

Epidemiology of Autoimmune Disorders with Special Reference to Rheumatoid Arthritis from a Tertiary Care Center

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ABSTRACT

Background: Autoimmune disorders (AID) are emerging non-communicable diseases and understanding their epidemiology could reveal information about their clinical characteristics and disease management. **Objective:** To record the different types of arthritis cases attending a tertiary care center and study the profile of rheumatoid arthritis cases. **Methods:** The different types of arthritis cases reported were recorded from both rheumatologic and orthopaedic units. Retrospectively data was collected from Medical records department. **Results and discussion:** Totally 1481 cases were taken for the study. The proportion of females getting affected with AID were high and the ratio of female: male was found to be 2.25:1. There were around 30 types of different arthritis cases which are reported. The different types of arthritis were rheumatoid arthritis (RA) (39%), fibromyalgia (13%), spondyloarthropathy (9%), systemic lupus erythematosus (6%), psoriatic arthritis (6%), Sjogren's syndrome (5%), reactive arthritis (5%), osteoarthritis (3%), and gout (3%). In sub-group analysis of RA patients, female preponderance was observed and the frequent biochemical investigations were erythrocyte sedimentation rate and rheumatoid factor. C-reactive protein, anti-cyclic citrullinated peptides, and vitamin D estimations were less frequent. The comorbid conditions were diabetes and hypothyroidism and concomitant arthritis were connective tissue disorders, Sjogren's syndrome, and fibromyalgia. Medication profile revealed polypharmacy with disease modifying antirheumatics, glucocorticoids, analgesics and non-steroidal anti-inflammatory drugs. **Conclusion:** This study provides basic information of different types of arthritis and RA was found to be the most common. Female preponderance, polypharmacy, comorbid conditions and concomitant arthritis may have implications for further research on the disease management.

Keywords: Autoimmune, Rheumatoid arthritis, Medication, Comorbidity.

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INTRODUCTION

Autoimmune Disorders (AID) are one of the most important non-communicable diseases and there are more than 80 autoimmune diseases affecting approximately 100 million people worldwide.¹ Information about these disorders is more from developed countries than from developing and

under-developed countries. In India, the field of rheumatology is emerging and data on the different AIDs is sparse. Epidemiological studies have highlighted AIDs as an important cause of mortality in developing countries. The prevalence of AIDs is estimated to be approximately 10% and pharmacotherapeutic success is attained in only few of the AIDs. Understanding of molec-



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ular biology has led to the advent of newer biologics but remission is still a major challenge in these chronic disorders. In AIDs, multiple inflammatory mediators are involved which may occur concomitantly. Both genetics and environment influence the susceptibility and remission of the disorder. There is large inter-individual variability, and there are multiple autoantibodies all of which complicate the diagnosis and therapeutic intervention.² Therapy with a strategy may show effectiveness for some years after which the drug effect wanes off. Combination or substitution therapy could maintain remission. Information regarding different types of arthritis cases, their profile, disease characteristics, comorbidities and medication profile are sparse and in this context we have reported our observations.

METHODS AND MATERIALS

The data was collected retrospectively over a period of 3 years from January 2009 to December 2012. The study was approved by the Institutional Human Ethics committee. The cases attending at the orthopaedic and rheumatology units were included in the study. Demographic profile like age, gender and type of arthritis were all recorded.

RESULTS & DISCUSSION

The distribution of different types of arthritis is represented in (Figure 1). Based on the articular mani-

festations, they were classified and represented in (Figure 2–7).

Description of Different Types of Arthritis Patients

Ankylosing Spondylitis (AS): It is a chronic systemic inflammatory disorder predominantly affecting the sacroiliac and lower spine joints. The treatment relies mainly on non-Steroidal Antiinflammatory Drugs (NSAIDs) and physiotherapy. In case of refractory subjects, Disease Modifying Antirheumatic Drugs (DMARDs) and Anti-Tumor Necrosis Factor- α (anti-TNF- α) drugs are effective.³

Dermatomyositis: It is an inflammatory myopathy which can affect children or adults. The clinical features include progressive proximal muscle weakness and skin rash. Methotrexate has been proved to decrease calcinosis. The other drugs implicated are intravenous methyl prednisolone, cyclosporine and intravenous immunoglobulin in steroid-resistant cases. Physiotherapy is also adjunct therapy.⁴

Fibromyalgia: It is a diffuse chronic musculoskeletal pain resulting in soft tissue tender points which reduces the pain threshold. The clinical features include fatigue, sleep disturbances, cognitive impairment, depression and anxiety. The therapy mainly resides on simple analgesics such as paracetamol, muscle relaxants, antidepressants, opioids and physiotherapy. Pregabalin has been proved to be effective in managing neuropathic pain associated with Fibromyalgia.⁵

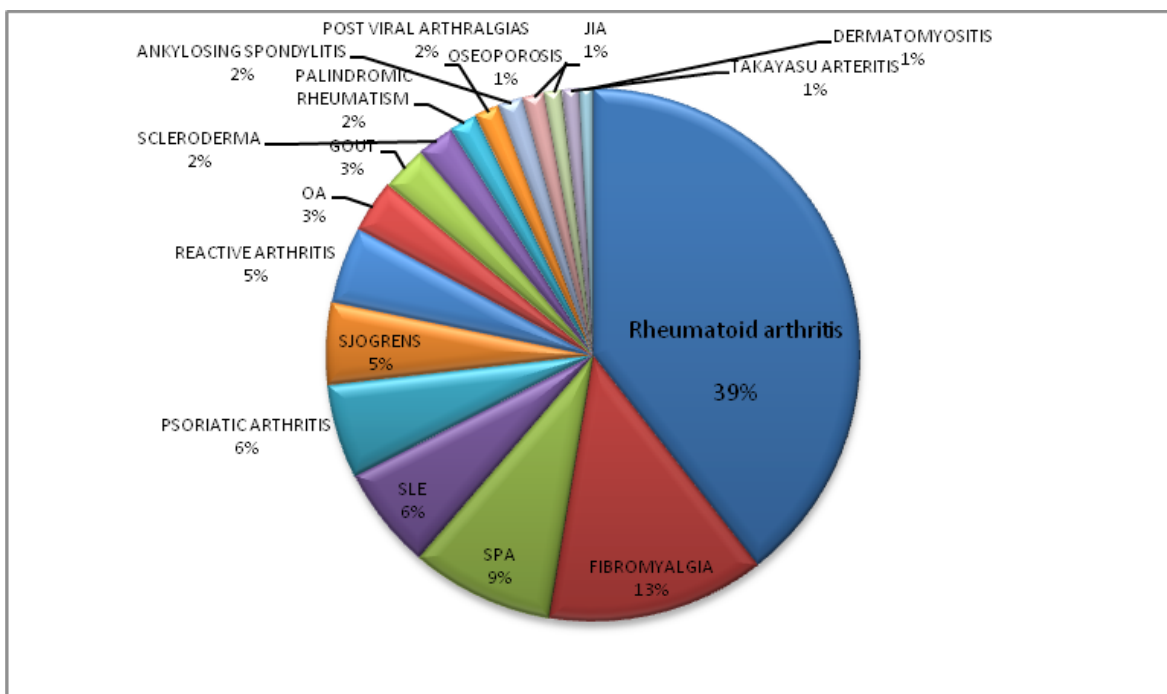


Figure 1: Different Types of Arthritis Cases Reported in Orthopedic and Rheumatology Units (N=1481)

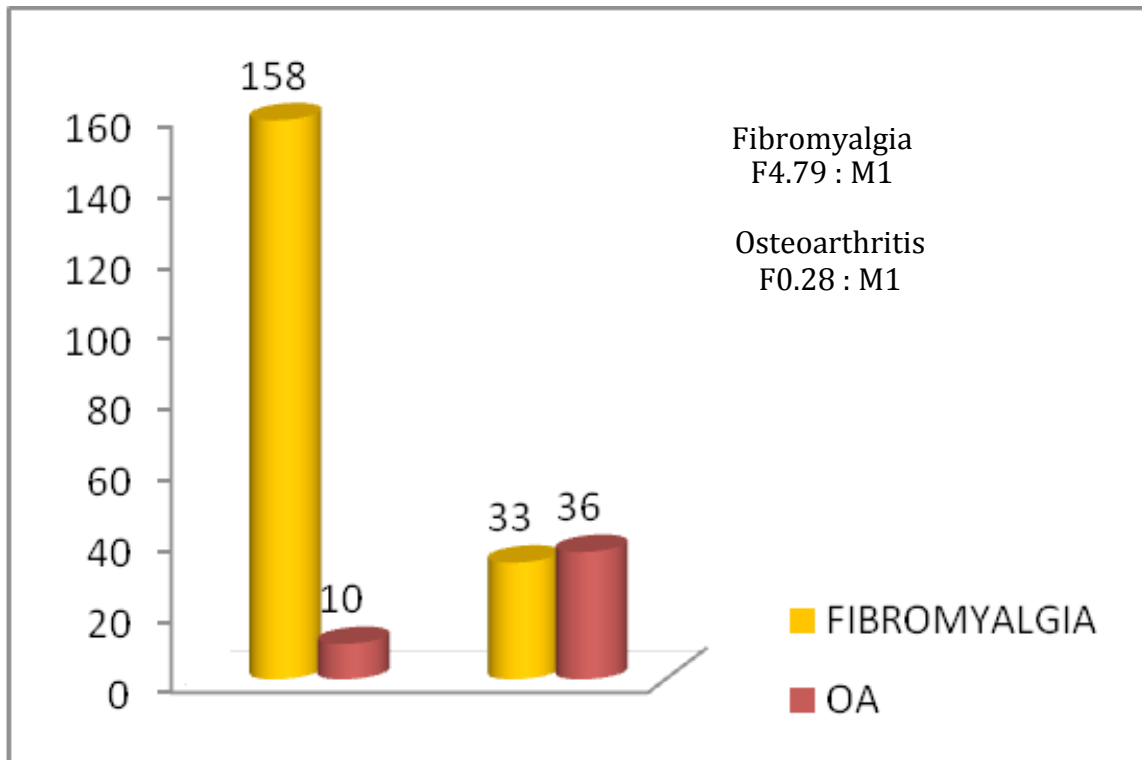


Figure 2: Non-Articular & non-inflammatory Arthritis
Fibromyalgia – Non-articular and non-inflammatory

Osteoarthritis – Articular & Non-inflammatory (may be acute monoarthritis involving 1-3 joints presenting as flare or chronic monoarthritis presenting as OA of hip or knee and chronic polyarthritis involving distal interphalangeal, proximal interphalangeal or first carpometacarpal joint)

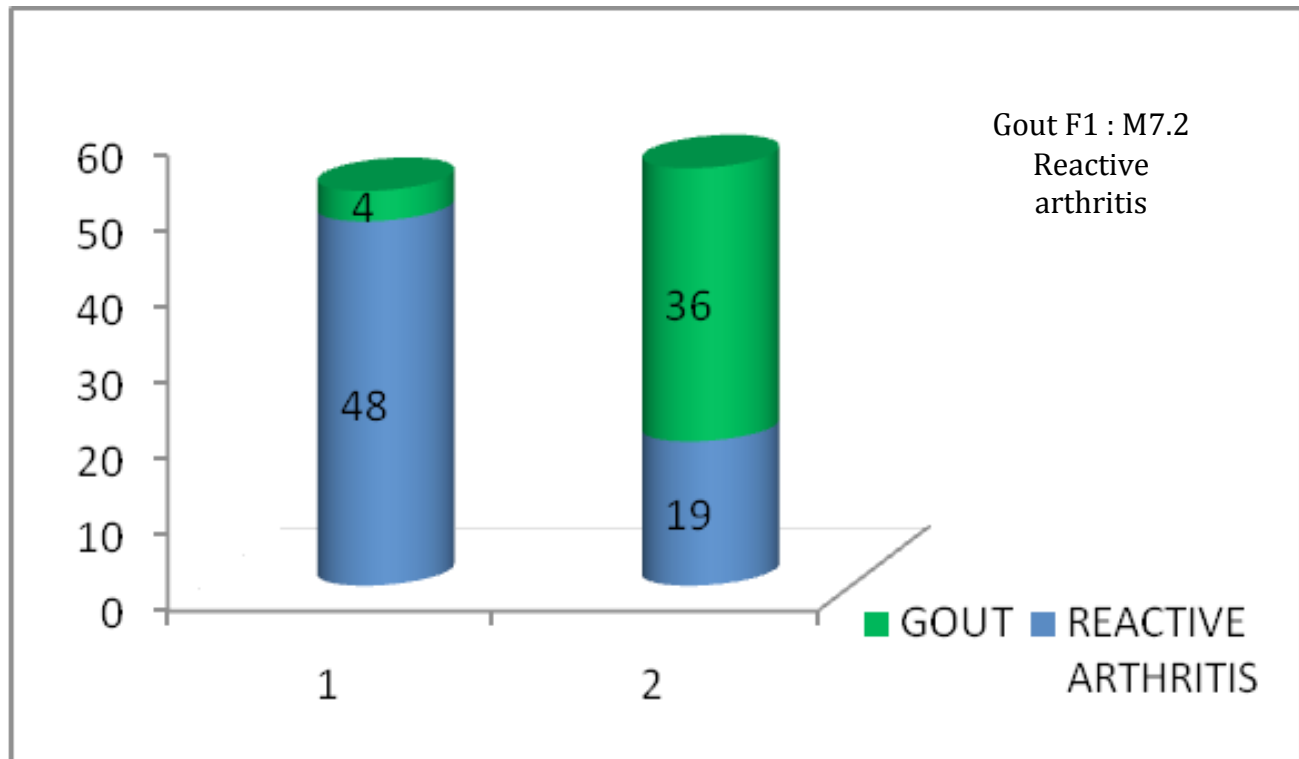


Figure 3: Articular - Acute inflammatory monoarthritis

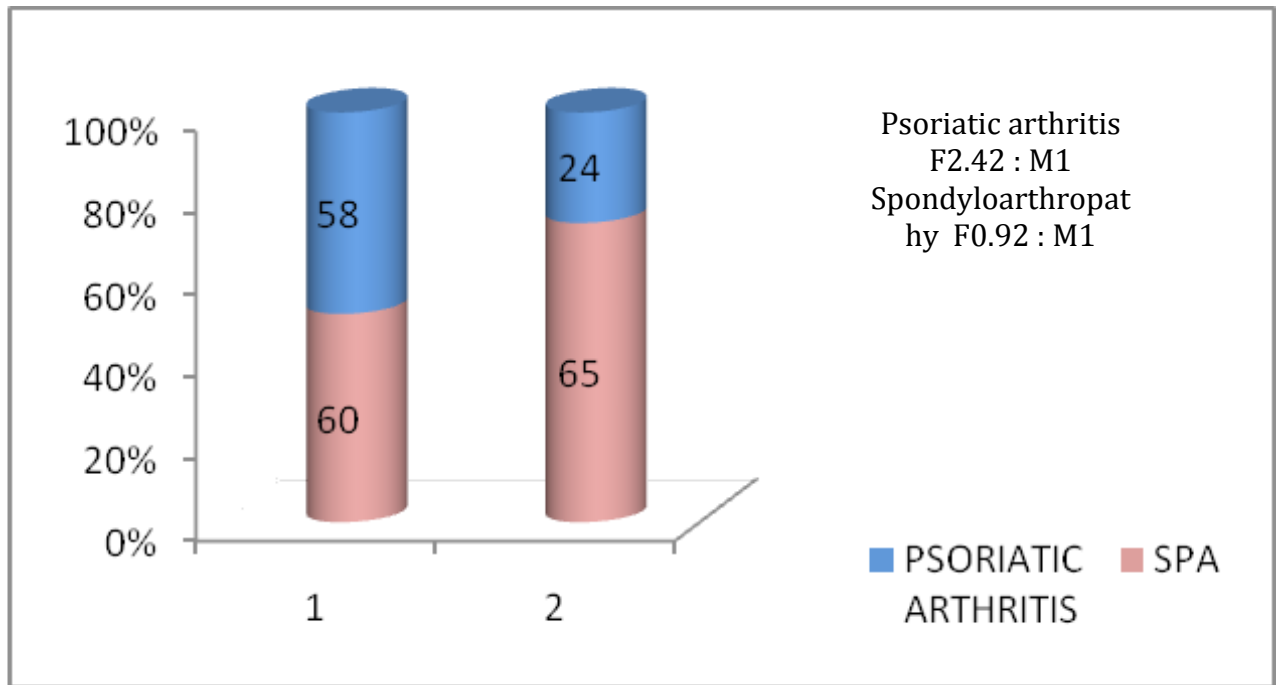


Figure 4: Articular – Chronic inflammatory monoarthritis

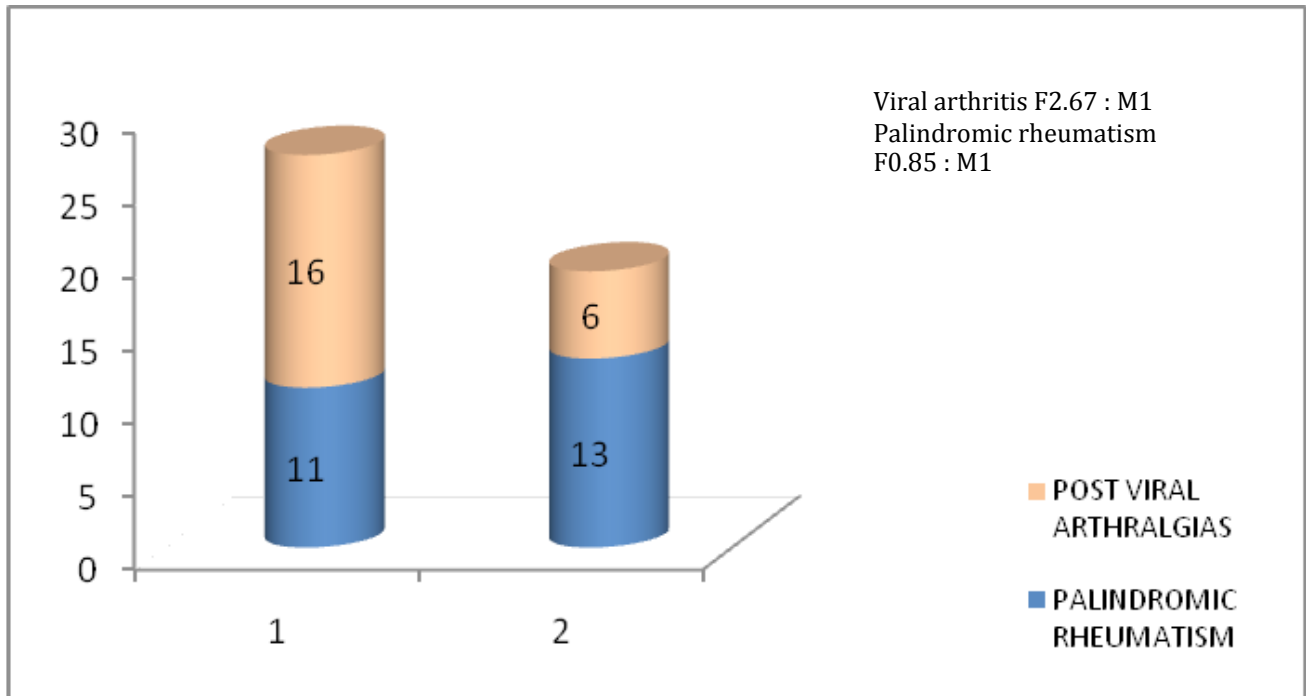


Figure 5: Articular – Acute inflammatory polyarthritis

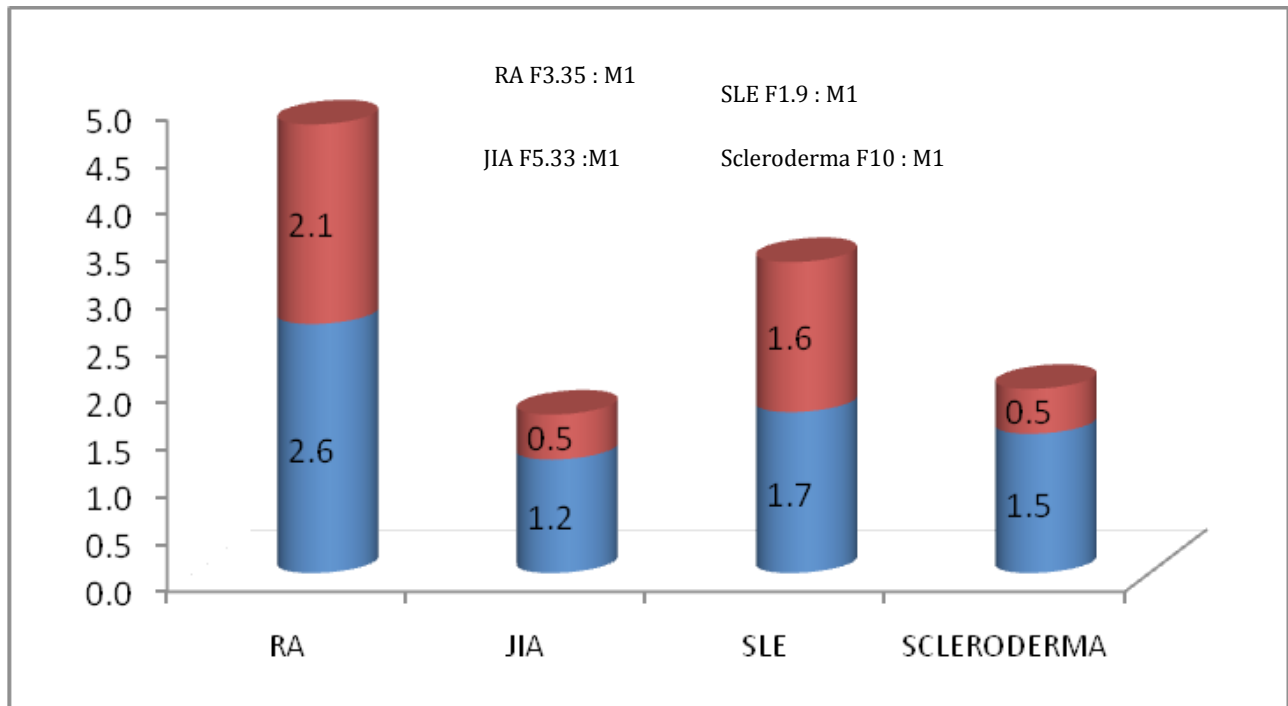


Figure 6: Articular – Chronic inflammatory polyarthritis
 The values are represented log to the base 2. RA=Rheumatoid arthritis, JIA=Juvenile idiopathic arthritis, SLE=Systemic lupus erythematosus

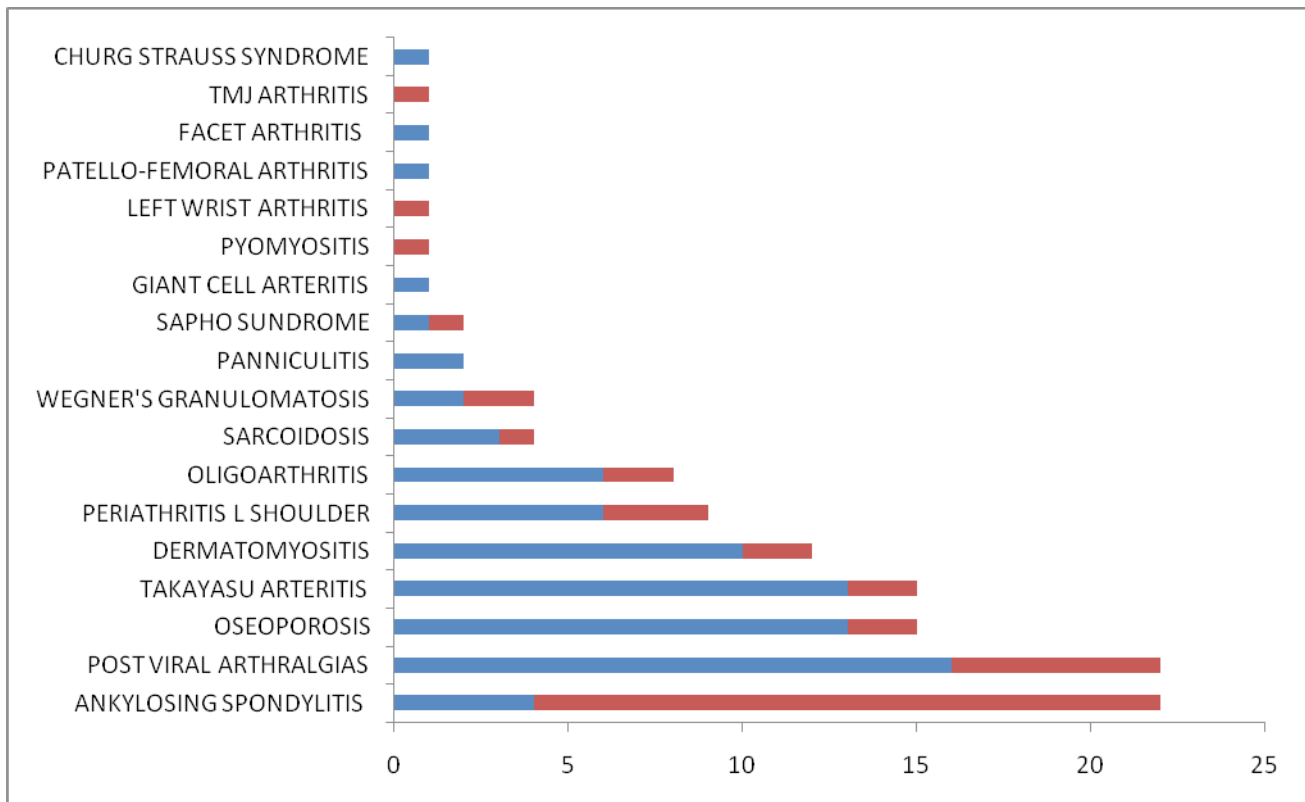


Figure 7: Other Types of Arthritis (Comprises 22% of other Autoimmune Disorders)
 (Blue line = no. of females; red line = no. of males)

Gout: It is a debilitating autoimmune disease resulting from hyperuricemia (serum urate levels > 6.8 mg/dl). It has been proposed that men have higher urate levels and in women estrogens increase the clearance of urate. In post menopausal women, the risk of gout is increased. The therapy relies on xanthine oxidase inhibitors (such as allopurinol and febuxostat), uricosurics (such as sulfinpyrazone and probenecid), uricolytics (such as rasburicase and uricozyme), losartan, *benzobromarone* and fenofibrate.⁶

Juvenile Idiopathic Arthritis (JIA): It is a type of arthritis with an unknown etiology presenting before 16 years of age, and lasting at least 6 weeks. JIA can cause growth failure, leg length discrepancy, scoliosis, joint contractures and secondary amyloidosis. Treatment includes NSAIDs, oral or intraarticular corticosteroids, conventional DMARDs, anti-TNF- α drugs (such as etanercept), IL-1 antagonists (such as anakinra, canakinumab and rilonacept), IL-6 antagonists (such as tocilizumab), and CD20 antagonists (such as rituximab).²

Osteoarthritis: It is a progressive joint disease which involves joint lining, cartilage, ligaments and bone. The treatment includes analgesics, NSAIDs, opioids, chondroitin sulphate, glucosamine, intraarticular corticosteroids, intraarticular hyaluronic acid and complementary alternative therapies. In the current study most patients were affected with knee Osteoarthritis and a male predominance was observed.⁷

Osteoporosis: It is characterized by low bone mass density and skeletal fractures due to micro architectural deterioration of bone tissue and impairment in bone remodelling process. Osteoporosis is classified as primary Osteoporosis which follows menopause, secondary osteoporosis which is due to glucocorticoid therapy, and tertiary Osteoporosis which may be juvenile, pregnancy related, or post partum. Pharmacological management includes bisphosphonates and hormone replacement therapy.⁸

Palindromic rheumatism: It refers to recurrent attacks of arthritis which can last from few hours to several days and appears like a flare at irregular intervals. A strong genetic association has been implicated such as HLA-DRB1*0803 and one-third to one-half of the patients progress to RA.

Panniculitis: It denotes inflammation of subcutaneous fat which may be affecting blood vessels or fat or both. It is of two types namely septal or lobar, and erythema nodosum is the most common clinical feature.⁹

Periarthritis: It is a kind of soft tissue rheumatism which occurs as a sequel of chikungunya infections, for which radiotherapy has been proved to be effective.¹⁰

Post Viral Arthralgia: It refers to arthritis following viral infection (such as chikungunya arthritis). It belongs to gene alpha virus which is an RNA virus transmitted by mosquitoes of *Aedes* family. The musculoskeletal symptoms begin after 1-12 days of the mosquito bite which could cripple the mobility. First line therapy includes use of NSAIDs, while DMARDs are preferred in persistent cases. A vaccine is also available. Environmental measures such as preventing exposure to mosquito bites and reducing the generation of mosquitoes are an effective way to encountering alpha virus infections.¹¹

Psoriatic Arthritis (PsA): It is an inflammatory arthritis that develops after cutaneous arthritis and is usually seronegative. It affects skin and joints, and therapy includes topical treatment, phytotherapy, and use of agents like NSAIDs, DMARDs, anti-TNF- α drugs such as infliximab and certolizumab. Newer drugs include anti-IL-12/23 p40 ustekinumab. Treatment outcomes could be measured with psoriasis area and severity index. In psoriasis, hyperproliferation of the epidermal layer of skin is the main clinical feature, and approximately 1/3rd of patients develop PsA.¹²

Pyomyositis: It is an infective disease of the skeletal muscle affecting the tropical population. It mainly affects youngsters and in the present study one case was reported. It has been found that presence of septic shock and comorbidity increases the mortality rate.¹³

Reactive Arthritis (ReA): It includes a triad of symptoms such as arthritis, conjunctivitis and urethritis. The other clinical features of ReA common with spondyloarthropathy include back ache, sacroilitis and a strong association with the HLA-B27 gene. The organisms implicated in the pathogenesis of ReA include *Chlamydia trachomatis*, *Salmonella typhimurium*, *Shigella flexneri*, *Campylobacter jejuni* and *Yersinia enterocolitica*. It is an acute form of arthritis and the pharmacotherapy includes use of antibiotics and analgesics.¹⁴

Scleroderma: It is also called as systemic sclerosis involving multi-system which causes wide spread vascular injury of the small arteries, progressive fibrosis of skin and also affects internal organs. Pulmonary arterial manifestations are treated with endothelin antagonists (ET-1 antagonists) such as bosentan and ambrisentan. and phosphodiesterase-5 inhibitors. Cardiovascular complications are treated with imatinib, and renal complications with angiotensin converting enzyme inhibitors (ACEI).¹⁵

Sjogren's syndrome: It affects exocrine glands which are moisture producing and clinically presents as dryness of mouth and eyes due to functional impairment of salivary and lachrymal glands. Pharmacological inter-

ventions include replacement or modulation of glandular secretions with oral muscarinics such as pilocarpine and cevimeline. The extra-glandular involvement is met with corticosteroids, methotrexate, and biologics such as β -cell targeted therapy with rituximab, T-cell targeted therapy with abatacept, and use of anti-TNF- α drugs (such as infliximab or etanercept) and IL-6 antagonists (such as tocilizumab).¹⁶

Systemic Lupus Erythematosus (SLE): It is a systemic inflammation disease in which a wide range of auto-antibodies are targeted towards multiple organ systems. It affects connective tissue of skin, joints, kidneys, heart, lungs and nervous system. Reports from the Indian population have suggested a higher incidence of mucocutaneous and renal involvement with lower incidence of neuropsychiatric, gastrointestinal and haematological involvement with the disorder.¹⁷

Spondyloarthropathy: It is an AID affecting the axial skeleton. It clinically presents as low back ache due to sacroilitis. The genetic predisposition implicated is HLA-B*27 and therapy is mainly with the use of NSAIDs and anti-TNF- α drugs.¹⁸

Takayasu's arteritis: It is otherwise called as pulseless disease and it is a rare chronic granulomatous vasculitis of aorta and its branches. The affected vessels may stenose or may develop aneurysms. The clinical presentation include claudication of limbs, decreased brachial pressure, arteriographic abnormality, and bruits. Its pharmacotherapy includes immunosuppressant therapy with methotrexate for vessel wall inflammation, percutaneous transluminal angioplasty, use of corticosteroids and anti-TNF- α drugs for refractory cases.¹⁷

The other types of arthritis cases were Churg-Strauss syndrome, giant cell arteritis, facet arthritis, patello-femoral arthritis, sarcoidosis, sapho syndrome, temporomandibular joint arthritis and Wegner's granulomatosis.

Rheumatoid Arthritis (RA): It is a chronic inflammatory disease characterized by erosive synovitis, polyarticular inflammation of small joints of hands, wrist and feet leading to stiffness and is associated organ damage leading to severe complications. In 2008, the prevalence of RA in India was reported to be at 0.5% and in 2009 it was reported to be at 0.75%, showing a drastic increase in RA population each year.¹⁹

For this study, around 570 cases of RA were identified and for sub-group analysis, but patients who had sufficient data were only included which came up to 438.

Female predominance was reported in previous studies 2-4:1 and in the current study the prevalence was found to be similar (3.35:1) with a mean age of 48 years. The prevalence of females among Latin Americans and South African blacks are as high as 7-8:1. It has been

reported that in women the disease activity is higher as compared to men.²⁰

Biochemical and Serological Profiles of RA Patients

Erythrocyte Sedimentation Rate (ESR) is a widely used marker and is based on aggregation of RBCs influenced by plasma proteins. In the present study, most of the patients had high ESR values (Table 1).²¹

Generation of antibodies to Fc portion of IgG known as Rheumatoid Factor (RF) is the hallmark of RA. The immunoglobulins IgM and IgA are directed against IgG. It has been reported that IgM-RF indicates severity of seropositive cases and is of prognostic value. IgM-RF is implicated in other autoimmune disorders and infections, and even healthier subjects have about 10% of IgM-RF. In the present study, nearly 59% of the patients were seronegative. Around 10% of the patients had very high titre values (Table 1).³

C-reactive protein is an acute phase reactant that is widely used and a rise in its concentration is correlated with disease activity. CRP is a better marker than ESR which could identify the inflammatory burden and it closely overlaps with TJC, SJC and pain scale (VAS). In the present study, 61% of the patients had high CRP values which reflected high disease activity (Table 1).²²

Anti-cyclic citrullinated peptide antibody (anti-CCP) positivity can be used to predict the severity of the disease and radiographic progression, where as anti-CCP negativity can delay diagnosis, and is suggestive of less aggressive radiographic progression and even unresponsiveness to conventional treatments. It is the best biomarker which can detect early arthritis and can identify the undifferentiated arthritis. Higher anti-CCP values are also implicated in oxidative stress in synovial fluid of RA patients. In our study, most of the patients had anti-CCP negativity which reflected a less aggressive stage of the disease with respect to radiographic progression, and the response to conventional treatments is doubtful (Table 1).²³

In previous studies, it has been identified that RA patients had lesser HDL and have the risk of developing coronary artery disease. In the current study, we found that 45% of the study population had lesser HDL. We also assessed other lipid fractions among the study population of which 12% had high LDL, 7% had high TGL and 5% had high cholesterol levels (Table 2).²⁴

Comorbidities of RA Patients

Comorbidities have been observed in 18% of the patients with diabetes mellitus (DM) as the common complication (Figure 8). In most RA patients, glucocorticoids are commonly prescribed and it could affect the

Table 1: Biochemical and Serological Profile of RA Patients (%)

Parameter	N	Anemic (<10%)			Borderline (>10–12.9%)			Healthy (13–16%)		Mean Hb ± SD (%)
		Anemic (<10%)	Borderline (>10–12.9%)	Healthy (13–16%)	Borderline (>10–12.9%)	Healthy (13–16%)	Mean Hb ± SD (%)			
Hemoglobin (gm/dl)	345 (79)	40 (12)	219 (64)	86 (24)				12 ± 1.64		
ESR (mm/hr)	N	Healthy (<12)		Mild inflammation (13–20)	Moderate inflammation (20–39)	High inflammation (40–59)	High inflammation (60–120)	Mean ESR ± SD		
		Healthy (<12)	Mild inflammation (13–20)	Moderate inflammation (20–39)	High inflammation (40–59)	High inflammation (60–120)	Mean ESR ± SD			
	346 (79)	41 (12)	46 (13)	155 (45)	59 (17)	45 (13)	36 ± 23.65			
RF (IU/ml)	N	Healthy (<20)		20–39	40–69	70–100	101–199	200–700	701–2000	
		Healthy (<20)	20–39	40–69	70–100	101–199	200–700	701–2000		
	213 (49)	125 (59)	17 (8)	21 (10)	16 (8)	19 (9)	9 (4)	6 (3)		
CRP	N	Healthy (<0.6)		0.6–0.9	1–1.9	2.1–3.7	4–6.4	7.1–11.2	15–23	
		Healthy (<0.6)	0.6–0.9	1–1.9	2.1–3.7	4–6.4	7.1–11.2	15–23		
	62 (14)	24 (39)	8 (13)	16 (26)	14 (23)	7 (11)	5 (8)	4 (6)		
ACCP	N	Positive		Negative						
		Positive	Negative	Positive	Negative					
	28 (6)	10 (36)	18 (64)							

N=Number of patients; SD = Standard deviation; ESR = Erythrocyte sedimentation rate; RF = Rheumatoid factor; CRP = C-reactive protein; ACCP = Anti-cyclic citrullinated peptide.

Table 2: Lipid Profile of RA Patients

Parameter	N=42 (9)	Lipid fraction (%)			Mean ± SD
		Unfavorable (<40)	Favorable (>40)	Mean ± SD	
HDL (mg/dl)		19 (45)	23 (55)	42 ± 10.96	
LDL (mg/dl)		Optimal (<130)	Borderline (130–160)	High (>160)	
		29 (69)	8 (19)	5 (12)	115 ± 31.13
TGL (mg/dl)		Optimal (<150)	Borderline (150–200)	High (>200)	
		30 (71)	9 (21)	3 (8)	119 ± 59.02
Cholesterol (mg/dl)		Optimal (<200)	Borderline (200–240)	High (>240)	
		34 (81)	6 (14)	2 (5)	174 ± 35.02

N=Number of patients; SD = Standard deviation; HDL = High density lipoprotein; LDL = Low density lipoprotein; TGL = Triglycerides.

therapeutic outcome of antidiabetic drugs which needs to be considered. Etoricoxib which is a COX-2 inhibitor is observed in most prescriptions and the cardiovascular risks associated with its use have to be considered in such comorbid conditions.²⁵

In the present study, hypothyroidism was found to be the next common comorbidity and most of them were

women. hypothyroidism is associated with increased risk of cardiovascular abnormalities which is unfavourable in RA patients.²⁶

Gastritis was found to be a comorbidity in 3 of the patients. NSAIDs should be used in caution in these cases and in the current study we observed etoricoxib was the preferred drug for chronic use.

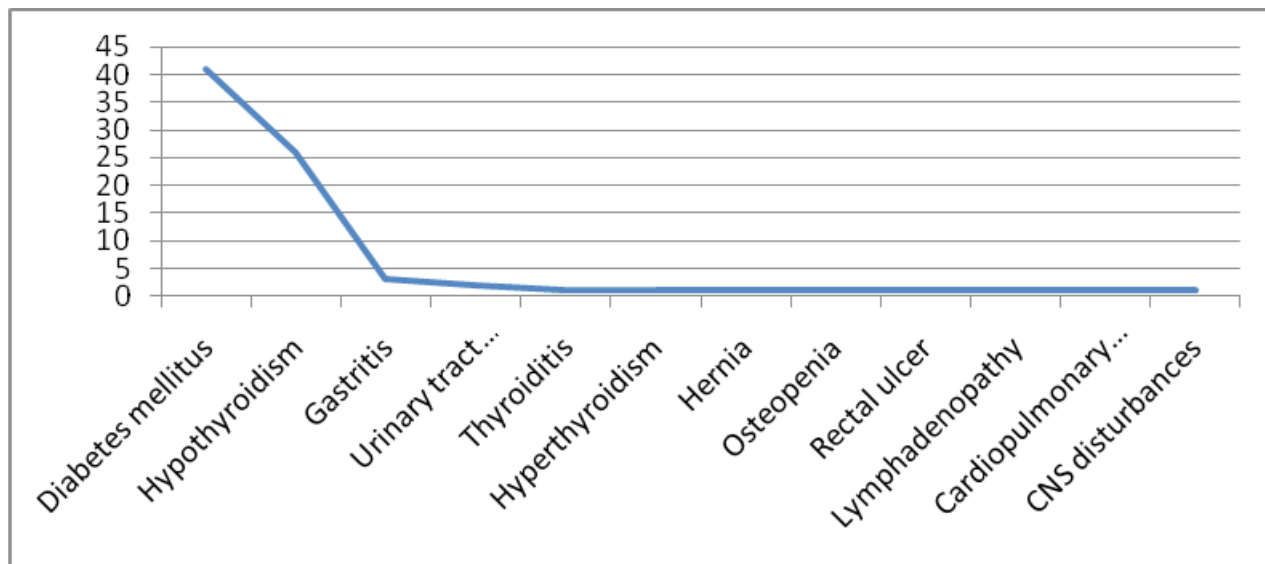


Figure 8: Comorbidities of Rheumatoid Arthritis Patients Represented in Numbers

The other comorbidities which are noted in the current study included hernia, osteopenia, rectal ulcer, lymphadenopathy, cardiopulmonary complications and neurological disorders. In case of any renal disease, NSAIDs should be used in caution and the dose of the anti-rheumatic drugs should be considered.

Coexistence of other AID

In this study, 7% of the RA patients had coexistence of other autoimmune disorders (Table 3). Connective tissue disorders were found to be more common followed by Sjogren's and fibromyalgia. Few patients had systemic lupus erythematosus, osteoarthritis, osteoporosis, cutaneous vasculitis and spondyloarthropathy.

Medication Profile

We observed the use of DMARDs in 90% of the prescriptions of which 77% of them included methotrexate (MTX). The dose of methotrexate at the start was found to be 7.5 mg/week and in many patients it had been increased to 10mg and 15mg/week during subsequent visits. The dose reduction was observed in only one case. All the MTX prescriptions were accompanied by folic acid supplementation 5mg/day on all days, except the day of MTX administration. The common complications of MTX included gastrointestinal disturbances and liver toxicity. In the current study, regular check-up for SGOT and SGPT had been observed for most of the patients. The most common combina-

Table 3: RA Coexistence with Other Autoimmune Disorders

Sr. No.	Concomitant autoimmune disorders with rheumatoid arthritis	N (%)
1	Connective tissue disorders	7 (21)
2	Sjogren's syndrome	6 (18)
3	Fibromyalgia	5 (15)
4	Lupus nephritis	4 (12)
5	Systemic lupus erythematosus	2 (6)
6	Osteoarthritis	2 (6)
7	Psoriatic arthritis	2 (6)
8	Osteoporosis	2 (6)
9	Cutaneous vasculitis	2 (6)
10	Spondyloarthropathy	1 (3)

N=Number of patients.

tion was found to be MTX with hydroxychloroquine (HCQ) 200 mg/day. The common complications of HCQ include ocular manifestations and regular checks are essential for these patients. Leflunomide (LEF) 10 mg/day was found in some of the MTX prescriptions and in some cases MTX was substituted with LEF. Sulphasalazine (SAAZ) 500 mg/day is used rarely and we could observe very few patients on SAAZ in this study. In biologics, a short course treatment with rituximab was observed in 2 patients.

Glucocorticoids are commonly prescribed in combinations with DMARDs. The glucocorticoids observed in the present study included intermediate acting drugs such as prednisolone (5 mg/day) and methyl prednisolone (4 mg/day). Short acting drugs such as deflazacort 6 mg/day was observed in a few prescriptions. We could not observe long acting drugs like dexamethasone or betamethasone in any of the prescriptions. Many patients had received intraarticular injection of hydrocortisone 80 mg.

The only non-steroidal antiinflammatory drug observed in the study is etoricoxib at 60 mg/day for most patients and 90 mg/day for few were observed.

In most of the prescriptions we could observe amitriptyline which may be prescribed for relief of chronic neuropathic pain. We observed duloxetine in some of the prescriptions which should be used in caution in hepatic insufficiency and we have not correlated their liver transaminase levels. Gender identity disorders is more common with duloxetine and its administration with DMARDs should be monitored.

The prescriptions for comorbid conditions included antihypertensives, antidiabetics and antihyperlipidemics. Many patients had preferred Complementary Alternative Medicine (CAM) like herbal medications which had been stopped. We tried to record such information but many of the patients were not able to describe the active principle and formulation which they had followed. Some of the patients had tried simple analgesics for temporary pain relief.

SUMMARY

The inflammatory type of arthritis reported are RA, PsA, ReA, AS, JIA and gout. The connective tissue disorders are SLE and scleroderma. Non-inflammatory arthritis include OA and FM and vascular type of arthritis include GCA and Takayasu arteritis.

In most of the autoimmune disorders, female predominance was observed with peak disease course in 3rd to 5th decade of their life.

Most of the patients prefer CAM which delays the diagnosis and leads to joint deformities and joint destruction and aggressive therapy is needed for rapid control of disease. Some of the patients suddenly discontinue the therapy and continue CAM due to adverse effects and cost of therapy of allopathic medications. In some cases, they take herbal medications along with allopathic medications and in such cases herb-drug interactions should be considered. The delay in lag time to approach a rheumatologist should be identified and appropriate measures should be taken to increase the awareness.

In RA patients, the frequent investigations are ESR and RF. ESR and RF are implicated as markers of inflammation of most diseases and assessment of other appropriate biomarkers such as CRP and anti-CCP could guide both diagnosis and treatment outcomes. However, due to cost constraints most patients do not check CRP and anti-CCP.

In most of the prescriptions, polypharmacy was observed and the impact of these combinations should be regularly monitored to ensure an effective and safe treatment. In an Indian context, many ADRs go unnoticed and the patients should be interviewed and counselled for better patient compliance.

The coexistence of other complications such as comorbidities and concomitant AID, possible drug-drug interactions and the need for aggressive therapy to control the disease activity is mandatory for chronic diseases like RA.

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CONFLICT INTEREST

Nil

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