Rajeev *S*harma*et al Estimation of Vitamin D Levels in Rheumatoid Arthritis Patients and its Correlation with the Disease Activity.. JAPI 2011;59:706-70
51. Gopinath K[1], Danda D. Supplementation of 1,25 dihydroxy vitamin D3 in patients with treatment naive early rheumatoid arthritis: a randomised controlled trial,Int J Rheum Dis. 2011 Oct;14(4):332-9
52. Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J Autoimmun. 2007;28:1–6.

53. Penserga EG[1], Natividad TA[2], Salido ES[1]; RADAR Study Group, Clinicl profile of 266 Filipino patients with rheumatoid arthritis included in the rheumatoid arthritis database and registry (RADAR) of the Philippine General Hospital,Int J Rheum Dis. 2015 May;18(4):433-8.
54. Frisell T[1], Saevarsdottir S[2], Askling J[3] Does a family history of RA influence the clinical presentation and treatment response in RA? Ann Rheum Dis. 2016 Jun;75(6):1120-5.
55. Smolik I[1], Robinson DB, Bernstein CN, El-Gabalawy HS.First-degree relatives of patients with rheumatoid arthritis exhibit high prevalence of joint symptoms. J Rheumatol. 2013 Jun;40(6):818-24.
56. Kjeldsen-Kragh Rheumatoid arthritis treated with vegetarian diets, Am J Clin Nutr. 1999 Sep;70(3 Suppl):594S-600S. University of Washington
57. Turesson, W M O'Fallon, C S Crowson, S E Gabriel, E L Mattes,Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years ,Ann Rheum Dis 2003;62:722–727
58. Stolt P[1], Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, Alfredsson L; group, Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis. 2003 Sep;62(9):835-41.
59. Heliövaara M[1], Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. ,Reunanen A.atol. 1993 Nov;20(11):1830-5.
60. Grassi W[1], De Angelis R, Lamanna G, Cervini C,

The clinical features of rheumatoid arthritis, Eur J Radiol. 1998 May;27 Suppl 1:S18-24.

61. Suresh E. Diagnosis of early rheumatoid arthritis: what the non-specialist needs to know. J R Soc Med2004;97: 421-6
62. Jacoby RK, Jayson MIV, Cosh A. Onset, early stages and prognosis of RA : Clinical study of 100 patients with 11 year followup. BMJ 1973.
63. Maria do Socorro Teixeira Moreira Almeida et al, Demographic and clinical features of patients with rheumatoid arthritis in Piauí, Brazil - evaluation of 98 patients, Rev. Bras. Reumatol. vol.54
64. Calgüneri M, Ureten K, Akif Oztürk M et ai, Extra-articular manifestations of rheumatoid arthritis: results of a university hospital of 526 patients in Turkey. Clin Exp Rheumatol. 2006;24:305-8.
65. Drosos AA, Lanchbury JS, Panayi GS, Mountsopoulos HM. Rheumatoid arthritis in Greek and British patients. Arthritis Rheum. 1992;35:745-8.
66. Bowman SJ[1].Hematological manifestations of rheumatoid arthritis. Scand J Rheumatol. 2002;31(5):251-9.
67. Silva I[1], Mateus M, Branco JC ,Assessment of erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) on rheumatoid arthritis activity prediction, Acta Reumatol Port. 2010 Oct-Dec;35(5):456-62.

68. Akil M, Amos RS. ABC of rheumatology: Rheumatoid arthritis clinical features and diagnosis. BMJ 1995; 310 587- 90.
69. Veeparen K, Mangat G, Wanti I, Dieppe P. The expression of rheumatoid arthritis in Malaysian and British patients: a comparative study. Br Rheumatol. 1993;32:541-5.
70. A LUTF, A RAZZAKH POIL, M HAMMOUDEH Characteristics of patients with rheumatoid arthritis in Qatar: a study of 100 patients managed by hospital based rheumatologists , Int J Rheum Dis. 2014 Jan;17(1):63-5. doi: 10.1111/1756-185X.12135. Epub 2013 Jul 16
71. Van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 2005;97:93–101.
72. Marwaha RK, Tandon N, Garg MK et al. Vitamin D status in healthy Indians aged 50 years and above. JAPI 2011;59:706-709.
73. Rajeev Sharma , Renu Saigal, Laxmikant Goyal et al ,Estimation of Vitamin D Levels in Rheumatoid Arthritis Patients and its Correlation with the Disease Activity , J Assoc Physicians India 62 (8), 678-681. 8 2014.
74. Rossini M et al, Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. Arthritis Res Ther. 2010;12):R216.
75. Cherniack EP. A Ray of Hope for Tender Joints: Vitamin D and Rheumatoid Arthritis. J Rheumatol 2011;38;5-7 .

Annexures

PROFORMA

Name : Age: Sex:

Address : Rheumatology OP No.

Clinical details

History :

Mode of onset :

Type of joint :

Pain : Y/ N Site:

Swelling : Y/N

Morning Stiffness : Y/ N Duration :

Fever :Y/N

<u>Mucocutaneous manifestations</u>

Eye : Skin : Photosen/ Rash / Others

Gastrointestinal Genitourinary

Past history : Infections

Food allergy

Personal history :Smoking

Diet : as per diet chart

Marital status : Married / Unmarried Plan of future pregnancy

No. Children : Abortion :

Examination

Pallor / jaundice / clubbing / oedema / fever / LNE

Skin lesions :

Rheumatoid nodule : Y/ N

Joint examination – inspection Palpation:

CVS: Murmurs / Rub / pericardial effusion PAH

Resp : Effusion / Fibrosis / ILD

CNS :

GIT :

Vasculitis : Y/ N Site

Endocrine :

Others :

Rheumatoid bad prognostic markers

Female : > 1 yr synovitis without remission Rh. Nodule

Extra art Rh.

High Anti CCP RA factor Joint Erosion High DAS

Investigations

Hb: TC: DC: Platelet : ESR :

Urine : Alb M/E: Pus cell : RBC : Cast

RFT : BU S.Cr. Uric K

LFT : Bil SGPT SAP Tot Pr/Alb :

Rheumatoid factor : Anti CCP

FBS : FLP TC: TG : LDL: HDL: VLDL:

ANA, Anti ds DNA

ANA profile :

X-rays : Hand

Wrist

CXR

Hip

Spine

USG / ECHO

ECG :

CT / MRI

DAS Calculation : DAS28 = 0.56*sqrt(tender28)+0.28*sqrt(swollen28)+0.70

In (ESR)+ 0.014* GH

സമ്മത പത്രം

കോഴിക്കോട് മെഡിക്കൽ കോളേജിലെ മെഡിസിൻ വിഭാഗത്തിലെ അസിസ്റ്റന്റ് പ്രൊഫസർ ഡോ: ഷിജി.പി.വി, ആമവാതത്തിന്റെ രോഗലക്ഷണങ്ങളെ കുറിച്ചും ഈ രോഗത്തിന്റെ തീവ്രതയിൽ വിറ്റാമിൻ ഡി യുടെ കുറവുകൊണ്ടുണ്ടാകുന്ന വ്യതിയാനങ്ങളെ കുറിച്ചും ഗവേഷണം നടത്തുന്നതായി അറിയുന്നു. ഗവേഷണത്തിന്റെ വിശദാംശങ്ങൾ ഡോക്ടർ എന്നെ വ്യക്തമായി പറഞ്ഞു മനസ്സിലാക്കിയിട്ടുണ്ട്.

എന്റെ അസുഖ വിവരങ്ങളും അതിന്റെ വിശദാംശങ്ങളും പഠനാവശ്യത്തിന് ഉപയോഗിക്കുവാൻ ഇതിനാൽ ഞാൻ (രോഗി / രോഗിയുടെ രക്ഷിതാവ്) സമ്മതം തരുന്നു. ഈ വിവരങ്ങൾ അന്യോപകാരപ്രദമാം വിധം പഠനാവശ്യങ്ങൾക്കല്ലാതെ മറ്റ് ദുരുപയോഗങ്ങൾ ഒന്നും ഉണ്ടാകില്ല എന്നും വ്യക്തമായി മനസ്സിലാക്കിതന്നെ ഞാൻ സമ്മതം നൽകുന്നു. പഠനത്തിൽ എന്റെ/രോഗിയുടെ സ്വകാര്യത നിലനിർത്താനും സംരക്ഷിക്കുവാനും ഇതുവഴി ഡോക്ടറെ ചുമതലപെടുത്തുന്നു. ഏതുഘട്ടത്തിലും ഈ പഠനത്തിൽ നിന്ന് സ്വന്തം ഇഷ്ടപ്രകാരം പിൻമാറാൻ അവകാശമുണ്ടന്നു ഞാൻ(രോഗി / രോഗിയുടെ രക്ഷിതാവ്) മനസ്സിലാക്കുന്നു.

ഇതോടൊപ്പം പഠനാവശ്യാർത്ഥം വേണ്ട രോഗനിർണ്ണയ സംബന്ധമായ ടെസ്റ്റുകൾ ചെയ്യുവാനും ഇതിനാൽ സമ്മതം തരുന്നു.

രോഗിയുടെ രക്ഷിതാവ് : രോഗി :

ഒപ്പ് : ഒപ്പ് :

പ്രധാന ഗവേഷകന്റെ പേര് : ഡോ: ഷിജി.പി.വി,

KEY TO MASTERCHART

Sex : Female : 1 ; Male : 2

Duration : In months

Type of onset : Mono-1,Oligo-2,Poly-3

Active : Yes=1, No=2

Fever : Yes=1, No=2

Morning stiffness : Yes=1, No=2

Mucocutaneous manifestations : Yes=1, No=2

Smoking : Yes=1, No=2

Marital status : Yes=1, No=2

Abortions : Yes=1, No=2

Dry eyes : Yes=1, No=2

RA nodule : Yes=1, No=2

Skin lesion : Yes=1, No=2

No. of swollen joint : Yes=1, No=2

No. of tendor joint : Yes=1, No=2

Vasculitis : Yes=1, No=2

Other systems : Yes=1, No=2

AntiCCP : Yes=1, No=2

RA Factor : Yes=1, No=2

Radiological findings: Yes=1, No=2

DAS : <3.1=1 ,3.2-5,1=2,>/5,2=.3.

ESR : >100=1,60-100=2,<60=3

Vit D : 20=1,20-30=2,>30=3

Hb : >12=1,10-12=2,7-10=3,<7=4

SlNo	Name	Age	Sex	Socio ec status		Address	Type of onset	Active	Fever	Morning stiffness	Mucocutaneous manifestations	smoking	Diet	Marital status	No.of children	abortions	dry eyes	RA nodule	Skin lesion	no. of swollen joint	No. of tendor joint	Vasculitis	Other systems	AntiCCP	RA Factor	Radiological findings	CBC	S. Vit D level	DAS	ESR
1	Rukiya	63	1	low	6	MPM	2	1	2	1	2	1	1	1	4	2	2	2	2	1	3	2	-	-	1	2	9.8	16.84	2	2
2	Sainaba	45	1	low	8	KKD	3	1	2	1	2	1	1	1	2	2	2	2	2	3	3	2	-	1	2		8.8	13.45	2	2
3	Rajani	34	2	low	16	KKD	3	1	2	1	2	1	1	1	5	0	2	2	2	5	8	2	-	1	2	2	9	12.54	2	2
4	Sudarshan	49	1	low	12	KKD	3	1	2	1	2	2	1	1	2	2	2	1	2	3	5	2	-	-	1	2	7.8	24.68	2	2
5	Kadeeja	76	1	low	5	MPM	2	1	2	1	2	1	1	1	3	2	2	2	2	1	3	2	-	1	2	2	13	5.33	2	2
6	raman	37	1	low	20	KKD	2	3	2	1	2	2	1	1	2	2	1	2	2	4	4	2	-		1	2	11	13.56	2	2
7	Sreelakshmi	52	1	mod	22	MPM	1	1	1	1	2	1	1	1	4	2	2	2	2	1	4	2	-	-	1	2	10	11.92	2	2
8	Deepa	32	1	mod	6	KKD	1	1	2	1	2	1	1	1	1	2	1	1	2	4	4	2	-	-	1	2	9.6	5.77	2	2
9	Abdulrahman	57	2	low	2	MPM	2	1	1	1	2	2	1	1	3	2	1	2	2	5	2	2	-	-	1	2	9	23.06	2	1
10	vasantha	38	1	low	6	KKD	1	1	2	1	2	1	1	1	2	2	2	1	2	0	4	2	-	2	2	2	8.2	22.1	2	3
11	Sainaba	52	1	low	8	MPM	2	1	2	1	2	1	1	1	2	2	2	2	2	5	3	2	-	-	1	2	8.5	18.48	2	1
12	Sathi	45	1	low	10	KKD	2	1	1	1	2	1	1	1	2	2	2	1	2	3	3	2	-	-	1	2	9	14.44	2	1
13	Annamma	50	1	low	12	Wyd	2	1	2	1	2	1	1	1	3	2	2	2	2	1	1	2	-	2	2	2	9.8	15.2	2	2
14	Ibrahimkutty	60	2	low	18	MPM	2	1	2	1	2	2	1	1	5		2	2	2	3	2	2	-		1	2	10	28.63	2	3
15	Sainaba	52	1	low	16	Tirur	3	1	2	1	2	1	1	1	5	2	2	2	2	5	3	2	-	1	2	2	7.8	13.45	2	2
16	Moosakutty	54	2	low	15	MPM	3	1	2	1	2	2	1	1	3		1	2	2	3	2	2	-		1	2	9.5	27.77	2	3
17	Khadiya kutty	54	1	low	16	Tirur	3	1	2	1	2	1	1	1	5	2	2	1	2	3	2	2	-	-	1	2	9.5	10.17	2	1
18	sreelakshmi	35	1	mod	18	Tirur	2	1	2	1	2	1	1	1	2	2	2	2	2	5	4	2	-	1	2		8.5	11.94	2	1
19	Bushara	37	1	low	20	MPM	1	1	2	1	2	1	1	1	2	2	2	2	2	6	4	0	-	-	1	2	9.2	6.91	3	1
20	usha	41	1	low	15	kannur	3	1	1	1	2	1	1	1	2	1	1	1	2	4	9	2	-	-	1	2	9.8	20.86	3	2
21	Annamma	46	1	low	12	Wyd	2	1	2	1	2	1	1	1	4	2	2	1	2	5	5	2	-	-	1	2	8.8	24.84	2	3
22	Thankamani	62	1	low	18	KKD	3	1	1	1	2	1	2	1	2	2	2	2	2	4	8	2	-	2	2	2	9.8	13.42	3	1
23	Meenakshiamma	81	1	mod	16	KKD	3	1	2	1	2	1	1	1	5	2	1	2	2	8	4	2	-	1	2	2	12	8.74	3	1
24	Nafesa	40	1	low	12	MPM	3	1	2	1	2	1	1	1	3	2	2	2	2	4	5	2	-	1	2	2	12	8.94	3	1
25	Fathima	65	1	low	16	KKD	2	1	1	1	2	1	1	1	2	2	2	2	2	1	1	2	-	1	2		9.4	13.03	2	2
26	Narayani	65	1	low	18	MPM	3	1	2	1	2	1	2	1	3	2	2	2	2	3	5	2	-	-	1		8.3	38.14	2	3
27	Chinnamma	58	1	low	9	Tirur	3	1	2	1	2	1	1	1	3	2	2	2	2	3	7	2	-	1	2		7.2	35.14	2	3
28	Nabeesa	50	1	low	22	KKD	3	1	2	1	2	1	1	1	5	2	2	2	2	5	10	2	-	-	1		10	26.29	2	3
29	Nabesa	42	1	mod	16	MPM	3	1	1	1	2	1	1	1	3	2	2	2	2	5	5	2	-	2	2		12	14.04	3	1
30	Ammini	48	1	low	14	KKD	3	1	2	1	2	1	1	1	3	2	2	2	2	4	4	2	-	-	1		8.6	14.42	2	2

SINo	Name	Age	Sex	Socio ec status		Address	Type of onset	Active	Fever	Morning stiffness	Mucocutaneous maniefstations	smoking	Diet	Marital status	No.of children	abortions	dry eyes	RA nodule	Skin lesion	no. of swollen joint	No. of tendor joint	Vasculitis	Other systems	AntiCCP	RA Factor	Radiological findings	CBC	S. Vit D level	DAS	ESR
31	Rajitha	32	1	low	14	KKD	3	1	2	1	2	1	1	1	2	2	2	2	2	4	3	2	-	-	1		9.8	20.17	3	3
32	jameela	39	1	low	12	KKD	1	1	2	1	2	1	1	1	5	2	2	2	2	6	8	2	-	1	2	2	12	10.84	2	2
33	Aleema	40	1	low	18	MPM	3	1	1	1	2	1	1	1	2	2	2	2	2	5	5	2	-	2	2	2	10	15.83	2	2
34	Khadiya kutty	43	1	mod	14	MPM	3	1	2	1	2	1	1	1	2	2	2	2	2	5	5	2	-	2	2		11	10.17	3	1
35	Annamma	46	1	low	24	Wyd	3	1	2	1	2	1	1	1	3	2	2	1	2	4	3	2	2	1	2		9.2	24.84	2	2
36	Bindu	38	1	low	24	KKD	3	1	2	1	2	1	1	1	2	2	2	2	2	3	2	2	2	1	2		9.5	18,23	2	3
37	seena	38		low	16	KKD	3	1	2	1	2	1	1	1	2	2	2	2	2	3	4	2	2	-	2		10	14.04	2	1
38	Annamma	45		low	18	MPM	3	1	2	1	2	1	1	1	3	2	2	2	2	2	4	2	2	1	2		8	18.04	3	3
39	rameshan	48	2	low	16	MPM	3	1	1	1	2	1	1	1	2	2	2	2	1	3	5	1	2	-	1	2	9	16.16	2	2
40	rani	65	1	low	16	KKD	1	1	1	2	2	2	2	2		2	2	2	2	1	1	2	2	1	2		13	13.02	2	2
41	ahmed kutty	56		low	15	MPM	3	1	1	1	2	2	1	1	3	2	2	1	2	2	5	2	2		1	2	11	12.12	2	3
42	VIMALA	58	1	mod	14	MPM	3	1	1	1	2	1	1	1	2	2	2	2	2	1	4	2	2	1	2	2	12	15.16	2	2
43	SANGEETHA	34	1	low	14	Wyd	1	1	1	1	2	1	2	1	1	2	2	1	2	1	1	2	2	1	2	2	8	12.04	2	2
44	sharnya	46	1	low	12	MPM	3	1	1	1	2	1	1	1	2	2	2	2	2	2	4	2	2	2	2	2	9	18.01	2	2
45	mohanan	45	2	low	6	KKD	2	1	2	1	2	2	1	1	3	2	2	1	2	1	1	2	2	-	1	2	10	20.04	2	3
46	mohanan	52	2	low	2	KKD	3	1	2	1	2	2	1	1	2	2	2	1	2	3	4	2	2	-	1	2	9	14.4	2	2
47	rajeswari	48	2	low	8	KKD	3	1	2	1	2	1	1	1	2	1	2	2	2	4	1	1	2	-	1	2	9	13.8	2	2
48	malu	52	1	low	16	KKD	3	1	2	1	2	1	1	1	3	2	2	2	2	3	2	1	2	2	2	-	12	12.8	2	2
49	fathima	38	1	low	3	KKD	3	1	2	1	2	1		1		2	2	1	2	3	3	2	2	1	2	-	11	13.6	2	2
50	sethumadavan	56	2	mod	14	MPM	3	1	2	1	2	2	1	1	2	2	2	1	2	3	3	2	2	-	1	-	10	11.2	2	2
51	nalinakshan	43	2	mod	18	KKD	3	1	22	1	22	2	11	1	2	2	2	2	2	34	2	2	2		1	1	11	10.2	2	2
52	uthara	39	1	mod	1	KKD	3	1	2	1	2	1	1	1	23	2	2	2	2	4	5	2	2		1	-	9.8	11.4	3	96
53	hema	55	1	low	13	KKD	3	1	2	1	2	1	1	2	0	2	2	2	2	4	6	2	2	1	2	-	8.5	15.6	2	3
54	lakshmi	34	1	low	14	KKD	1	1	2	1	2	1	1	1	1	2	2	1	2	5	4	2	2	-	1	-	9.6	20.6	2	2
55	Fathima	45	1	low	14	kannur	3	1	2	1	2	1	1	1	2	2	2	2	2	4	5	2	2	-	1	1	11	13.5	2	2
56	suraj	38	2	low	18	Wyd	2	1	2	1	2	2	1	1	2	2	2	1	2	5	3	2	2	-	1	-	11	20.2	2	3
57	subaida	56	1	low	8	KKD	3	1	2	1	2	1	1	1	2	2	2	1	2	2	5	2	2	1	2	-	11	9.4	3	2
58	sheena	55	1	low	6	Wyd	33	1	2	1	2	1	1	1	3	2	1	2	2	1	4	2	2	1	2	1	11	7.8	2	2
59	sheeja	54	1	low	4	KKD	3	1	2	1	2	1	1	1	2	2	2	1	2	5	6	2	2	2	2	-		2.2	2	2
60	VIMALA	45	1	low	8	KKD	3	1	2	1	2	1	1	1	3	2	2	2	2	5	6	2	2	2	2	-		13.5	2	3

CONTROL							
Sl.No	**Age**	**Vit - D Level**		**Hb**		**ESR**	
1	60	25.32	2	12.3	1	20	3
2	42	18.4	1	12.6	1	22	3
3	36	15.2	1	13	1	23	3
4	51	25.1	2	12.6	1	30	3
5	73	18.54	1	12.8	1	10	3
6	34	20.2	2	12.7	1	9	3
7	49	22.5	2	12.2	1	22	3
8	34	17.35	1	12.3	1	16	3
9	59	18.1	1	12.5	1	12	3
10	35	24	2	12.6	1	16	3
11	49	24.5	2	12.4	1	12	3
12	43	23.01	2	12.5	1	15	3
13	53	22.12	2	11.8	2	30	3
14	58	24.67	2	12.2	1	22	3
15	54	19.5	1	12.8	1	21	3
16	56	24.87	2	12.6	1	23	3
17	52	16.52	1	11.2	2	10	2
18	37	23.5	2	12.5	1	4	2
19	39	18.2	1	12.4	1	102	1
20	44	22.5	2	12.2	1	45	3
21	48	23.85	2	12.6	1	32	3
22	59	18.5	1	12.2	1	33	3
23	78	19.95	1	9.8	3	32	3
24	44	20.25	2	12.2	1	21	3
25	63	21.4	2	12.4	1	27	3
26	67	19.89	1	12.4	1	28	3
27	55	25.01	2	12.5	1	21	3
28	53	24.53	2	12.6	1	26	3
29	45	24.52	2	12.5	1	25	3
30	46	23.85	2	10.5	2	28	3
31	35	24.86	2	10.8	2	26	3
32	41	22.59	2	12.3	1	21	3
33	38	20.52	2	12.2	1	28	3
34	46	24.52	2	9.8	3	23	3
35	49	18.52	1	12.2	1	36	3
36	42	24.23	2	12.2	1	40	3
37	40	20.02	2	12.5	1	32	3
38	43	23.25	2	11.9	2	35	3
39	47	22.56	2	12.5	1	36	3
40	62	20.58	2	12.4	1	34	3
41	58	23.52	2	12.2	1	38	3
42	54	20.52	2	12.2	1	32	3
43	36	21.32	2	12.3	1	33	3
44	49	24.12	2	12.3	1	32	3
45	48	21.02	2	11.8	2	36	3
46	56	21.25	2	10.9	2	68	2
47	44	20.89	2	11.8	2	44	3
48	56	22.98	2	12.2	1	42	3
49	43	20.12	2	12.3	1	34	3
50	49	19.28	1	12.2	1	36	3
51	38	23.52	2	12.2	1	34	3
52	36	22.45	2	12.6	1	32	3
53	53	20.56	2	12.2	1	34	3
54	38	18.25	1	12.2	1	32	3
55	49	22.56	2	12.4	1	36	3
56	43	23.25	2	12.2	1	34	3
57	52	15.258	1	12.5	1	28	3
58	53	18.25	1	10.6	2	29	3
59	51	24.56	2	12.2	1	42	3
60	48	21.12	2	12.3	1	38	3

ABBREVIATIONS

RA	: Rheumatoid arthritis
ACR/EULAR	: American College of Rheumatology/ European League Against Rheumatism
DAS	: Disease Activity Store
HLA	: Human Leukocyte Antigen
PTPN22	: Protein Tyrosine Phosphorylase Non Receptor 22
Anti CCP	: Anti Cyclical Citrullinated Peptide
ILD	: interstitial lung disease
CRP	: C Reactive Protein
ANA	: Anti nuclear antibody
MRI	: Magnetic Resonance Imaging
ULN	: Upper Limit of Normal
HAQ	: Health Assessment Questionnaire
RADAR	: Rapid Assessment of Disease Activity in Rheumatology
RADAI	: Rheumatoid Arthritis Disease Activity Index
RANK L	: Receptor Activator of Nuclear factor B Ligand
PTH	: Parathyroid Hormone
TH cell	: T Helper cell
NHANES	: National Health and Nutrition Expansion Survey
TLR4	: Toll Like Receptor 4