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Review : RHEUMATOLOGY



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RHEUMATOLOGY

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Introduction

Rheumatology is a relatively new branch, though some of the rheumatic diseases like osteoarthritis are amongst the oldest if not the oldest human sufferings. For years and centuries rheumatic diseases were taken as part of being alive! Something that one had to just endure. No more so.

What has changed the scenario ? There are many reasons like the realization of the importance of rheumatic diseases, advances in diagnostics and therapeutics, and inputs by a band of scientists and physicians willing to forego the glamour of other specialities and take to rheumatology.

It is impossible to cover rheumatology in an issue of this size and purpose. I, after much discussion with my colleagues chose four disorders which form the major chunk of day to day rheumatology.

I do hope the readers find the issue helpful.

Dr. V. R. Joshi

Acknowledgements

The illustrations that appear in the article on Rheumatoid Arthritis and osteoarthritis are taken from IRA Rheumatology Compendium 2006 with permission.

RHEUMATOID ARTHRITIS

Dr. C. Balakrishnan*

Introduction :

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease with predominant articular affection. It leads to progressive joint damage, significant morbidity, and shortened life-span. There is progressive functional decline resulting in considerable socio-economic burden. By no means, is rheumatoid arthritis a benign disease !

Over the last few decades, the knowledge and concepts associated with RA have undergone a sea of change. It is now realized that early and effective control of inflammation is essential to prevent long-term ravages of the disease. Though the aetiopathogenesis is still far from clear, impressive strides have been made in its understanding at the molecular level. This has led to the development of many new molecules (and many more are in the pipe-line) aimed selectively at specific targets which are thought to orchestrate the disease process.

Epidemiology

Depending upon the criteria used, the prevalence of RA has been reported to be between 0.3% to 1.5%. There is paucity of good epidemiological studies from India. Available data estimates a prevalence of 0.75%. The disease is 2.5 times more common in females with a peak incidence between 4th and 6th decades. Genetic factors seem to be important. There is higher concordance of the disease in monozygotic twins. No clustering of cases has been noted to incriminate any specific environmental factor.

Pathology

Articular

Pathologically the joint affection is characterized by synovial hypertrophy, synovial effusion, pannus formation and cartilage and bone destruction. There is hypertrophy of synovial lining A and B cells (multiplication + hypertrophy). The synovium is infiltrated with T cells (mainly CD4+, with type 1 bias), B cells, plasma cells, macrophages, dendritic cells and mast cells. There is increased vascularity. At places there is formation of germinal follicles. The CD4+ T cells are seen in close cell to cell contact with macrophages and dendritic cells, suggesting immune activation. The infiltrating cells and synovial cells have an activated phenotype. In established and advanced disease, there is loss of articular cartilage and characteristic juxta - articular erosions.

Extra-articular

Histopathologically rheumatoid nodules show fibrinoid necrosis surrounded by palisading cells arranged radially; granulation tissue and inflammatory cells are present. Tenosynovitis consists mainly of nonspecific inflammatory infiltrate. Rarely nodules with central necrosis are present.

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Similar pathology is present with pleural and pericardial involvement. Pulmonary interstitial fibrosis is similar to idiopathic pulmonary interstitial fibrosis. Salivary and lacrimal gland pathology resembles that seen in primary Sjogren's syndrome. Peripheral vascular involvement (vasculitis) occurs but is rare.

Pathogenesis

The current thinking is that RA is the result of interplay of genetic factors, environmental factors, and an auto-reactive immune system. Sex hormones and stress may also play a role.

Genetic factors

It is estimated that the overall contribution of genetic susceptibility to disease causation is less than 60% (37-60%). RA is a polygenic disorder and there is a strong association with class II HLA molecules - HLA DR-4, DR-1 and DR-10.

These HLA molecules share a common susceptibility epitope. Other HLA molecules such as DQ, DP and non-HLA molecules also contribute to disease susceptibility. The exact mechanism(s) by which the HLA molecules confer susceptibility is not clear. It is also possible that the shared epitope determines disease severity and progression.

Infectious agents

Mycobacterium tuberculosis, Proteus mirabilis, E.coli, EBV and retroviruses have all been implicated. However so far there is no definite proof of their involvement. It is felt that they act as antigenic triggers and the resulting inflammation and immune response lead to autoimmunity. Alternatively molecular mimicry may be involved.

Immune mechanisms

In spite of the large number of T-cells present in rheumatoid synovium their importance and/or role in the pathogenesis of RA is doubted. This is because of paucity of CD4 + T-cell specific cytokines and failure of therapy directed at CD4+ T-cells.

As against this B cells which form a small percentage of synovial cells seem to be important. Apart from the presence of antibodies such as rheumatoid factor, anti CCP antibodies, therapy directed against B-cells has proved effective.

The mediators of synovial inflammation are (i) cytokines of which TNF- α and IL-1 are most important. There is an overwhelming abundance of proinflammatory cytokines in the synovium. (ii) Prostaglandins, (iii) Complement activation products and chemokines.

Metalloproteinases, cathepsins, aggrecanases and reactive oxygen species are involved in cartilage and bone destruction. Inhibitors of these enzymes are present but in inadequate concentration.

The initiation of autoimmunity is most likely an epiphenomenon. The suspected self antigens include immunoglobulin IgG, type II collagen and peptides derived from constituents of articular cartilage. Non articular antigens such as heat shock protein (HSP) may be involved.

A schematic diagram of the pathogenesis of RA, as understood, is depicted in figure 1.

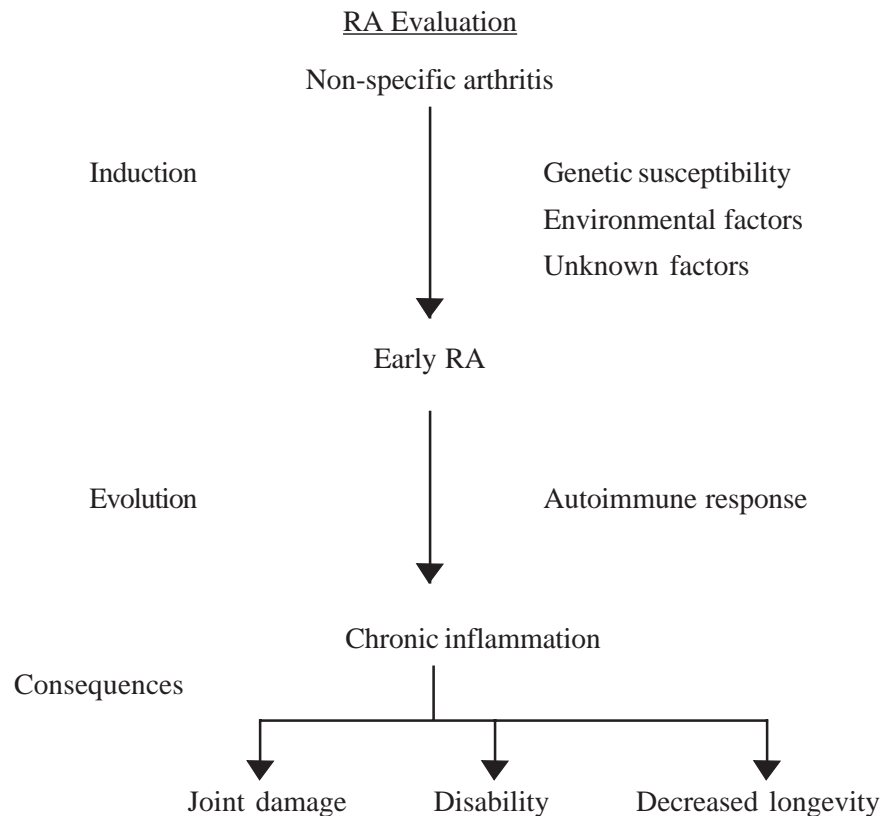


Fig 1 : Evaluation of Rheumatoid Arthritis

Clinical features

RA is characterized by progressive damage of synovial joints. A proportion of patients could have variable extra-articular and systemic manifestations. Usually there is an insidious onset of pain with symmetric swelling of small joints. The onset can be acute or sub acute. The other patterns of presentation include palindromic onset, monoarticular presentation, extra-articular synovitis (tenosynovitis, bursitis) and polymyalgia rheumatica-like onset especially in the elderly.

Morning stiffness is a typical feature of RA. It is prolonged and usually lasts for more than ½ to 1 hour. It's presence denotes active disease. It diminishes or disappears as the disease activity is controlled.

Articular manifestations

RA can affect any joint, but most commonly involves metacarpophalangeal, proximal interphalangeal, metatarsophalangeal, wrist and knee joints. Articular and periarticular manifestations include joint swelling and tenderness to palpation, with morning stiffness and severe over period of motion impairment in the involved joints. Obvious inflammation of joints is seen in early, active disease. If the disease is not controlled early, there is progressive joint damage and development of deformities. Late in the disease joints might appear 'cold' and interpreted as minimally active. This is not so as the disease continues unabated with progressive joint destruction and functional deterioration.

*Early rheumatoid arthritis*

Spontaneous remissions in RA of longer than six months duration are rare. Symptoms due to joint damage do not respond to anti-inflammatory therapy or local corticosteroid injection(s). Joint deformities are the result of immobilization, bone and cartilage destruction and changes in soft tissues around the joint viz. ligaments, tendons and muscles.

Extra-articular manifestations

Subcutaneous nodules can occur in any region; they are most commonly seen on the extensor aspect of the forearm. Other common sites are Achilles tendon, ischial area, MTP joints and flexor surface of fingers. Often subcutaneous nodules develop in crops. They can disappear. Methotrexate treatment is sometimes associated with subcutaneous nodules. An important differential diagnosis of subcutaneous nodules is tophi of chronic tophaceous gout.

Dry eyes and mouth are often not complained of or realized by the patient and patients need to be specifically questioned. Other ocular manifestations include episcleritis and scleritis. The latter is a manifestation of rheumatoid vasculitis. It may lead to perforation of sclera (scleromalacia perforans). Corneal melt is a rare but serious manifestation and needs to be treated energetically with steroids and cyclophosphamide pulses.

*Nodule with olecranon bursa*

Interstitial lung disease is a serious manifestation and an important cause of increased mortality. Other pulmonary manifestations include inflammation of crico-arytenoid joint, pleurisy and lung nodules. Rarely a subpleural nodule may rupture into the pleura causing pneumothorax or empyema. Clinically significant cardiac (pericarditis, nodules in myocardium, valvular affection), gastric and renal involvement (amyloidosis) are rare barring drug induced, GI, renal and pulmonary complications.

Complications

Cervical spine involvement (atlantoaxial instability, subaxial spine involvement) can cause cervical cord myelopathy. Compressive neuropathies occur, the most common being involvement of median

nerve at the wrist (carpal tunnel syndrome). Ulnar and other nerves may be similarly affected. Mononeuritis multiplex is a manifestation of systemic vasculitis of RA. Amyloidosis is rare. With more aggressive and early therapy these complications are far less common today than in the past. Accelerated atherosclerosis is now an important complication.

Investigations

Haemogram often shows microcytic hypochromic anaemia of chronic inflammation, raised platelets and elevated ESR/CRP levels. Anaemia needs to be differentiated from iron deficiency anaemia that often complicates the picture. Thrombocytopenia is due to drugs used to treat RA. Rheumatoid factor positivity increases with the disease duration with up to 80% of patients with established RA being RF positive. Radiography in the early stages reveals soft tissue swelling around the joints and juxta-articular osteopenia. Most patients develop erosions and joint space narrowing within six months to three years of disease onset.



Xray hands showing joint space narrowing and erosions



Nodule with olecranon bursa

In the past 10 years, ultrasonography has gained acceptance for studying joint, tendon and bursal involvement in RA. Ultrasonography may improve the early clinical assessment and the follow-up of these patients, showing such details as synovial thickening and increased vascularity even within apparently uninvolved finger joints. MRI can detect erosions very early (within few weeks). However at present both ultrasonography and MRI of the joints are not advised routinely for lack of expertise and costs.

Course and Prognosis

Spontaneous remissions possibly occur, but are uncommon with established disease (of more than 6 months duration). Most of the joints get affected early in the disease course (within the first year). Damage occurs early in the disease (within a few weeks of disease onset) and tends to be progressive. Untreated patients develop significant disability after five years of disease duration. Life-span is reduced. Ischaemic heart disease, infections and respiratory failure are leading causes of death. Others are GI bleeding, perforation and renal failure (due to NSAIDs).

Diagnosis of RA

There is no single diagnostic test for RA. Investigations are used largely to support the clinical diagnosis. It is important to realize that the American College of Rheumatology (ACR) criteria (Table - 1) of RA are met with in patients with established RA and not fulfilled in early RA patients (ERA). A history of persistent joint pain, stiffness and swelling that is worse in the morning and after inactivity, presence of (symmetrical) swelling and tenderness of the small joints of the hands and feet (and to a variable extent of the larger joints) lasting for more than 12 weeks should

alert one to the possibility of ERA. These findings are not exclusive to ERA and therefore relevant differential diagnoses should be ruled out (table 2).

No laboratory tests or histologic findings are diagnostic of RA.

Table 1 : ARA classification criteria *
Morning stiffness
Arthritis of 3 or more joint areas
Arthritis of hand joints – Symmetric arthritis
Rheumatoid nodules
Serum rheumatoid factor
Radiographic changes

A patient should satisfy at least four of above seven criteria. First 4 criteria must be present for at least 6 weeks.

* For definitions of each criterion refer Arth. Rheum. 1988; 31 : 315 -324

Rheumatoid factor (RF)

Presence of RF in the serum is detected by the so called RA test. The test is positive in almost 80% of patients. i.e. 20% RA patients are sero negative. Further, RFs are present in many other disorders and hence by themselves or in isolation (i.e. without RA symptoms and signs) are of no diagnostic value. The test is positive in chronic infections such as tuberculosis, leprosy, viral illnesses (rubella, infectious mononucleosis) and chronic inflammatory diseases (chronic liver disease, sarcoidosis, interstitial lung disease, mixed essential cryoglobulinaemia and hyper gammaglobulinaemic purpura).

Table 2 : Differential diagnosis for ERA
<ul style="list-style-type: none"> • Viral arthritis - Usually lasts for few weeks; • Reactive arthritis - more common in males; follows GI or urinary tract infection • Seronegative spondyloarthropathy - males affected more commonly • Connective tissue diseases - characteristic extra-articular features are present • Polymyalgia rheumatica - affects elderly. Stiffness more than arthritis • Polyarticular gout - tophi present. Diagnosis confirmed with either H.P. of tophus or microscopic examination of aspirated material • Fibromyalgia - soft tissue pains. Investigations essentially normal • Medical conditions presenting with arthropathy - presence of specific disease manifestations. Keeping an open mind is important.

Anti-CCP antibodies

Recently tests for antibody against citrullinated peptides (anti-CCP antibodies) have become available. Although this antibody test has not replaced RF, the specificity for the diagnosis of RA is improved when both RF and anti-CCP tests are used together especially in ERA (specificity almost 100%; sensitivity ~ 60%). Further anti-CCP antibodies predict persistent erosive disease in those with early and palindromic arthritis and in differentiating elderly onset RA from Polymyalgia rheumatica.

Therapy of RA

The traditional management of RA i.e. the 'treatment pyramid', has been given up ever since it was recognized that RA is not a "benign condition with good prognosis". Erosive change, leading to joint destruction, often occurs in early disease and early loss of function may be irreversible. In addition, evidence is now available that early and aggressive intervention can improve long term disease outcome. The aim is to induce and maintain good control if not remission as early as possible.

All patients with persistent inflammatory joint disease (>12 weeks duration) should be considered for Disease Modifying Anti-Rheumatic Drug (DMARD) therapy.

NSAIDS

NSAIDS if judiciously used provide safe and effective anti-inflammatory and analgesic therapy in majority of patients (table 3); NSAIDs should always be used along with a DMARD. Any NSAID with acceptable efficacy and tolerability can be used. Initially full doses are needed but as the DMARDS take effect NSAID can be tapered out. Long acting NSAIDS given at night are usually preferred to control the early morning disability. Short acting NSAIDS are preferred during pregnancy and lactation. COX-2 inhibitors are as efficacious as other NSAIDS but have less GI side effects. Care should be taken in patients with recent acid peptic disease. Coxibs do not affect the platelet function but renal adverse effects are similar to conventional NSAIDS. Over the last few years rofecoxib and valdecoxib have been linked to increased cardiovascular mortality and withdrawn. Etoricoxib and naproxen appear to be devoid of cardiovascular effects. NSAIDS should be used with great caution (or avoided) in patients with established cardiovascular disease. Analgesics and spasm relievers can be used along with or as the only drugs when NSAIDS are contraindicated.

Table 3 : Doses of some commonly used NSAIDS

Drug	Daily Dose
Ibuprofen*	1200 - 3600 mg (3-4 divided doses)
Naproxen *	750 - 1500 mg (1-2 divided doses)
Ketoprofen*	150 - 300 mg (2-4 divided doses)
Indomethacin*	75 - 200 mg (2-3 divided doses)
Diclofenac*	150 - 200 mg (2-3 divided doses)
Aceclofenac*	200 mg (2 divided doses)
Piroxicam*	20 mg (Once a day)
Nimesulide**	200 mg (2 divided doses)
Meloxicam**	7.5 - 15 mg (Once a day)
Celecoxib***	200 - 400 mg (1-2 divided doses)
Etoricoxib ***	120 to 180 mg (1-2 divided doses)

*Non selective cyclooxygenase (COX) inhibitors

**Preferential COX-2 inhibitors

***Selective COX-2 inhibitors

Steroids

Steroids have been used in RA for a long time. Studies show that up to 40% to 60% of RA patients are on a small dose of steroids and patients on steroids (side-effects apart) seem to do well in spite of long term use. The recommended mode of steroid use is usually as a bridge therapy until the DMARDS start acting. As with NSAIDS steroids are never to be used in isolation. Steroids can either be used in the oral form or parenteral form (IV, IM). In RA, osteoporosis is an important side-effect of steroids especially when used for long periods. Prevention of osteoporosis is important. Routine calcium and vitamin D supplements are given and if more than 7.5mg of prednisolone or its equivalent are needed per day, then oral bisphosphonates are advised.

DMARDS

Methotrexate, leflunomide, sulfasalazine and chloroquine or preferably hydroxychloroquine are the most commonly used DMARDS. Older drugs like gold salts and d-penicillamine are no more in use due to toxicity. Choice of DMARD (Tables-4) should take into account patient preferences and existing co-morbidity. Although more than one drug is being used as the initial DMARD, weekly methotrexate in the absence of contraindications is now the drug of choice. Its efficacy, toxicity profile, compliance, the fact that patients stay on it for long periods, and its ability to reduce mortality has made it the drug of choice. Sulphasalazine and leflunomide are used as alternative initial DMARD in some centres.

Over the last few years aggressive combination therapy with close follow-up to reduce and ameliorate synovitis has been shown to improve short term outcomes. It is recommended that after initiation of therapy these patients should be followed up every 4-6 weeks with a view to escalate and add DMARDS as the situation demands to control the synovitis early. Hydroxychloroquine, sulphasalazine and small dose oral steroids (7.5-10mg/day) are the usual drugs that are combined with methotrexate. Although the FDA has not given approval for a combination therapy of methotrexate and leflunomide, a recent consensus statement opined that in refractory cases, this combination may be used before considering biological agents.

Lately quite a few biological agents have been used in RA. At present these are being used in resistant and recalcitrant disease. There are few ongoing studies of these agents in ERA. Until more is known, presently biologicals are not recommended for routine use in ERA.

Table - 4 - Characteristics of commonly used DMARDS

Drug	Route	Daily Dose	Dosing schedule	Time to benefit
Chloroquine (CQ)	Oral	150 mg base (2 mg/kg/d)	OD	2 - 4 months
Hydroxychloroquine (HCQ)	Oral	200 - 400 mg (max 6.5 mg/kg/d)	OD	2 - 4 months
Methotrexate* (MTx)	Oral / parenteral (SC, IM or IV)	7.5 - 25 mg* (before food)	Weekly; single or in divided doses	1 - 2 months
Sulfasalazine (SSZ)	Oral	1.5 to 3.0 g (usual 1.5 - 2 g) (max 40 mg/kg/d)	Daily in divided doses	2 - 3 months
Leflunomide**	Oral	10-20 mg/d	Single dose	6 - 8 weeks

Modified from Indian Guidelines for the management of Rheumatoid arthritis. *J. Assoc. Physicians India* 200, Vol. 50, Pg 9.

* There is now increasing data that up to 25 mg of methotrexate is well tolerated and more effective. Such increase should be carried out cautiously and in consultation with a rheumatologist. Dose should be lowered in the presence of renal failure. Routine folate supplementation minimum 5 mg/wk, is advocated (not to be given on the day of methotrexate). Alcohol intake in excess and administration of live vaccines should be avoided.

**Leflunomide has a very long half-life. An initial dose of 100mg daily x 3 days is advised. However due to side-effects, there is a trend to avoid it. This results in delayed response (few months).

Therapy of resistant disease and use of TNF- α blockers

As TNF- α blockers are expensive, every effort must be made to control the disease with a combination of DMARDs at their optimal doses. Usually subcutaneous methotrexate in doses of up to 20-25mg/week with or without full doses of sulfasalazine or leflunomide is tried. Since toxicity is an issue at these doses, frequent monitoring is necessary. (Table 5)

Table 5 - Toxicity monitoring of common DMARDs

Drug	Toxicity	Base-line	Periodic monitoring	Action***
Chloroquine/ Hydroxychloro- quine	Retinal toxicity	Eye check up	Every 3 - 6 months Every 6 months	Macular change - stop CHQ
Methotrexate	Hepatotoxicity, myelosuppression, megaloblastosis, pulmonary toxicity	CBC, platelet count, S. creatinine, SGPT, S. albumin S. Alk. Phosphatase X-ray chest HBV, HCV, HIV in high-risk patients	Every 4 - 8 weeks SOS	CBC* Dropping S. albumin** New or increasing cough / dyspnoea** > 2 N SGPT** Rise in S. creatinine - reduce dose
Sulfasalazine	Blood dyscrasias, haemolytic anaemia decrease in sperm count	CBC SGPT G6PD in high-risk patients sperm count	4 weekly for 3 months and then every 3 months sperm count ?	CBC* SGPT, SGOT, > 2 N**
Leflunomide	Hepatotoxicity, myelosuppression, megaloblastosis, pulmonary toxicity	CBC, platelet count, S. creatinine, SGPT, S. albumin S. Alk. Phosphatase X-ray chest HBV, HCV, HIV in high-risk patients	Every 4 - 8 weeks SOS	CBC* Dropping S. albumin** New or increasing cough / dyspnoea** > 2 N SGPT** Rise in S. creatinine - reduce dose

Modified from Indian Guidelines for the management of Rheumatoid arthritis. J. Assoc. Physicians India 200, Vol. 50, Pg 9.

For more details on toxicity, etc, relevant source material should be referred to.

*CBC with WBC < 4000/mm³, and / or neutrophils < 2000/mm³, and / or platelets < 1 lac/mm³, MCV > 105 fl-hold therapy. Consult a rheumatologist.

** withhold drug. Consult a rheumatologist

At the moment, TNF- α blockers are used in patients who are combination DMARD resistant. Some of the key guidelines regarding the use of these agents are given in Table 5. Infliximab and etanercept are currently available in India. Infliximab is given as an infusion (3mg/kg each) at 0, 2 and 6 weeks followed by maintenance dose every 8-12 weeks as needed. Etanercept is given as a subcutaneous injection once (50mg) or twice (25mg each) a week. Both agents are used in combination with methotrexate. Infections, aplastic anaemia, demyelinating neurological diseases, ANA positivity and rarely drug induced lupus have been reported with TNF- α blockers. Amongst infections, tuberculosis is particularly important in our context.

Other biologicals include adalimumab and rituximab. Adalimumab is yet unavailable in India. Recently rituximab (which is an anti-CD20 B cell targeted therapeutic agent) has been advocated for those with anti-TNF- α resistant RA. However as with the anti-TNF agents it is expensive.

It is important to inform the patients that biologicals are not a cure. About 40% of patients may not respond adequately to a biological. In them it is recommended to switch the biologicals around to see if they respond (which they often do). The whole field of treatment with biologicals is under intense study and recommendations, indications, combinations etc. will evolve as more and more experience is gained. (Table 6).

Table 6 : Key guidelines for the use of biologicals

- | |
|---|
| <ul style="list-style-type: none"> • Patients must have failed at least 2 DMARDS including MTX (20-25mg/wk) • Must have active disease • No major infections in the preceding 6 months • No malignancies in the preceding 12 months • Non pregnant, non breast feeding women • Etanercept or infliximab can be used depending on the patient's preference • Methotrexate is often used along with Infliximab to reduce the formation of antibodies. Methotrexate can be combined with etanercept, also combination has been shown to give better results |
|---|

Role of physiotherapy

Although the Cochrane database is not very forthcoming on the benefits of physiotherapy, Stenstorm et al in a recent review stated that both aerobic and strengthening exercises are of benefit for patients with RA. They recommended moderate to hard intensity aerobic exercises for up to an hour three times a week. This includes swimming, walking, cycling and other aerobic exercises. Similarly they also recommended moderate to hard intensity strengthening exercises (static or dynamic) including resistance training. Physiotherapy should be limited to gentle range of movement exercises when the disease is active and then slowly on to the above exercises as disease gets controlled. Initiation of physiotherapy from the beginning helps to maintain range of movements of

the joints and prevents development of deformities.

Role of occupational therapy

Skilled occupational therapy advice should be available to those experiencing limitations in function. There is some evidence that resting and working splints can be used to provide pain relief.

Role of surgery

Surgery is an integral part of the treatment. In patients with early disease, persistent synovitis in spite of adequate treatment is an indication for surgery - synovectomy. In the later stages when there is significant joint damage and disability one needs to take recourse to joint replacement. Joint fusion is advised when joint replacement is not possible. Other indications for surgery include carpal tunnel syndrome, symptomatic atlanto-axial subluxation, tendon rupture etc.

Future

Even though giant strides have been made in understanding the disease, we are still far away from the elusive cure. It is quite likely that in the years to come majority of patients will be offered a combination of biologicals to control RA. We will also have markers at baseline which will predict which patient will have aggressive disease. It is also likely that pharmacogenetics may give clues as to which drug may be the best for a particular patient. Advances in genetics may also predict whether siblings will develop the disease.

Conclusion

RA is a controllable but not yet curable disease. The best option is to diagnose it early and start treatment with DMARDS which can effectively control the disease. Maximum suppression of disease activity with a close watch on adverse effects of drugs is warranted. Combination DMARDS may be needed for those with aggressive disease. Anti-TNF- α therapy and other biologicals do offer hope for those with DMARD resistant disease but they are expensive and do not cure the disease.

SPONDYLOARTHROPATHY

Dr. Rohini Samant*

The term spondyloarthropathy (SpA) includes a group of heterogeneous disorders, the single somewhat unifying feature being their strong but not universal association with HLA B27 antigen. In 1974, Moll and Wright proposed that these disorders be broadly termed as seronegative spondyloarthropathies. Today the accepted term is spondyloarthropathy.

These disorders affect the axial skeleton, of which sacroilitis is the hallmark, peripheral joints and entheses i.e. the sites of tendon and fascia attachment to bone. Ocular inflammation in the form of conjunctivitis, skin lesions, iridocyclitis, aortitis and apical lung fibrosis are some of the systemic manifestations. The morbidity of SpA is comparable to that of rheumatoid arthritis. There is a significant socioeconomic impact of the disease since predominantly young individuals are affected. The term spondyloarthropathy encompasses the following conditions whose association with HLA B27 is as mentioned in brackets.

- Ankylosing spondylitis (90%)
- Reactive / Reiter's arthritis (75%)
- Psoriatic spondyloarthropathy (50 - 75%)
- Enteropathic SpA (30 - 70%)
- Undifferentiated spondarthropathies (25 - 50%)

PREVALANCE

The prevalence of SpA as a group is between 0.6 - 2.0%. Prevalence of ankylosing spondylitis (AS) in the general population is about 0.2% (0.1 - 1.1%). Among HLA B27 positive individuals the prevalence of AS is 2%. Stated the other way round, 98% of HLA B27 positive individuals do not develop AS. Among B27+ve first degree relatives of patients with AS, 20% can develop AS. HLA B27 negative relatives carry virtually no risk of developing AS. The prevalence of SpA is greater in males with a male to female ratio of 2-3:1. The disease onset is generally in the second or third decades of life (range 15-40 years).

PATHOGENESIS

One of the possible pathogenic mechanisms is molecular mimicry between certain bacterial proteins and self-derived peptides (HLA-B27) leading to mounting of immune response against the self antigens. In reactive arthritis, antigens of several organisms like Chlamydia, Yersinia, Salmonella, Shigella and Campylobacter have been identified in synovial fluid. Persistence of infection is probably important in the pathogenesis of reactive arthritis. However, antibiotic treatment has not been effective in treating reactive arthritis.

In AS, the contribution of genetic factors to pathogenesis is as high as 90%. The class I MHC genes including HLA-B27 account for about 50% of the total genetic susceptibility. None of the non MHC genes have yet been identified with certainty. The exact mechanisms by which HLA B27 confers disease susceptibility is not known.

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In early AS, dense mononuclear infiltrates are seen invading the cartilage. There are T cells and macrophages in this infiltrate which secrete TNF alpha, this is the principal cytokine implicated in perpetuating the inflammatory response.

There is evidence of intimate association of bowel inflammation with these disorders. Bowel inflammation may be obvious as in IBD or silent as in AS. The exact significance of this association is not fully understood.

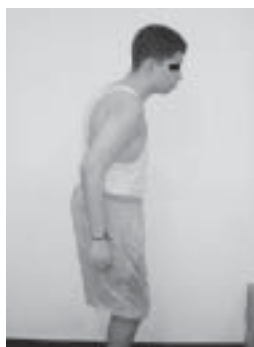
CLINICAL FEATURES

ANKYLOSING SPONDYLITIS

The symptoms usually begin in late adolescence and early adulthood. Onset of symptoms after the age of 40 years is uncommon. In a small proportion of patients the disease onset is in childhood (Juvenile ankylosing spondylitis). AS is 3 times more common in males.

A small proportion of patients may be completely asymptomatic. The common presenting complaint is inflammatory low back pain for more than 3 months duration characterized by prolonged (> 1hr) early morning and late night or inactivity stiffness and worsening of pain. The pain is often difficult to localize and is felt deep in gluteal area. There is often great difficulty in turning sideways or getting out of bed. Exercise and hot bath relieve the pain. In early stages constitutional symptoms like fever, weight loss, malaise may be present in some patients. The buttock pain is often typically alternating and radiating upto the knees. Chest pain on deep breathing, neck pain, feeling of tightness and stiffness in chest and abdomen are often elicited on direct enquiry.

Pain and tenderness at heel and other sites of entheses like the ischial tuberosity and spinous processes of vertebrae should be sought during examination. An asymmetric peripheral large joint arthritis involving predominantly the hips, shoulders, knees, ankles and infrequently manubrio-sternal, sterno clavicular and the small joints may be present. Occasionally the disease begins with hip and shoulder symptoms. Early involvement of hip indicates poor prognosis. The disease classically progresses from lumbar spine to thoracic and finally to cervical spine. The tempo of progression is variable. In severe, untreated patients the disease may progress to complete ankylosis of the spine involvement. Breathing increasingly becomes diaphragmatic.



Typical Posture of ankylosing spondylitis

Osteoporosis is related to persistent systemic inflammation and is a risk factor for vertebral fractures (upto 62% of patients). Increased disease activity has been found to correlate with decreased levels of 1,25 (OH) D₃. There is a higher incidence of spinal cord injuries after fracture dislocation of spine in AS. Extraskeletal manifestations include acute anterior uveitis (25-30%

patients), almost always unilateral. Residual visual impairment is uncommon. Acute iritis may be the first manifestation of AS in some patients. Cardiovascular, pulmonary and neurologic manifestations are uncommon. Amyloidosis is rare.

PSORIATIC ARTHRITIS :

The arthritis mostly follows the skin lesions but can occasionally precede skin lesions. The arthritis can be isolated peripheral arthritis, or spondylo-arthropathy or a combination of both.

Isolated spondylarthritis is rare in patients with psoriatic arthritis and is seen in only 2 - 4% of patients of psoriasis. However spinal involvement is seen in 40% of patients with peripheral arthritis.

Spinal involvement may go undetected (asymptomatic) unless specifically looked for. Spondylitis differs from AS in many ways. It may be present without involvement of sacroiliac joints or be asymmetric, and affect spine randomly. Patients with spinal involvement tend to be older males. Spinal involvement is not as severe as in AS.

Pain of peripheral arthritis is generally less than that of rheumatoid arthritis. DIP involvement is common as are nail changes. Pitting of nails is a characteristic feature. Enthesitis is common. Ocular involvement can occur. Cardiac and pulmonary involvement is rare.



DIP involvement in psoriasis

Radiologic changes include asymmetric sacroiliitis and syndesmophytes involving non contiguous vertebrae (skip lesions). In the DIP, PIP and MCP joints erosive changes leading to a typical pencil in cup deformity may be seen.

REACTIVE ARTHRITIS

Reiter's triad consists of reactive arthritis, conjunctivitis and urethritis or cervicitis.



Reactive arthritis typical palatal ulceration



Kerotoderma blenorrhagica of palms

The arthritis is acute in onset, oligoarticular or sometimes polyarticular with predominant lower limb involvement, and occurs 3-4 weeks after an enteric or genitourinary infection. Low back or

buttock pain (due to sacroilitis) occurs in 50% of cases. Dactylitis i.e. inflammation of the entire digit is frequently seen (sausage toe or finger). In addition, patients have pain at enthesal sites, the most common being heel pain. Signs and symptoms of conjunctivitis are often mild. Acute anterior uveitis characteristically affects one eye. Genitourinary tract [GUT] inflammation, in males, presents as mild dysuria or mucopurulent discharge; women may complain of dysuria, and/or vaginal discharge.

Oral mucosal lesions (typically painless), circinate balanitis, keratoderma blenorrhagica, hyperkeratosis and parakeratosis of nails may occur. There is no pitting of nails. Uveitis and cardiac conduction defects are seen in some patients. Some patients may have significant weight loss. Almost half of the patients have no obvious antecedent infection. The arthritis usually subsides within 3 - 6 months. Recurrences occur in 15 - 30%. Upto 15% patients develop chronic arthritis. Approximately 10% develop AS. Long term disability is mainly due to foot pain and joint deformities.

IBD ASSOCIATED ARTHRITIS

20% of patients with ulcerative colitis / Crohn's develop SpA. The arthritis can be of 3 types. Peripheral pauciarticular (< 5 joints), polyarticular (> 5 joints) or spondarthritis with or without peripheral arthritis. First two types of arthritis may precede the diagnosis of IBD. Peripheral arthritis reflects the activity of IBD; spinal disease may be asymptomatic and does not necessarily reflect activity of bowel disease. Clinically and radiologically, spine involvement resembles idiopathic AS. Erythema nodosum, pyoderma gangrenosum, deep painful oral ulcers, acute anterior uveitis, fever and weight loss are some of the extra-articular manifestations.

JUVENILE SPONDARTHRTIS

This is characterized by lower limb oligoarthritis and enthesitis in HLA B27 +ve boys over 8 years of age. A family history of spondarthritis is often present. Evolution to AS often occurs around puberty.

UNDIFFERENTIATED SPA

This term refers to conditions which have features of SpA but do not fall into any of the above mentioned categories. In a study of HLAB27+ve patients in this group, 34% remitted, 25% developed AS, 26% had recurrent oligoarthritis.

LABORATORY ABNORMALITIES

Laboratory abnormalities reflect the extent of inflammation. In active disease, there is anaemia with a raised ESR and thrombocytosis. CRP values are more sensitive, particularly when the inflammation is restricted only to the spinal joints. P-ANCA (atypical) are present in upto 60% of patients; tests for RF and ANA are negative. Synovial fluid in reactive arthritis shows high polymorphonuclear counts and may be mistaken for pyogenic arthritis. Negative culture and relatively less reduction of glucose help to differentiate reactive arthritis from pyogenic arthritis.

IMAGING

Pelvis with S-I joints

Plain X-ray of sacroiliac joints is graded as below :



Xray pelvis showing bilateral sacroiliitis



Xray showing typical bamboo spine

Gr.O - normal,

Gr. I - minimal change

Gr. 2- minimum abnormality. Small localized areas with erosions and/or sclerosis without alteration in joint width

Gr. 3: Unequivocal abnormality

Gr. 4: Total bony ankylosis

Lateral lumbar spine -

Features seen on lateral X-ray of spine are:

- Squaring of vertebra
- Small erosions at the attachment of annulus fibrosus to the vertebral body - Romanus lesion
- Ossification of interspinous ligaments
- Ankylosis of facet joints
- Spinal fractures (seen in severe AS). These occur at the cervico- thoracic / thoraco -lumbar junction, at sites where intervertebral disc and posterior ligaments are fused.

Peripheral joints -

Commonly involved joints are the hip, knee, shoulder, ankle and acromio-clavicular joint. Bilateral hip involvement is characteristic of AS. Chronic inflammation and new bone formation leads to joint destruction and ankylosis. Joint space widening, osteolysis, pencil in cup deformity and new bone formation are characteristic of psoriatic arthritis. Periostitis may be seen in reactive and psoriatic arthritis.

TREATMENT

Ankylosing Spondylitis

NSAIDs are the cornerstone of therapy. NSAIDs relieve pain and stiffness and facilitate physical therapy, maintain mobility and prevent development of deformities.

Physical therapy is as, if not more, important than medication. The modalities used are heat, exercises for the neck, back, peripheral joints, deep breathing and swimming.

Life long regular exercises improve pain, function and stiffness in AS. 2-4 hours / week of exercise is adequate.

Conventional DMARDs

Salazopyrine is useful in peripheral arthritis but not in axial disease.

Methotrexate may be useful in peripheral arthritis and of no value in axial disease.

Leflunomide may be an alternative available to treat peripheral arthritis.

Local steroid injections are indicated when the inflammation is limited to a single joint or at sites of enthesitis. IV methyl prednisone is useful in relieving pain and increasing mobility in patients with severe axial and peripheral disease.

NEWER THERAPIES

Bisphosphonates: Bisphosphonates suppress inflammation and cartilage and bone erosions. Parenteral (IV) dosing induces clinical and immunological effects not seen with oral bisphosphonates. Maximum response is seen after 3-6 months of monthly injections

Dose : Pamidronate is given as an IV infusion of 60 once a month for 3 - 6 injections. A flu-like syndrome is the chief side effect after first one or two infusions. This can be managed with paracetamol.

Thalidomide Inhibits TNF- α production and leucocyte chemotaxis to the site of inflammation. It has been found useful in several open trials but the overall numbers are still small. Peripheral neuropathy and gastrointestinal intolerance are the dose limiting side effects of thalidomide. The drug is not to be used routinely or without proper consultation.

Dose - Starting dose is 50 mg per day. The dose is increased gradually upto a maximum of 300 mg per day depending upon the response and tolerance.

TNF- α blockers These have revolutionized the therapy of AS. The two main biologic agents in use in India today are the chimeric monoclonal antibody infliximab and the soluble TNF- α blocker etanercept. Infliximab binds to both the soluble and membrane bound TNF- α receptor. Both the agents have been found to be useful in controlling the enthesitis, spinal and peripheral joint inflammation, stiffness and improve the quality of life of patients. Infliximab in particular is also very useful in managing the anterior uveitis seen in patients. Repeated infusions of TNF- α blockers are however necessary to maintain remission. Infliximab is given as an IV infusion in a dose of 3-5 mg/kg per infusion, given at 0, 2 and 6 weeks and repeated as needed (usually at intervals of 8-12 weeks). Etanercept is given subcutaneously in a dose of 25 mg biweekly or 50 mg weekly. The main side effects are increased susceptibility to infections particularly reactivation of pulmonary tuberculosis. A recent history of tuberculosis precludes use of these drugs.

ADJUVANT THERAPIES

- Low dose amitryptiline to improve sleep and fatigue
- Muscle relaxants to relieve muscle spasm
- Patient education about disease, importance of regular exercise and activities of daily living e.g. use of wide rear view mirror while driving, workplace modification etc. is an important component of total management.

- Treatment and prevention of osteoporosis with regular calcium and Vit. D; supplements and bisphosphonates

SURGERY

Surgery is necessary for hip involvement due to the disease or avascular necrosis due to steroids. The surgical options include total or surface hip replacement when the hip joint is damaged. Arthrodesis / excision of femoral head are only rarely used due to the success of hip replacement. Significant spine deformity can be partially corrected with surgery.

Summary of treatment of AS

Mild disease : NSAIDs with regular exercises

Mild disease with arthritis : salazopyrine, methotrexate and leflunomide for peripheral arthritis in addition to regular exercise. Local steroid injections when the inflammation is limited to a single joint or at sites of enthesitis.

Moderate to severe AS : characterized by high NSAID requirements, high disease activity, morning stiffness >45 minutes despite NSAIDs.

Spinal disease and enthesitis - Pamidronate and thalidomide

Local steroid injection

Systemic corticosteroids

TNF- α blockers

Peripheral arthritis/enthesitis Local steroid injection

Systemic corticosteroids

TNF- α blockers

Reactive arthritis

Acute arthritis is treated with NSAIDs in full doses. Indomethacin is particularly effective but any other NSAID can be used. Persistent arthritis is treated with sulfasalazine. TNF- α antagonists have not been used enough to recommend their use in recalcitrant cases.

Psoriatic arthritis

Peripheral arthritis is treated with NSAIDs for symptomatic relief. Methotrexate and sulfasalazine are effective in peripheral arthritis. TNF- α blockers are very effective in the control of the disease and are used to treat severe, uncontrolled disease.

IBD related arthritis

Peripheral arthritis usually responds to treatment of the inflammatory bowel disease. Spinal disease, enthesitis and peripheral arthritis are treated with combination of DMARDs with pamidronate, systemic corticosteroids and TNF- α blockers; Infliximab is preferred in patients of Crohn's disease.

CONCLUSION

Spondyloarthropathy is a common form of arthritis affecting young people with morbidity comparable

to that of rheumatoid arthritis. Recognition of patterns of disease symptoms is important in making a diagnosis. Exercise is as important as medication in treatment. Spinal pain and enthesitis are not well controlled with conventional disease modifying drugs which are effective only for the peripheral arthritis. Newer modalities of treatment like bisphosphonates, thalidomide and TNF- α blockers are useful to control severe manifestations.

Gr. 2 and above are sufficient for a definite diagnosis of AS



Bilateral sacroiliitis Gr. 3

Similar criteria are used for lumbar and cervical spine on a scale of 0-4 (normal, suspicious mild, mod, severe). These 3 scores are added up to produce BASRI - S (2-12 points) and also the hips (2-16) BASRI - hip.



X-ray cervical spine - lateral showing fusion of the facet joints

MRI grading with STIR images is useful in early stages of disease when X-rays may be normal. Bone oedema, enthesitis, sclerosis, erosions, syndesmophytes, partial fusion and ankylosis are the features seen on MRI.



MRI – Sacroiliac joint showing bilateral sacroiliitis

OSTEOARTHRITIS

Dr. Gurmeet Mangat*

Introduction

Osteoarthritis (OA) is the most common arthritic disorder the world over. It is also the most common cause of disability amongst the elderly. With increasing longevity the number of OA patients is on the increase. This has significant social and economic implications, apart from its impact on the quality of life of patients. Radiologic OA is more common than clinical OA.

Risk Factors

Age

The normal ageing process is thought to cause increased laxity around joints, reduced joint proprioception, cartilage calcification and reduced chondrocyte function. All these factors can lead to osteoarthritis. The Framingham Study found that 27% of those aged 63 to 70 and 44% over 80 years age group had radiographic evidence of knee osteoarthritis.

Table 1

- | |
|--|
| <ul style="list-style-type: none"> • OA < 0.1% below 35 yrs of age
10 - 20% between 65 - 74 yrs of age
30% above age of 75 yrs. • Females > men
(exception hip OA) |
|--|

Black females > white females

Aetiology

OA is commoner in those performing heavy physical work, especially if this involves knee bending, squatting or kneeling. Dockers and miners have a higher prevalence of knee osteoarthritis than those with sedentary jobs.

Exercise

There is increased risk of OA in high impact sports. Primary quadriceps weakness is a risk factor for its development. Muscle weakness leads to decrease in joint stability and reduced shock absorbing capacity of the muscle.

Gender and ethnicity

Under the age of 50, men have a higher prevalence while over the age of 50 (post-menopausal) women have a higher overall prevalence. Menopause may be trigger. OA is generally commoner in Europeans than in Chinese, Africans and Asians. OA of the hand is more common in European women than in Afro-Caribbean women.

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Genetics

There is increased concordance for OA in monozygotic twins compared with dizygotic twins. Many genes have been linked to OA. The genes involved code structural proteins of the extracellular matrix of the joint and collagen proteins. Children of parents with early onset osteoarthritis are at higher risk of developing it themselves.

Obesity

This is the strongest modifiable risk factor. Increasing weight increases the risk of contralateral OA of the knee in women with established OA of one knee. Being overweight in the 4th decade is a risk factor for developing knee OA in later life. In women, losing 5 kg of weight reduces the risk of symptomatic knee by 50%.

It is likely that the development of OA is multifactorial and more than one risk factor could act as cause of the clinical disease.

Pathology

Normal Cartilage Structure

The major constituents of articular cartilage are water, proteoglycans and collagen. Type II collagen predominates. Other types of collagen are present in smaller amounts. Collagen forms a network that provides a scaffolding. It maintains the structural integrity of the cartilage. Proteoglycans are large molecules made up of a protein core and glycosaminoglycans (principally chondroitin sulphate and keratan sulphate). These are linked to hyaluronic acid forming proteoglycan aggregates. Proteoglycans are highly hygroscopic and give a sponge like quality to the cartilage, allowing free egress and ingress of water which permits exchange of waste products and nutrients, as also deformability.

OA Cartilage

The main pathologic findings in OA involve the cartilage. There is fissuring ulceration and ultimately loss of cartilage, a change in the cartilage constituents, break down of collagen frame work, loss of proteoglycans, reduced number of chondrocytes and increased water content. These changes alter the quality of the cartilage. It loses its elasticity, resilience and deformability and becomes fibrous in quality. There is a change in the quality of synovial fluid, due to depletion of hyaluronic acid, resulting in loss of viscosity and ability to withstand shear forces. There is an increase in the activity of matrix metalloproteinase (MMP) enzymes. These breakdown the cartilage.

Pathogenesis

The initial event or trigger is trauma or mechanical stress which stimulates chondrocytes. Initial response is an attempted repair. Later catabolic processes predominate. Catabolism is under the influence of interleukin - 1 (IL-1) and tumour necrosis factor α (TNF- α) especially the former. There is increased synthesis of degradative enzymes [matrix metalloproteinases - MMP] which overcomes its normal inhibitors, the tissue inhibitors of MMP (TIMPS)].

With progressive cartilage damage, crystals of basic calcium phosphate are shed in the joint cavity. These evoke an inflammatory response and contribute to progression of osteoarthritic process.

Rest of the joint tissues also undergo changes. There is (mild) synovial inflammation, new bone formation (osteophytes), hardening of subchondral bone (eburnation), subchondral cyst formation and capsular thickening. The result is alteration in joint mechanics, which further stresses the joint. A vicious cycle thus sets in. Therefore, once initiated, osteoarthritic process often tends to continue unabated. There is reflex inhibition of muscles acting on and supporting the joint. There is loss of muscle mass and muscle strength. This results in joint instability and diminished shock absorbing capacity of the muscle. Loss of muscle support is an important factor involved in disease progression.

OA is thus the result of both mechanical and biologic events that lead to an imbalance of degradative and reparative processes. The disease involves all tissues of the diarthrodial joints.

Clinical Features

OA is a disease of middle aged and elderly persons, females being affected more commonly. Pain with stiffness and limitation of movements are the main presenting symptoms. The onset is usually gradual. Pain worsens with activity involving the joint and is relieved by rest. Initially the pain may be intermittent. As the disease advances pain becomes continuous and can disturb sleep. Pain at rest or in sleep indicates advanced disease.

The early morning stiffness (EMS) seen in OA is of a shorter duration (< 30 minutes, mostly of a few minutes duration) in contrast to the prolonged EMS seen with rheumatoid arthritis. Pain and stiffness are often worse in damp, cool and rainy weather.

Knee is the commonest joint affected. There is difficulty in sitting, squatting (using Indian toilet), walking and negotiating stairs. Quadriceps weakness causes instability and buckling. Hip pain is felt in groin which sometimes radiates to anterior thigh and up to knee and can be mistaken for knee pain. Involvement of first MCP joint leads to diminished dexterity of hands. Lumbar and cervical spine involvement causes neck and low back-pain respectively. If nerve roots and spinal cord are compressed, radicular and myelopathic features are superimposed.



OA of DIP & PIP Joints



OA knees

The usual signs are bony enlargement, localised joint (bone) tenderness, painful limitation of joint movements and a palpable coarse crepitus. Additional features include contractures, joint instability and locking of knee. Varus deformity is characteristic of OA knee. Patients walk with a limp or with a sway. In the presence of inflammation, effusion and local warmth may be present. Inflammation is most commonly seen in knees and hands (DIP and PIP joints). When inflammatory features are significant, superimposed gout or infection should be suspected. Bony enlargement at DIP and PIP joints typically causes Heberden's and Bouchard's nodes - classical of primary

generalised OA. Limitation of movement along with paravertebral muscle spasm are seen with spine involvement. Extension is painful and limited with involvement of facet joints of the lumbar and cervical spine. Common subsets of OA are boxed.

Subsets of OA

Isolated large joint OA

Nodal generalised OA

Erosive OA

Spine OA

Investigations

X-rays confirm the presence of OA. The classic features (best seen in knee) are localised narrowing of joint space, marginal osteophytes and subchondral bone sclerosis. With advancing disease there is formation of subchondral cysts. Still later there is medial subluxation of femur on tibia. Loose bodies may be present. Unlike RA, juxta articular osteopenia is not a feature of OA. In erosive / inflammatory OA of DIP and PIP joints, central erosions along with the other changes produce a typical seagull appearance.



Xray knee showing loss of medial compartment joint space

Usual laboratory tests are of little value in the diagnosis of OA. They are useful to diagnose comorbid conditions like diabetes mellitus, ischaemic heart disease, renal insufficiency, etc. They also act as base-line investigations while monitoring the therapy. Low titer rheumatoid factor and mildly elevated ESR can be non specific findings in the elderly. Very high ESR however warrants attention (malignancy, TB) especially with lumbar spine affection. Synovial fluid examination is indicated only when crystal arthropathy or septic arthritis is suspected. X rays help in confirming diagnosis and monitoring disease progression. X ray - clinical dissociation is not uncommon, however.

Diagnosis

Diagnosis of OA is usually not difficult. The characteristic pattern of joint involvement in primary OA is affection of DIP, PIP, 1st CMC, hip, knee, 1st MTP and cervical and lumbar spine. Not all joints are always affected. Generalised OA is characterized by Heberden's (DIP) and Bouchard's nodes (PIP). It is often familial and mostly affects females in their middle ages (around menopause). In non nodal generalised OA, there is often an element of inflammation. Generalised OA can be distinguished from RA by the pattern of joint involvement (MCP and PIP in RA, DIP, PIP and 1st CMC in OA). Lumbar and cervical spine OA needs to be differentiated from other causes of spine and soft tissue affection. In the West, polymyalgia rheumatica (PMR) is a common differential diagnosis. PMR is rare in India.

OA involving MCP, elbow, shoulder and ankle should suggest a secondary form of OA e.g. secondary to CPPD deposition, trauma etc.

Treatment

The aims of treatment are : i) relief of pain, ii) maintaining or improving joint function and iii) limiting physical disability. Therapy is best guided by the severity and distribution of joint involvement. Comorbid disorders need to be kept in mind. Guide-lines for treatment of OA have been formulated.

Patient education

This is the most vital part of the treatment. Patients should realize that as yet we do not have the medication that can reverse the changes of OA. Treatment will depend on the severity of symptoms and the extent to which the OA is hampering activities of daily living.

Life style changes

Patients are told to avoid postures and activities which could hasten the OA. For example those with knee OA are advised to avoid squatting and sitting cross-legged. Those with OA of the 1st CMC joint are given advice to reduce the stress on the thumb. Appliances and tools which help in the activities of daily living for e.g. opening of jar caps etc are useful.

Relief of symptoms

Topical NSAIDS are of some benefit if they are used for short while (2-4 weeks). However they can only be used in superficial joints. The amount used at a time depends on the size of the joint.

Due to the long term safety, Paracetamol should be used as the first line agent in those with OA. Care should be taken to prescribe the optimal dose. Up to 4gms a day of paracetamol in divided doses may be needed in patients to control the pain. Other analgesics including dextropropoxyphene, codeine, tramadol etc can be added in severe cases but again for a short while.

NSAIDS can reduce short term pain in osteoarthritis of the knee slightly better than placebo, but the current analysis does not support its long term use. As serious adverse effects are associated with oral NSAIDs, only limited use has been advised. The choice of NSAIDs will depend on efficacy, side-effects profile and associated co-morbid conditions.

Intra-articular steroids are used if the usual measures do not provide adequate relief. It is routinely used in OA knee, OA 1st CMC and rarely in OA hip. Triamcinolone hexacetonide and methylprednisolone acetate are the preferred choices due to the longer duration of action and less chance of steroid crystal arthritis. Usually, over one year period, not more than 3 injections are administered in a particular joint.

Neutraceuticals

There is some evidence to suggest that Glucosamine and Chondroitin can help reduce pain in patients with hip or knee OA. Glucosamine should be given in dose of 1500mg/day and Chondroitin in the dose of 1200 mg/day. These may take up to 2-3 months to provide benefit.

Exercise

Inactivity due to the pain of osteoarthritis leads to reduction of muscle bulk and joint instability. Regular physiotherapy is needed to build muscle strength and endurance, improve flexibility and

joint motion, and improve aerobic activity. Evidence suggests that being given a specific programme to do with "follow up" is probably more effective than advice alone.

Intra-articular Hyaluronic acid injections

Hyaluronic acid injections have been found to be superior to placebo in reducing pain and the need for steroid injections for 12 months. Symptoms relief usually starts within a month and at times persists for up to 12 months. They are as efficacious as NSAIDs for up to 6 months after injection. Hyaluronic acid injections are usually offered to those whose symptoms continue unabated in spite of usual measures.

Surgery

Patients with disabling pain or significant physical disability (inability to perform activities of daily living) should be offered joint surgery. Patients of OA knee complicated by internal derangement may be treated with arthroscopic debridement and if necessary meniscectomy. High tibial osteotomy is a good option for younger patients with disease limited to medial compartment. Total joint replacement is advised to patients with advanced OA with significant pain and disability. Joint replacement invariably relieves pain. It improves joint function though not to full normalcy. Infection and loosening are the two major concerns. Knee apart, hip joint replacement is a highly effective intervention. With spine involvement, surgery is indicated if progressive neurodeficit is present.

Other Therapies

Intra-articular injections of hyaluron (3 - 5 inj given at wkly intervals) give relief which may last from 6 months to a year, when the injections can be repeated. It does not alter the natural history of the disease process. Chondroitin sulphate (800 mg/d) and glucosamine (1.5 g/d) given orally have been shown in some studies to give pain relief after 4 - 6 weeks of treatment. The relief is sustained with continued therapy. Some reports also suggest chondroprotective effect with prolonged therapy (2 - 3 years). These are used singly. There is no data yet to suggest that combination therapy is better. Oral doxycycline has been used. It acts by reducing synthesis of MMP and thus reducing joint destruction but is not an accepted therapeutic agent yet. Colchicine (0.5 mg BD/TID) has been used to treat inflammatory OA. IL-1 receptor antagonists are under trial. The preliminary reports are encouraging.

Conclusion

OA is a common disorder. Hand, knee, and spine are the most commonly affected joints. Obesity, trauma, stress are important causative factors. Diagnosis is clinical. X-rays support the diagnosis. Comorbid conditions need to be kept in mind while advising NSAIDs. Non pharmacologic measures (weight reduction, ADL) play an important role in OA management. Analgesics, NSAIDs, joint support, exercises and assistive devices are the main therapeutic measures. Surgery also plays an important role. Newer therapies offer hope of better disease control.

SOFT TISSUE DISORDERS – FIBROMYALGIA

Dr. V. R. Joshi*

There are 640 muscles in human body. In adults, muscle mass constitutes 40% of body weight. Majority of patients presenting to a GP with rheumatic complaints have a soft tissue disorder, rather than arthritis. There are almost no diagnostic tests. Diagnosis needs accurate anatomical diagnosis of the structures involved. This is helped to some extent by ultrasound and magnetic resonance imaging (US or MRI), which can visualize soft tissues and identify the tissue pathology.

Soft tissue problems can be diffuse or localized. They can be acute when the cause is generally identifiable e.g. viral infection or trauma. The situation is different in diffuse pain syndromes where aetiology is usually less apparent. Repetitive trauma is usually responsible for chronic localized soft tissue problems.

Approach to Diffuse Musculoskeletal Pain

Many known rheumatic and nonrheumatic disorders can start off as diffuse musculoskeletal pain, e.g. rheumatoid arthritis, spondyloarthropathy, generalised osteoarthritis, systemic lupus erythematosus, vasculitis, polymyositis - dermatomyositis, polymyalgia rheumatica, hyper and hypothyroidism, osteomalacia, osteoporosis, hypermobility, metastatic bone disease, myeloma, HCV, EBV, CMV infections, chronic fatigue syndrome (CFS), psychogenic rheumatism, glucocorticosteroid withdrawal and post chemotherapy arthralgia. Some other causes seen in the west are Lyme disease and silicone breast implants. Most of these conditions can be suspected with a thorough history and physical examination coupled with appropriate laboratory investigations. e.g. Vit D and vit B₁₂ deficiencies are common and should be excluded.

One useful strategy is to review a patient with undiagnosed diffuse pain syndrome periodically for 6 months to 1 year for evolution or otherwise into a definite disorder. An elevated ESR or CRP is especially a good indicator for adopting such a course of action.

FIBROMYALGIA (FM)

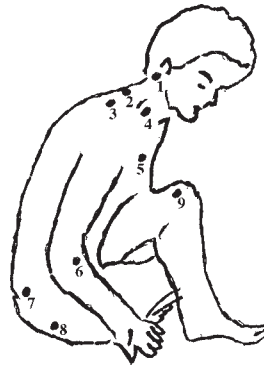
Fibromyalgia is the commonest rheumatic cause of chronic diffuse pain. Its prevalence varies from 1 - 5%, being the second commonest (OA is the most common) rheumatic disorder seen in general practice. FM shows a distinct female preponderance (M : F = 1 : 8). The disease is common between 3rd and 5th decades, though no age group is immune. It is not an inflammatory, degenerative or an autoimmune disorder. Its exact aetiology and pathology are not known.

Clinical features

The dominant complaint by the patient is diffuse soft tissue pains, typically concentrated in axial locations such as neck and low back. Patients describe their pain more vividly than say patients of rheumatoid arthritis. There may be associated stiffness, usually generalised, being worse in the morning. The intensity of pain and stiffness can wax and wane. Exacerbating factors include, poor sleep, emotional distress, moderate physical activity as well as inactivity and humid weather. The disease affects work capacity significantly. Fatigue, decreased strength and endurance are commonly complained of.

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Patients often complain of a feeling of swelling of the affected part, though it may not be evident to the examiner. Paraesthesias are often complained but clinical and electrophysiology studies are typically normal. Majority of the patients acknowledge to poor, non refreshing sleep. Depression is common.



Fibromyalgia – Typical Locations

Disorders considered psychosomatic e.g. irritable bowel syndrome, tension headache, dysmenorrhoea are commonly present in these patients.

Diagnosis

For the diagnosis to be considered history should include the presence of at least 3 months of wide-spread pain, that is bilateral, both above and below the waist, and include axial skeletal pain.

Table 1 The tender spots : Each on both sides

- The insertion of suboccipital muscles
- The anterior aspect of the intertransverse spaces at C5 - C8
- The midpoint of the upper border of the trapezius
- The origin of the supraspinatus, above the scapula spine near the medial border
- The second rib, just lateral to the costochondral junction
- Two centimeters distal to the lateral epicondyle
- The upper outer quadrant of the buttocks in the anterior fold of muscles
- Just posterior to greater trochanteric prominence
- The medial fat pad proximal to the knee joint line

The diagnosis is based on identifying characteristic tender spots (18 in all). (Table - 1) Tender points are not specific for FM, but it is their number and severity and low threshold that is characteristic of FM. The number of tender points has no correlation with the other clinical features. Though for classification 11 tender points should be present, in practice a patient can have less number of tender points. To be sure, control points, which are usually not tender, such as mid-forehead, mid forearm, thumb, and anterior thigh, shin (mid - tibia) should be simultaneously checked. In-patients with psychogenic rheumatism even these points are tender. Normal persons can have few mildly tender points. Trigger points are not a common feature of FM. ACR criteria have been formulated to classify FM (Table - 2). These carry 88% sensitivity and 81% specificity.

Table - 2 ACR Criteria for the Diagnosis of Fibromyalgia

<ul style="list-style-type: none"> At least 3 months of widespread pain defined as : Bilateral Above and below the waist, including axial skeletal pain AND Pain to palpation with 4 kg pressure at a minimum of 11 out of 18 predetermined tender points* Exclusions <p>The diagnosis of other diseases does not exclude the diagnosis of fibromyalgia</p>
<p>* At bed -side pressure that blanches the nail of the finger is applied.</p>

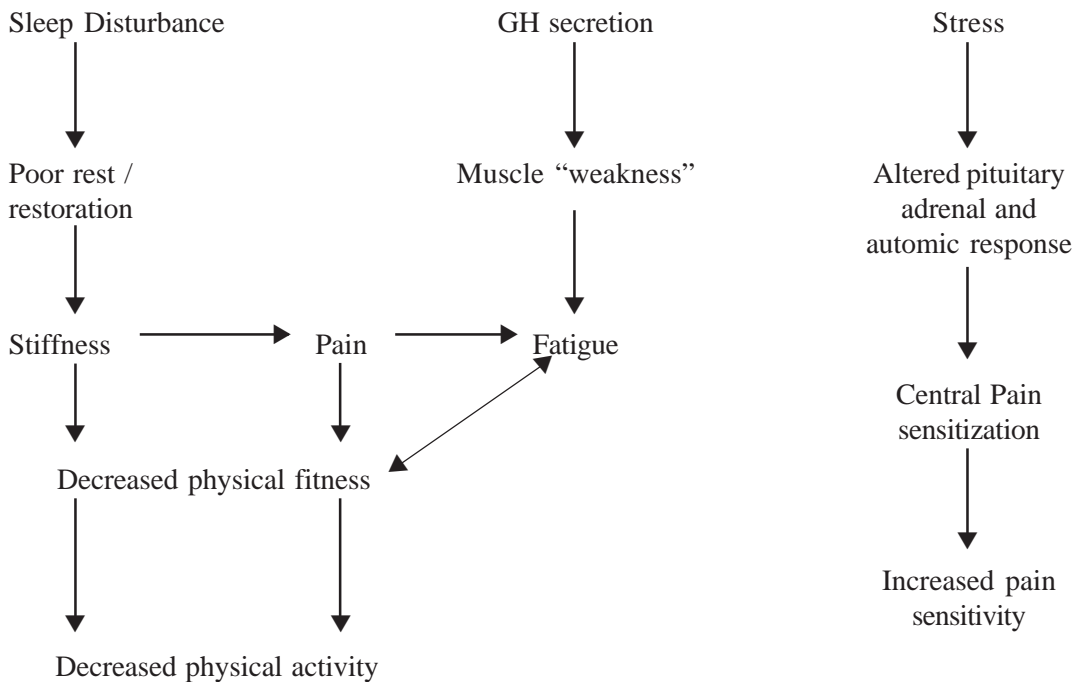
Investigations are more to exclude other disorders or to identify their concurrent presence as many patients of RA and SLE have secondary FM.

Myofascial pain needs to be differentiated from FM. These patients have localized, usually unilateral pain. There is no generalised stiffness, and fatigue. Local therapeutic measures such as stretching, heat, local injection of an anaesthetic or corticosteroid are enough. An aggravating or precipitating activity can generally be identified. The differentiation from psychogenic rheumatism has already been described.

Chronic fatigue syndrome (CFS) has many features in common with FM. CFS is characterized by disabling fatigue (more than pain) of more than 6 month's duration. There is history of recurrent pharyngitis, adenopathy and low grade fever. These features usually suggest a viral infection. Though suggestive, a viral cause has not been proven. Fatigue apart, tender points similar to FM are present. CFS and FM can co-exist.

Pathophysiology (Fig-1)

Fig 1 : Pathogenesis of fibromyalgia



Many abnormalities have been described. These are :

- i) Diminished blood supply to muscles along with decrease in high energy phosphate bonds
- ii) Generalised lowered pain threshold. Patients with FM have allodynia as well as hyperalgesia. This is the result of increased proprioceptive and decreased antinociceptive mechanisms at the spinal cord and cortical level. Limbic system may have a role in pain processing and reactivity
- iii) Decreased cerebral blood flow to thalamus and caudate nucleus. This may explain the diminished inhibitory pain modulation
- iv) Neurohormonal dysregulation : Almost all hormonal feed back mechanisms controlled by the hypothalamus are dysfunctional. There is decreased growth hormone secretion, diminished TSH and T4 response to TRH, and decreased adrenal response to ACTH
- v) Increased substance P levels in CSF : The down stream effectors of substance P are IL-8 (sympathetic pain), IL-6 (hyperalgesia, fatigue and depression). Increased levels of substance P in serum are associated with sleep disturbance, and correlate with decreased levels of serotonin precursor tryptophan. Substance P along with neurokinin A, CGRP can cause abnormal oedematous response of skin to mechanical stimuli.
- vi) Decreased serotonin blood levels - an expression of lowered activity of descending inhibitory pathways which have a greater degree of control over deeper tissue - pain than on cutaneous pain
- vii) +ve ANA
- viii) Dermal epidermal immune complex deposition
- ix) Tonic sympathetic hyperactivity
- x) Microtrauma of muscles or tendons. Variable changes have been described on histopathology of muscles.

None of these truly represent or explain the syndrome.

There is no evidence to suggest presence of premorbid depression in these patients though FM patients, often develop reactive depression. An important association is sleep disturbance. FM patients sleep lightly and wake up frequently at night. Sleep studies have shown disruption of stages 3 and 4 of non REM sleep. This deep delta wave sleep has an important restorative function. Restoring stage 3 and 4 sleep relieves symptoms like fatigue. Sleep apnoea, nocturnal myoclonus, bruxism and restless leg syndrome are also described, but their clinico-pathological relevance is not clear. Daytime restlessness due to dysesthesia may be present.

Treatment

Most important aspect of treatment is education. Patients need to be assured of 3 things.

- i) It is not a psychological disorder
- ii) It is not a life threatening disease or a disease with severe disability
- iii) Though not curable, effective treatment is available. The aim is to improve patient's quality of life. Patient's participation in therapeutic programme is absolutely essential.

Treatment attempts to deal with the symptoms of FM and the physical and psychological consequences of the disorder with drug therapy, exercise and cognitive behavioral therapy.

Drug therapy consists of tricyclic anti-depressants. Amitriptyline is the most commonly used agent. These produce restorative sleep, diminish fatigue, pain and improve sense of well-being. There is no effect on trigger points. Amitriptyline should be taken at least 1½ hours before sleeping time. Even so, drowsiness and anticholinergic effects can be troublesome. It is better to start with a low dose i.e. 10 or 12.5 mg which can be increased slowly to 25 mg or more. Tranquillizers and sedatives alone are not effective but if indicated can be combined with a tricyclic antidepressant. Similarly SSRS are alone not effective but can be combined. NSAIDS have no effect. Unless pain is significant and disturbs sleep, narcotics should be avoided. Antihistamines, muscle relaxants etc have been used.

Patient should be taught good sleep hygiene. Aerobic exercises should not be done within 4 hours of bedtime. Gentle stretching and relaxation exercises prior to sleep may help to get refreshing sleep.

In some patients there is marked deconditioning. This perpetuates fatigue and pain and makes the muscles more susceptible to trauma and damage. Exercise may exacerbate pain in some patients. Prior to stretching, muscles should be warmed up either actively by gentle exercise or passively by warm bath. The amount of stretching is important. Stretching to the point of resistance and then holding the stretch causes muscle relaxation (via Golgi tendon apparatus). Stretching to the point of pain precipitates muscle spasm and is counter productive. The stretch should be sustained for 60 seconds - one can start with 10 -15 sec stretch and work-up. Concomitant with stretching and strengthening exercises, patient should also undertake aerobic conditioning with pool exercises, walking and stationary cycling. Duration and intensity of exercise should be increased slowly.

Other measures include meditation, acupuncture, injection of tender points and massage.

Managing time and planning activities is crucial to FM management. Cognitive behavioural therapy helps to restructure maladaptive coping habits into effective coping habits. Patient should continue pleasurable activities. Accompanying disorders need to be treated optimally.

Prognosis

Though a chronic disorder, 20 - 25% may achieve remission especially those with less severe symptoms and of younger age. Others need long-term treatment.

Recommended Reading

General

1. Primer on the Rheumatic diseases J. H. Kipper. Ed. 11th edition. 1997. Arthritis Foundation USA
2. Kelly's text book of rheumatology. E D Harris, R C Budd, G F Firestein, M.C. Genovese, J. S. Sergent, S. Ruddy, C. B. Sledge, Eds VII Ed. 2005; Publ. Elsevier saunders
3. Manual of Rheumatology. P. K. Pispati..... Ed., 2nd edition, Publ. Indian Rheumatology Association.

Rheumatoid arthritis

1. Reveille J. D. The genetic contribution to the pathogenesis of rheumatoid arthritis *Curr Opin Rheumatol.* 1998; 10 : 187-200.
2. Pincus T., Callahan L. F. Taking mortality in arthritis seriously - predictive markers, socio-economic status and comorbidity. *J. Rheumatol* 1986; 13 : 841-845.
3. Cooper N. Economic burden of rheumatoid arthritis : a systemic review *Rheumatology* 2000; 39 : 28-33.
4. Anderson R J, Rheumatoid arthritis : Clinical and laboratory features in Klippel J. H. ed. *Primer on the rheumatic diseases*, 11th Ed., Atlanta, Arthritis Foundation, 1999, 161-167.
5. Gordon P, West J, Jones H et al. A ten year prospective follow-up of patients with rheumatoid arthritis 1986-96. *J. Rheumatol.* 2001; 28 : 2409-2415.
6. Visser H, Le Cessie S., Vos K et al How to diagnose rheumatoid arthritis early : a prediction model for persistent (erosive) arthritis. *Arthritis Rheum.* 2002; 46 : 357-365.
7. K. P. Machold, V. Nell, T Stamm, D. Aletaha, J. S. Smolen. Early rheumatoid arthritis *Curr Opin Rheumatol.* 2006; 18 (3) : 282-8.
8. Mikulus TR, Saag K. G. Comorbidity in rheumatoid arthritis. *Rheum Dis Clin North Am.* 2001; 27 : 283-303.
9. M. J. Kaplan. Cardiovascular disease in rheumatoid arthritis *Curr Opin. Rheumatol* 2006; 18 (3) : 289-97.
10. Aho K., Heliövaara M, Maatela J et al. Rheumatoid factors antedating clinical rheumatoid arthritis *J Rheumatol.* 1991; 18 : 1282-1284.
- 10a. Wolfe F, Cathey MA, Roberts F. K. The latex test revisited. Rheumatoid factor testing in 8287 rheumatic disease patients. *Arthritis Rheum.* 1991; 34 : 951-960.
11. Schelleknes GA, Visser H, de Jong BAW et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide *Arthritis Rheum.* 2000; 43 : 153-163.
12. Van der Heijde D. How to read radiographs according to the sharp/van der Heijde method. *J. Rheumatol.* 2000; 27 : 261-263.
13. Van der Heijde DMFM, Van't Hof MA, van Riel PLCM et al. Judging disease activity in

- clinical practice in rheumatoid arthritis : first step in the development of a disease activity score. *Ann Rheum Dis* 1990; 49 : 916-920.
14. M. A. Quinn, S. Cox The evidence for early intervention *Rheum Dis Clin. N. Am* 2005; 31(4) : 575-89.
 15. Dalen J. Selective Cox-2 inhibitors, NSAIDS, aspirin and myocardial infarction *Arch Intern Med.* 2002; 162 : 1091-1092.
 16. FitzGerald G A, Patrono C; The coxibs, the selective inhibitors of cyclooxygenase - 2. *N. Engl. J. Med.* 2001; 345: 433-442.
 17. Wolfe M M, Lichtenstein D R, Singh G. Gastrointestinal toxicity of non-steroidal antiinflammatory drugs *N Engl. J. Med.* 1999; 340 : 1888-1889.
 18. Simon L S, Smolen J S, Abramson S B et al. Controversies in Cox 2 selective inhibition *J Rheumatol.* 2002; 29 : 1501 - 1510.
 19. S. P. Ardoin, J. S. Sundy. Update on nonsteroidal anti-inflammatory drugs *Curr Opin. Rheumatol.* 2006; 18 (3) : 221-26.
 20. Suarez - Almazor M E, Belseck E, Shea B et al. Antimalarials for treating rheumatoid arthritis. *Cochrane Database syst Rev.* 2000; 4 : CD 000959.
 21. Emery P, Breedveld F C, Lemmel E M et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000; 39 : 655-665.
 22. J'Dell JR, Haire CE, Erikson N et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine, and hydroxychloroquine or a combination of all three medications *N Engl J Med* 1996; 334 : 1287 - 1291.
 23. Choi H K, Herman M. A., Seeger J. D. et al. Methotrexate and mortality in patients with rheumatoid arthritis ; a prospective study. *Lancet* 2002; 359 : 1173-1177.
 24. Weinblatt M E, Reda D, Henderson W. et al. Sulfasalazine treatment of rheumatoid arthritis: a metaanalysis of 15 randomized trials *J. Rheumatol.* 1999; 26 : 2123 - 2130.
 25. D. I. Cohn, S S Lim. New role for an old friend : prednisolone is a disease-modifying agent in early rheumatoid arthritis *Curr Opin Rheumatol.* 2003; 15 (3) : 185 - 92.
 - 25A. Keystone E C, Haraoui B. Etanercept Rheumatoid Arthritis. St. Clair W E, Pisetsky D S, Haynes B F. Ed. *Rheumatoid arthritis.* 1st Ed. Philadelphia Lippincott Williams and Wilkins. 2004, 3663 - 369.
 - 25B. St Clair W E - Antibodies to tumour necrosis factor a : Infliximab and Adalimumb. Ed. *Rheumatoid arthritis.* 1st Ed. Philadelphia Lippincott Williams and Wilkins. 2004, 370 - 384.
 - 25C. Impareto A K, Smiles S., Abramson S. Long term risks associated with biologic response modifiers used in rheumatic diseases. *Curr. Opin. Rheumatol* 2004; 16 : 199 - 205.
 26. Saag K. G., Criswell L A, Sems K M et al. Low dose corticosteroids in rheumatoid arthritis. A meta-analysis of their moderate - term effectiveness *Arthritis Rheum.* 1996; 39 : 1818 - 1825.
 27. American college of rheumatology Ad Hoc Committee on Glucocorticosteroid induced osteoporosis. Recommendations for prevention and treatment of glucocorticoid induced

- osteoporosis 2001 update *Arthritis Rheum.* 2001; 44 : 1496 - 1503.
28. C.Turesson, E L Matteson. Management of extra-articular disease manifestations in rheumatoid arthritis *Curr Opin. Rheumatol* 2004; 16 (3) : 206-211.
 29. Felson D T, Anderson J. J., Boers M et al. American College of Rheumatology Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 1995; 38 : 727-735.
 30. American College of Rheumatology. Subcommittee on Rheumatoid arthritis G 2002. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum.* 2002; 46 : 328 -
 31. Cooper S M. A perspective on the use of minocycline for rheumatoid arthritis *J. Clin. Rheumatol.* 1999; 5 ; 233 - 238.
 32. Cush J. J., Tugwell P, Weinblatt M, Yocum D. US consensus guidelines for the use of cyclosporine A rheumatoid arthritis. *J. Rheumatol* 1991; 18 : 1485-1489.
 33. C. Savage C., William St Clair E, New therapeutics in rheumatoid arthritis. *Rheum Dis. Clin. N. Am.* 2006; 32 (1) : 57-74.
 34. Hakkinen A. Effectiveness and safety of strength training in rheumatoid arthritis *Curr Opin. Rheumatol* 2004; 16 (2) : 132-137.
 35. de Jong Z, Vlieland TPMV. Safety of exercise in patients with rheumatoid arthritis. *Curr opin. Rheumatol* 2005; 17 (2) : 177-182.
 36. Steultijens EMJ, Dekker J, Boutler LM et al. Occupational therapy for rheumatoid arthritis : a systematic review *Arthritis Rheum.* 2002; 47 : 672-685.

Spondyloarthropathies

1. Braun J., Sieper J. Ankylosing spondylitis *Lancet* 2007; 369 : 1379-90
2. Dongados M., Van der Linden S., Juhlin R. et al. The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. *Arthritis Rheum* 1991; 34 : 1218-27.
3. Brewerton DA, Hart FD, Nicholls A, Coffrey M, James DC, Sturrock R. D. Ankylosing spondylitis and HLA-B27 *Lancet*, 1973; 301 : 904-07.
4. Van der Linden S., Valkenberg H., Cat A. The risk of developing ankylosing spondylitis in HLAB27 positive individuals : a family and population study, *Br J Rheumatol* 1983; 22 (suppl.) : 18-19
5. S. D. Reveille. The genetic basis of ankylosing spondylitis *Curr opin. Rheumatol.* 2006; 18 (4) : 332-41.
6. Van der Linden S., Van den Haijde; Ankylosing spondylitis clinical features. *Rheum. Dis. Clin. North Am.* 1998; 24 : 663-76
7. Braun J., Ballow M., Sipper J. Radiologic diagnosis and pathology of the spondyloarthropathies *Rheum Dis Clin. North Am* 1998; 24 : 697-735
8. Braun J., Landwee R., Herman KG et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab : results of a multicenter, randomised, double-blind, placebo controlled magnetic resonance imaging study.

9. J.C. Davis, F. Huang, W Maksymowych. New Therapies for ankylosing spondylitis : Etanercept, Thalidomide, and Pamidronate. *Rheum. Dis. Clin. North Am.* 2003; 29 : 481-94.
10. A. Anandarajah, C. T. Ritchin. Treatment update on spondyloarthropathy. *Curr. Opin. Rheumatol* 2005, 17 (3) : 247-56.
11. A. Kavanaugh, Z. Tutuncu, T. C. Sanchez. Update on anti-tumour necrosis factory therapy in spondyloarthropathies including psoriatic arthritis. *Curr Opin. Rheumatol* 2006; 18(4) : 347-53.
12. Tae-Hwan Kim, Wan-Sik Uhm, R. D. Inman. Pathogenesis of spondylitis and reactive arthritis *Curr opin rheumatol* 2005; 17 (4) : 400-5.
13. Zochling J, Van der Heigde D, Burgos-Vargas et al ASAS/EULAR. *Ann Rheum Dis* 2006; 65 : 442-52.
14. Keat A. Reiter's syndrome and reactive arthritis in perspective *N. Engl. J. Med.* 1983; 309 : 1606.
15. Amor B. Reiter's syndrome diagnosis and Clinical Features *Rheum Dis Clin. North Am.* 1998; 24 : 677-95.
16. Lambert, J. R., Wright V., Psoriatic spondylitis *Q. J. Med.* 1977; 46 : 411
17. Laurent, M. R. : Psoriatic arthritis *clin rheum dis.* 1985; 11 : 61 -
18. Zeilder H; Mau W., Khan M. A. Undifferentiated spondyloarthropathy *Rheum Dis Clin. North Am* 1992; 18 : 187-202.

Osteoarthritis

1. L. Sharma, D. Kapoor, S. Issa. Epidemiology of osteoarthritis - an update. *Curr Opin Rheumatol* 2006; 18 (2) : 147-56.
2. R. F. Loeser Jr. Aging and the etiopathogenesis and treatment of osteoarthritis. *Rheum. Clin. N. Am.* 2000; 26 (3) : 547-567.
- 2a. J. A. Buckwalter, J A Martin. Sports and osteoarthritis *Curr opin. Rheumatol.* 2004; 16 (5) : 634-39.
3. P. Dieppe, K. D. Brandt. What is important in treating osteoarthritis ? Whom should we treat and how should we treat them. *Rheum Dis Clin N Am* 2003; 29(4) : 687-716.
4. R. B. Raffa. Mechanism of action of analgesics used to treat osteoarthritis pain *Rheum Dis Clin. N Am* 2003; 29 (4) : 733-46.
5. Jean-Yues Reginster, O. Bruyere, M P Lecalt, Y Henrotin Naturoceptic (glucosamine-chondroitin sulfate) compounds as structure modifying drugs in the treatment of osteoarthritis. *Curr Opin. Rheumatol.* 2003; 15 (5) : 651-55.
6. K. Bennell, R. Hinman Exercise as a treatment for osteoarthritis. *Curr opin. Rheumatol.* 2005; 17(5) : 634-40.
7. H.A. Bischoff, E M Roos. Effectiveness and safety of strengthening, aerobic and coordination exercises for patients with osteoarthritis. *Curr opin Rheumatol* 2003; 15 (2) : 141-44.
8. Stemenda C., Brandt K., Heilman D et al. Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med.* 1997; 127 : 97-104

9. Cushnaghan J, Mccarty C., Dieppe P. Taping the patella medially : A new treatment for osetoarthritis of the knee joint ? *BMJ* 1994; 308 : 753.
10. K. Krohn. Footwear alternations and bracing as treatments for knee osteoarthritis *Curr Opin Rheumatol.* 2005 : 17 (5) : 653-56.

Fibromyalgia

1. K. Mannerkorpi. Exercise in fibromyalgia *Curr opin. Rheumatol.* 2005; 17(2) : 190-94.
2. Bennett R. M. The rational management of fibromyalgia patients. *Rheu. Clin. N. Am.* 2002; 28 (2) : 181-200.
3. Barkhuizen. A. Rational and targeted pharmacologic treatment of fibromyalgia. *Rheum Clin. N. Am.* 2002; 28 (2) : 2612-290.

Recommended reading

1. Jennifer Burkham, Edward D Harris (Jr) : Fibromyalgia, a chronic pain syndrome in Kelly's Text Book of Rheumatology. Edward D, Harris Jr, Ralph C Budd, Garry S Firestein, Mark C, Genovesse, John S. Sargent, Shuan Ruddy, Clement B. Sledge Ed. Elsevier Saunders Publ. VII Ed. pg 522-536
2. Bruce Freundlich, Lawrence Leventhal : Diffuse pain syndromes. In primer on the rheumatic diseases John H Klippel Ed., Publ. Arthritis Foundation 11th Ed. pg. 123-127.
3. Robert M Bennett : Rational management of fibromyalgia. *Rheum Dis Clin. N. Am* 2002; 28 : 181-200.
4. Dah Buskila : Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome. *Curr Opin Rheumatol* 2001; 13 : 117-127
5. K P White, M Speechley, M Harth et al : Coexistence of chronic fatigue syndrome with fibromyalgia syndrome in general population : a controlled study *Scand J Rheumatol* 2000; 29 : 44-51.
6. Kaisa Mannerkorpi : Exercise in fibromyalgia. *Curr Opin Rheumatol* 2005; 17 : 190-194
7. Haiko S Prott : What can rehabilitation achieve in patients with primary fibromyalgia *Curr Opin Rheumatol* 2004; 16 : 157-163

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