

Study on Osteoarthritis at Tertiary Care Centre and How to Diagnose and to Differentiate Primary from Secondary Osteoarthritis and Methods of Managements and Prevention and Rationale of NSAIDs Prescriptions in Osteoarthritis

Samikrishnan Perumal¹, Senthilkumar Balasubramanian², Senthakrishna Thangaraj³

¹Associate Professor of Rheumatology, Department of Rheumatology, K. A. P. Viswanatham Government Medical College, Mahathma Gandhi Memorial Hospital, Tiruchirappalli-01, Tamil Nadu, India

²Assistant Professor of Rheumatology, Senthilkumar Balasubramanian, K. A. P. Viswanatham Government Medical College, Mahathma Gandhi Memorial Hospital, Tiruchirappalli-01, Tamil Nadu, India

³Medical Officer, Urban Health Centre, Salem Municipal Corporation, Salem, Tamil Nadu, India

Abstract: Aim: To evaluate the most useful and easily available diagnostic approaches on osteoarthritis. To identify quite beneficial modalities of non-pharmacologic management in osteoarthritis. To identify the suitable pharmacologic treatments of OA in above middle ages and in old ages. Objective of the Study: As everyone aware, osteoarthritis is a commonest disability prone disease. As against in the past, quite large number of cases are presenting with this disease, not just in old but from above Middle Ages. All over the globe, in both sexes, the life expectancy is being appreciably increased. Likewise, because of the rise in affluency and easy reach of opulent diets, most of them appears plumb and bellies and unfortunately, it's all, often being seen in young and in middle ages. Thus, it ultimately leads to secondary flat foot and increase in intra-articular hypertension, medial and lateral tibiofemoral compartmental stress and repetitive injuries to internal structures of joints. When any one of these modifiable, non-modifiable and perpetual and repetitive causes are not removed, then, one must welcome, early onset of osteoarthritis. There are numerous cases are coming with features of OA to rheumatology out-patient department, I have aimed to do this systematic and prospective study on osteoarthritis from August 2006 to August 2020 and it was conducted in three different centres, namely in rheumatology out-patient department of the Government Mohan Kumaramangalam Medical College and Hospital, Salem where I have been there for more than a decade as Senior Assistant Professor of Rheumatology and K. A. P. Viswanatham Government Medical College, Mahathma Gandhi Memorial Hospital where I have been promoted as Associate Professor of Rheumatology, Tiruchirappalli and another one from Akitha Hospital, Centre of Excellence for Autoimmune Diseases, Seelanaickenpatti, Salem. Results: More than a decade of my experiences on 3208 osteoarthritis cases from rheumatology out-patient department of Government Mohan Kumaramangalam Medical College and Hospital where I have been there for more than a decade as Senior Assistant Professor of Rheumatology and K. A. P. Viswanatham Government Medical College, Mahathma Gandhi Memorial Hospital where I have been promoted as Associate Professor of Rheumatology, Tiruchirappalli and from Akitha Hospital, Centre of Excellence for Auto Immune diseases, Salem, Tamil Nadu State, India are have been included for this systematic and prospective on going study on osteoarthritis with basic diagnostic work up, and wherever necessary, appropriate non-pharmacologic and pharmacologic treatments have been suggested. By and large, the osteoarthritis, quite often rheumatologist are being seen OA cases with lot of wrong or misdiagnosis and with erroneous treatment and exposed strong dose of steroid and with various DMARDs as rheumatoid arthritis. Thus, in this article, I have taken meticulous attempts to convey to our colleagues to the ways to do basic diagnostic workup and disclose what are the common pitfalls could come across by treating doctors either in investigation or in diagnosis of OA before initiations of proper treatment. Conclusion: Proper clinical diagnosis and relevant basic investigations are enough for diagnosing osteoarthritis. At an early stages itself, when the modifiable and non-modifiable causes for the OA are identified and when it is removed or effectively modified with meticulous non-pharmacologic or by pharmacologic management, then there won't be any necessity for pain killers are required and in near future, as there are more promising treatments like cartilage repair, stem cell therapy and gene therapy are in the reach of everyone and surely, there is a visible hope for OA populations that, they can lead not just pain free life and they can aim for disease free life.

Keywords: Osteoarthritis, NSAIDs

1. Introduction

There are no specific investigations for diagnosing osteoarthritis. OA diagnosis is purely can be made from detailed history, complete physical examination and radiological investigations. But it is wise to investigate the given patient before initiation of your own treatment, because, certainly they might have taken many forms of treatments including steroids (oral, parenteral or intra-articular), all types of NSAIDs (sometimes double or triple analgesics), and all modes of treatment options available under the sun, and further, as we are going to

treat a disease of above middle age, it is always better to rule out co-morbid conditions. The non-pharmacologic treatment is an adjunctive therapy for the management of OA. Our goal is to control pain, disability and to improve quality of life. Unless the patient is subjected to non-pharmacologic therapy, our goal is not reachable just by pain killers. There is no unique treatment protocol is available to manage all OA patients, everyone is different in their mode of presentations and affliction of joints, the severity of OA, pain tolerance, type of occupation, purpose of joint mobility and their existing or associated illnesses are the determining factors for selecting the

appropriate treatment. The pharmacologic therapy an integral and paramount part of management of OA, vary from external applicant, oral and parenteral NSAIDs, disease modifiers, intra-articular steroid, visco-supplement, stem cell therapy, cartilage transplantation and etc. Each one has its own merits and demerits; thus, it is the duty of the physicians to select the suitable and appropriate one for their individual patients.

Diagnosis of Osteoarthritis

Laboratory Investigations

Complete Haemogram

Cell counts are usually normal, normocytic hypochromic anaemia; occasionally neutrophilia can be present, due to an acute episode of arthritis and synovial effusions, infection (iatrogenic) or by osteonecrosis. Acute phase reactants like ESR and CRP are normal or can be raised due to above said reasons and in erosive hand OA.

Biochemical Investigations (RFT, Uric Acid, Calcium, Blood Sugar, LFT, Newer Serum and Urine Markers of Bone and Cartilages)

Doing RFT is mandatory in all cases of OA. Always, it is best to do before and after initiation of NSAIDs, and DMOADs. In the presence of elevated or upper limit of normal RFT, beware about initiating or continuing NSAIDs, colchicine and diacerein. Mere presence of hyperuricemia is not going to label the diagnosis of gout or for even for initiating treatment for crystal arthritis. Do not reflexively write allopurinol, febuxostat just after seeing the value of elevated uric acid. Even a single dose of allopurinol is enough to cause or precipitate renal failure. Rather, the presence of hyperuricemia may give clue for diagnosing plaque or non plaque psoriasis due to rapid cellular turnover. Serum calcium estimation is not only useful for supplementing or treating for bone mineral loss or replacement, but it is occasionally useful to identify, the suspected cases of Paget's disease (with back pain, knee pain and deformity), hyperparathyroidism.

Blood Sugar

Diabetes per se is a worsening factor for OA, and if it is uncontrolled for prolonged periods, results in cardio nephropathy, and neuropathic joints. Therefore, the uses of NSAIDs are directly prohibited.

Liver Function Test and Pancreatic Enzymes

Sometimes, doing AST, ALT, alkaline phosphatase and s. amylase are helpful in some or all cases of OA. I have seen and heard that, number of patients with OA are known chronic alcoholic and often addict to one or other form of spirits. Almost all alcoholics, they have their ready-made comments, "I took it only to relieve pain". By virtue of age and pre-existing obesity, they are further prone for weight gain, hyperuricemia, gastroduodenal ulcers, chronic pancreatitis and hepatic complications, and including fatty liver. Therefore, use NSAIDs with caution.

Newer serum biochemical markers

Newer serum biochemical markers for cartilage and bone turnover- for Type I and Type II collagen markers like – C & N terminal – telopeptide and COMP can be useful, but it is difficult to do in routine clinical practice.

Urine analysis

Urine analysis, though appear simple, it gives lot of information's for the management of OA. Even before alteration of biochemical parameters, history of oliguria in NSAID received patients is the important clue for its toxicity. Look for albuminuria, if present, order for 24 hours UAE (urinary albumin excretion) and presence of new onset haematuria and RBC cast which can be caused by tubulointerstitial injuries by NSAIDs. Never forget crystals, demonstration of various crystals in urine are helpful for labelling diagnosis and management. Likewise, just by urine tests, we can identify the site of pathologic lesions of the joints by estimating COMP (cartilage oligomeric matrix protein), keratan sulphate, hyaluronan, type III collagen N terminal –propeptide and glucosyl galactosyl pyridinoline but yet no standardized ways of estimating these molecules and it need further study.

Serum Iron and Thyroid Function Tests

Ask for serum iron, TIBC and TSH, free T3 and free T4 hormones. Haemochromatosis is one of the known causes for secondary OA, but iron overload per se is not causing OA, rather these patients are likely prone for CPPD arthritis. Likewise, hypothyroid patients usually are not developing OA as against the expectation, but once on thyroxine replacement, they are rapidly showing evidence of HA or CPPD arthritis.

Serum Vit D3

Vitamin D3 found to be useful either to prevent or slow the progression of OA. As per Indian study, 70% of population are having Vitamin D3 deficiency due to lack of facility for Vit. D3 fortified food, poverty for balanced diet and lack of exposure to sun, even in sun plenty country of ours. Serum Vit. D3 less than 20 ng/ml, denotes deficient person, 21-29 ng/ml indicates, they are insufficient. Anything more than 30 ng/ml is enough.

Rheumatoid Factor and Anti- CCP

Sometime, these laboratory tests are done, only to rule out inflammatory arthritis in the given situation of erosive hand OA, and generalized OA or occasionally rheumatoid disease per se can coexist with OA. In fact, RF can be positive in low titer even in simple osteoarthritis as in general population.

Synovial Fluid Analysis

Synovial fluid analysis is not mandatory in osteoarthritis. Occasionally it can be done, to determine the cause of arthritis, particularly to rule out inflammatory or crystal arthritis. Joint fluid is usually sterile, clear, yellowish

white, viscous and forms 4 to 5 cm string (string test) and cell counts are about 200 cells per cmm^3 , mostly of lymphocytes. In inflammatory arthritis and crystal induced arthritis, viscosity is increased, and cell counts vary from 2000 to 20,000 per cmm^3 , and mostly of neutrophils. Synovial glucose is as that of plasma level and protein is usually half the value of serum, and if it is raised, indicates underlying infection as the cause. Uric acid is usually high in gouty arthritis. Synovial fluid LDH estimation may show increased levels in RA, gout and septic arthritis. Unless there was an iatrogenic infection, synovial fluid is negative for bacterial growth. In post-traumatic effusion, fluid is either haemorrhagic or serosanguinous, with hemosiderin pigments. Synovial fluid analyses are never complete, without looking for crystals in synovial fluid.

Crystals and Osteoarthritis

Whenever recalcitrant synovial effusion or persistent arthritis is present, never forget to look for crystals. Confirming the crystals are generally considered as the gold standard in clinically suspected cases of crystal induced arthritis. Synovial fluids contain a number of crystals, such as MSU (monosodium urate), CPPD, HA, BCP, cholesterol and particulate matters like degenerated cartilage, synovial fragments, fibril or rice bodies and occasionally steroid crystals can be seen if they have received intra-articular procedures etc.

Whenever synovial fluid on macroscopic examination per se appear as white solid and chalky deposits, it denotes gout and it can be proved by demonstration of crystals and if aspirate appear as milky paste or liquid, it suggest HA disease and gold glistening appearance can be due to cholesterol laden chronic shoulder effusion or an aspirate from olecranon bursa.

The standard approach for crystal examination, aspirated joint first to be examined under light microscope and crystals usually found near the edge of the cover slip, and sometimes, it can be seen inside the cells. Monosodium urate crystal appear as long slender needle and it can be up to 30μ whereas CPPD crystals of 3-7 μ size are look like rhomboid and square in shape. HA crystal present as round and shining solid deposits of about 3-15 μ .

Oil immersion may help identify small crystals like cholesterol, cartilage or synovial fragments and it appear as small, round, and glistening bodies. Whenever miss to pick up crystal by light microscope, it may be due erroneous aspiration from adjacent sympathetic effusion or subject the sample for polarizing microscopy.

Compensated Polarized Light Microscopic Examination

Polarizing light microscopic examination is the gold standard investigation for MSU and CPPD crystals. MSU appear as bright, slender, needle like, strong, negative birefringence crystals, and it is appearing yellow or blue when its orientation of light is parallel or perpendicular to

the compensator, and whereas CPPD crystals are weakly positive, non birefringence.

Radiological Investigations

Among non-invasive investigations, x-rays play an important role in diagnosis and assessing prognosis or progression of osteoarthritis of different joints. Though it is helpful in OA, we may miss to diagnose early OA where cartilage degeneration is the primary pathology. Theoretically speaking, MRI, power doppler and of course, arthroscopes are there for early OA assessment, but the radiological features of mere joint space narrowing's are nothing but due to cartilage losses. To pick up, pathological features of OA, the proper positioning, views, and penetrations of the x-rays are vital. Let me discuss about the x-rays of most the common to the least common joints of OA.

Do and Don'ts while taking knee X-rays

Do's

Always ask for x-rays of both knees – AP in standing (weight bearing) either in straight extended view (SEV) or in 15° fixed flexion view (FFV) with buttock touching on x-rays plate and lateral views are taken in perpendicular to AP in standing or else can be taken in sitting with knee in 90° flexion, and skyline view at 30° knee flexion to look for superior patellofemoral joint. Order for AP in standing view (FFV) with under penetration for the suspected cases of CPPD and HA crystal diseases.

Don'ts

Never take knee x-rays in lying (except in bedridden, and when they are unable to stand).

Never attempt to take unilateral knee, because that knee pain may be a complication of opposite knee pathology by unnoticed change in gait, and with one knee X-ray, we can't design to provide footwear modification. Unilateral knee x-rays may be useful only for fracture etiology.

What is use of X-ray views are in interpretation and diagnosis?

1. AP in standing view is helpful to assess all the features of primary and secondary OA, to look for medial and lateral tibiofemoral joints, osteophytes, loose bodies, CPPD arthritis, wrapping of patella and including for the condylar displacement and in planning for surgical and medical osteotomy and for designing footwear modification with insoles etc.
2. Skyline view is useful for chondromalacia, for assessing patellofemoral joint space and for subluxation of patella
3. Lateral view for patellofemoral JS, CPPD arthritis, wrapping of patella etc.

Common pitfalls while taking knee joint X-rays

Unilateral X-rays not at all helpful in the management plan of OA knee. When patients come with severe varus

deformity, radiographer may find it difficult to accommodate in AP view. In that case, we must ask radiographer to take X-ray knee AP in standing view of individual leg, subsequently.

What are the features to be looked for in X-rays of knee? (Figure 1.1, 1.2)

In primary OA, the presence of eburnation, asymmetrical Joint space narrowing, minimal soft tissue swelling,

subchondral sclerosis or enchondral sclerosis, intercondylar spike, osteophytes (usually large), condylar displacement or subluxation, subchondral cyst, usually no osteoporosis but rather osteosclerosis, patellar dislocation, varus or valgus deformities, condylar enlargement, erosions with sclerotic borders, osteophytic fractures, loose bodies or rice bodies in joint spaces, complete loss of joint spaces in all three compartments and complete loss of architecture of knee joints.



FIGURE 1.1 showing early lateral TF joint space narrowing, subchondral sclerosis and early valgus deformity. FIGURE 1.2 showing similar changes with an early osteophyte and condylar displacement.



CPPD Arthritis

X-rays features of CPPD arthritis can vary from simple calcification of articular cartilage to severe destructive osteoarthritis. It can be of either with linear calcification, punctate bead like calcification, wrapping of patella and with any of the above and with complete destruction of joints. (vide. Figure 1.7 to 1.12)



Figure 1.7 showing nonlinear, punctate bead like CPPD calcification of cartilage present. Figure 1.8 showing linear calcification of cartilage, joint space narrowing, thick osteophytes and wrapping calcification of patellae.

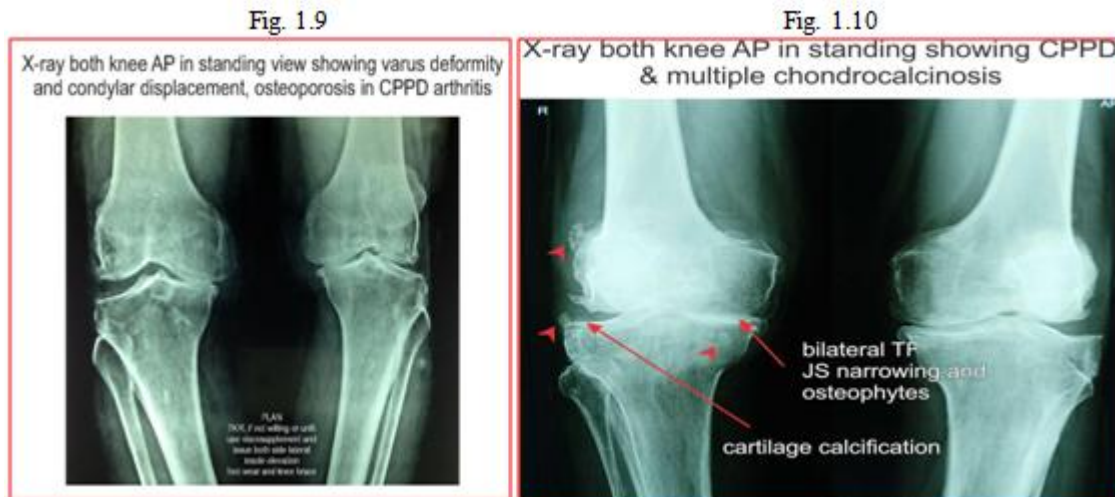


Figure 1.9 and Figure 1.10 showing CPPD and destructive OA with condylar displacement etc.



Figure 1.11 and 1.12 showing CPPD with both TF and patellofemoral joint space narrowing with multiple chondrocalcinosis. (courtesy: Samikrishnan Perumal)

How to identify Secondary OA.....?

Whenever anyone patient is present with joint pain, one must do clinical examinations, skiagram of the relevant

Inflammatory Arthritis and Secondary OA

joints and look for radiological features. If you come across with following findings such as uniform joint space narrowing, marked soft tissue swelling, osteoporosis, osteophytes (less commonly present, if at all present, it is only small and marginal), enchondral or subchondral sclerosis, subchondral cysts, pathological fractures,

subluxation and varying deformities, fibrosis or bony ankylosis with complete loss of architecture of joint with normal or smaller sized condyles with shortening of limb than the opposite joint and limb. Presence of one or all these features, invariably it goes in favour of secondary osteoarthritis.

Box.1.1

Kellgren and Lawrence Grading of Knee Osteoarthritis	
Grade of OA	Description
0 – None	No radiographic findings of osteoarthritis
1 – Doubtful	Doubtful narrowing of joint space and possible osteophytic lipping
2- Minimal	Definite osteophytes, definite narrowing of joint space
3- Moderate	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour
4- Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

Box.1.2

Bentley’s Modification of Ahlback’s Radiologic Grading of Osteoarthritis	
Grade of OA	Description
I	Narrowing of joint space
II	Narrowing of joint space with marginal osteophytes
III	Narrowing of joint space with marginal osteophytes and subchondral sclerosis
IV	Obliteration of joint space with erosion of bone and or subchondral cyst
V	Obliteration of joint space with instability and subluxation of joint

X-ray of Hands

Required views for OA hands are posteroanterior, oblique and lateral views are required. What are all the features to

be looked? The ABCDs approach to interpreting hand radiographs. It is best to have a systematic approach in reading X-rays of the hands. The actual order is less important, but one useful strategy is the ABCDs approach.

Figure 1.13



Box.1.3

ABCDs approach to interpreting hand radiographs	
Alignment	look for dislocations, subluxations DIP and PIP, squaring of base of thumb, subluxation of CMC joint.
Bone	Mineralization- Periarticular Osteosclerosis, usually no periarticular osteopenia or osteoporosis
	New bone formation- osteophytes,
	Joint spaces- narrowing’s in DIP, PIP
	Erosions- centrally located, osteophytes at margin with raised lips appear as sea gull-wings at DIP joints
Cartilage	Fractures- mallet fingers by avulsion fracture of proximal interphalanx base
	Joint spaces- reduced by loss of disc cartilage in CMC joints
Soft Tissue swelling	Calcifications
	Distribution of joint involvement- DIP, PIP, and CMC joints, symmetry usually maintained, rarely involve MCP joints
Soft Tissue swelling	Swelling – early OA periarticular swelling in DIP and PIP, swelling due Heberden’s nodes, and Bouchard's nodes

Radiological Classification of CMC OA (according to Eaton and Littler)

Stage 1:

Synovitis phase

Slight widening of the joint space

Articular contours are normal

< 1/3 subluxation of the joint (in any plane)

Stage 2:

Significant capsular laxity

1/3 subluxation of the joint

Osteophytes, < 2 mm in diameter are present (usually adjacent to volar or dorsal facets of the trapezium)

Stage 3:

> 1/3 subluxation of the joint

Osteophytes, > 2 mm in diameter are present

Slight joint space narrowing

Stage 4:

Major subluxation of the joint

Very narrow joint space

Cystic and sclerotic subchondral bone changes are present

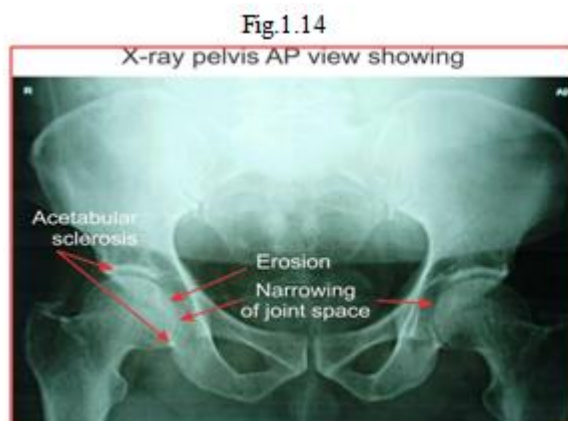
Significant erosion of the scaphotrapezium joint.

X- ray of Pelvis and Hip Joints

Following X-ray views are required for hip OA and occasionally in osteoarthritis of SIJ. X- ray pelvis AP, X- ray Pelvis- AP in internal rotation and in external rotation (Frog leg view), X- ray hip joints-lateral view.

What are the findings to be looked for in hip OA?

In properly positioned pelvis AP view, width of joint space is to be measured (point between acetabulum to vertical line drawn to midpoint of femoral head), anything less than 2 mm is reduced joint space, subchondral sclerosis (either in superior, inferior, medial or axial surface of acetabulae), marginal osteophytes, erosions, subchondral cyst and altered shape of femoral head can be noted. (Figure 1.14&1.15) Very rarely protrusioacetabuli can be seen when medial or axial disease is worsened by repeated injuries.



The following features can be noted in hip OA, such as joint space narrowing (<2.0 mm), subchondral sclerosis of superior acetabulae in pressure or impact prone area, subchondral sclerosis of inferior acetabulae in pressure or impact prone area, subchondral sclerosis of medial or axial surface acetabulae in pressure or impact prone area, marginal osteophytes (thin to large), erosions, altered shape of femoral head, subchondral cyst.

X- ray grading of hip OA

Kellgren grading of OA hip

Grade 1: (doubtful OA) with possible narrowing of the joint space medially and possible osteophytes around femoral head

Grade 2: (mild OA), with definite narrowing of the joint space inferiorly, definite osteophytes, and slight sclerosis

Grade 3: (moderate OA) with marked narrowing of joint space, slight osteophytes, some sclerosis and cyst formation and deformity of the femoral head and acetabulum

Grade 4: (severe OA) with gross loss of joint space with sclerosis, marked deformity of the femoral head and acetabulum and large osteophytes

Conventional radiograph grading of hip OA

Grade - 0: normal

Grade -1: possible joint space narrowing

Grade -2: definite joint space narrowing, defined osteophytes and some sclerosis in acetabular region

Grade -3: marked joint space narrowing, small osteophytes, some sclerosis and cyst formation and deformity of femoral head and acetabulum

Grade- 4: gross loss of joint space with above features plus large osteophytes and increased deformity of the femoral head and acetabulum.

X-Ray of shoulder joints.

Required x- rays for diagnosing OA of shoulder joints are X-Ray shoulder AP in internal rotation and external rotation at 45° abduction, X-ray axillary view- best for assessing glenohumeral joint space, X-ray scapular Y view- Normally head of humerus is present in centre angle of Y, and if any deviation, indicate shoulder dislocation

What we see in shoulder OA? (vide. Figure 1.16& Figure 1.17)



Figure 1.16 features inside the box itself. Figure 17 shows diffuse osteoporosis, erosions, cystic changes (courtesy: Samikrishnan Perumal)

and osteophytes, anterior, superior and inferior dislocation or migration of shoulder.

Narrowing of glenohumeral joint space (best seen by axillary view), subchondral sclerosis, marginal osteophytes, superior or inferior and medial labral erosions (most commonly inferior labral tear by recurrent shoulder dislocation), erosions of humeral head, subchondral cyst, altered shape of humeral head (loss of light bulb sign), acromioclavicular joint space narrowing

Radiological features of Milwaukee Shoulder

It can present with soft tissue swelling, joint space narrowing, subchondral sclerosis, cysts, capsular calcifications, rotator cuff tear, erosions, intra articular loose bodies, erosions of humeral head, acromioclavicular joint and occasionally complete or partial destruction of humeral head and outer 1/3 clavicle and acromion. (vide. Figure 1.18 & 1.19)



Figure 1.18 Right shoulder shows boggy swelling with fluctuation without tenderness, other joints were normal and 125 ml of straw coloured fluid aspiration was done. Figure 1.19 shows osteosclerosis, erosions of humeral head, glenoid labrum, clavicle and calcific deposits

are elbow in AP view (with fully extended elbow with forearm in supination), elbow in lateral view (with 90° flexion at elbow). Following radiological features of OA can be seen, such as subchondral sclerosis of radiohumeral joint (almost 100% get affected), narrowing of joint space, osteophytes (sometime large bridging osteophytes) are seen. When elbow joint is affected with OA, associated MCP OA can be present, this is called Missouri metacarpal syndrome). It can also affect humeroulnar joint with osteophytes emerging from both side of olecranon, large enough to immobilize the elbow with fixed flexion deformity.

X-rays of Elbow Joint with OA

Though primary OA rarely occur in elbow joints, certain occupations can cause osteoarthritis of elbow. (vide-pathogenesis on elbow OA).Required X-ray views

Osteoarthritis of Temporomandibular Joint

Commonly ordered X-rays of TMJ are on open mouth and closed mouth view, and oblique view (on tilting head to avoid overlapping TMJ joint of opposite side). The radiographic features are flattening, and osteophytes are commonly seen (27%), erosions: 13%, sclerosis: less common (9%). Majority patients (58.3%) with TMJ osteoarthritis are not having clinical or detectable radiological features. But due availability of CT scan and MRI, we can pick up early sign of TMJ osteoarthritis.

Osteoarthritis Spine and X-rays of Spines

Commonly ordered X-rays for osteoarthritis of spines are as follows- X-ray of cervical spine – AP and lateral, X-ray of lumbar spine – AP, lateral and oblique view to look for both side pars articularis of facet joint, X-ray of dorsal spine – AP and lateral (dorsal spine rarely involved by OA).

Spinal OA commonly involves facet joints (superior and inferior facets), results in sclerosis and joint space narrowing and painful restriction of flexion, extension and side to side movements. When it develops spondylophytes, it can either irritate the exiting nerve roots or it can compress root and cause radiculopathy. Spinal osteoarthritis can produce discovertebral lesions with marginal spondylophytes, and cause restriction of spinal movements on frontal and lateral plane. Hypertrophy of the ligamentum flavum, and ossification of the posterior longitudinal ligaments can occur. Ligamentum flavum hypertrophy can cause spinal canal

narrowing. Occasionally, cervical disc prolapses, or subluxation of vertebrae can produce compressive myelopathy, or it can be precipitated by whiplash injuries or by undue manipulations of neck by traditional bone setter. It may present with differential weakness of all four limbs with more weakness in lower limb than upper limb. When dorsal spine involved, it can either present as dorsal spinal pain or truncal neuropathy. Lumbar or lumbosacral spondylosis can present with mechanical back pain and depends upon the root or radicals compromise, lumbar radiculopathies or cauda equina syndrome when it involves S2, S3 and S4 roots. Spondylolisthesis, most commonly (95%) occur at L5 and S1 level, and in second or third degree of listhesis, can have neurological symptoms. Radiologically, the lateral and oblique view, the normal facet joints are appear as scotty dog sign, where transverse process appear as nose, pedicle forming the eye, inferior facet as front leg and superior facet forming the ear and pars interarticularis (portion of lamina that lies between the facet) is equivalent to the neck of dog. When there is disruption of pars interarticularis by spondylolisthesis, the break in neck area appear as dog has collar or scotty dog collar sign.

Ankle and Foot OA

The required X-ray views are ankle in AP view and lateral view and X-ray foot- AP and oblique view. OA of ankle joints are rare. When it gets involved, there will be loss of joint spaces in tibiofibular, tibiotalar and talonavicular joint spaces, subchondral sclerosis and osteophytic overgrowth will be seen. (Figure 1.20&1.21)



Figure 1.20 showing talocalcaneal and tibiotalar OA with subchondral sclerosis and early osteophytes.

Figure 1.21 showing post traumatic talonavicular OA with sclerotic border and with osteophytes and it simulate as gouty arthritis. However, 1st MTP is normal. (by Samikrishnan. P)

In long standing OA or in preexisting flat feet with secondary OA, there will be loss of ankle mortise, with slipping of tibiofibular joint with tibia at lower level than fibular styloid process leading to collapse of medial longitudinal arch further worsening the walking ability of the patient. Talotibial or talonavicular OA, result in difficulties in hind foot walk or walking over uneven surfaces. In foot, 1st MTP OA is more common, presenting with narrowing of joint space, sclerosis and osteophytic

growth, hallux valgus, hallux rigidus, mallet toes and very rarely can cause hallux varus. Chronic pars planus can cause metatarsal head dislocation or fracture.

Role of Power Doppler Ultrasound

In fact, because of its availability, affordability, reproducibility, absence of radiation, no need of invasive processes, made this modality as the first choice of imaging investigation for the evaluation and monitoring of osteoarthritis and other inflammatory arthritis and due to its economic benefit and virtual real image, power doppler US is considered as poor man's MRI. The advanced improvements in its technology, it can pick up even

minimal structural alteration of cartilages, synovium, effusion, capsular thickening, meniscus tears, tendon calcification, baker's cyst, ruptured baker's (mimics of DVT) and of course osteophytes.

The normal articular cartilage rich in water contents, hence it appears as sharp, (2-3 mm in large joints and 0.2 to 0.4 mm in small joints) anechoic band at outermost surface of the bone whereas once OA set in, cartilage water is lost, then the size of the cartilage band is thinned out and its echo's became altered and scattered and advanced cases, as margins became eroded, it looks sharp, irregular, hyperechoic band. The articular effusion can be picked up easily by anechoic or hypoechoic image within the joint, nature of fluid and its quantity can be accurately measured. Likewise, joint aspiration, and intra articular procedures and it can be helpful in monitoring response to treatment.

While examining the hip joint, whenever the distance between the surfaces of femur to joint capsule is more than 7 mm, or right and left hip joints difference of more than 1 mm, indicate that, there is an arthritis of hip with true effusion.

In crystal induced arthritis, the ultrasound appearance of double contour sign is diagnostic of gout and CPPD, with further precision, the intratendinous calcifications are suggestive of CPPD arthritis whereas over the surface of cartilages or tendon, is indicative of gout. To confirm this, synovial fluid analysis for crystals will yield diagnostic proof.

Role of MRI

MRI scan is a precise modality of investigation for an early and pre radiographic evaluation of OA. We can assess the exact, entire anatomical structural alteration of pathology and we can monitor the pathogenic initiation, perpetuation and progression of OA and it is possible to do three-dimensional reconstruction of any part of joints, but delineation of calcifications and bony changes can be poor.

Role of CT – Scan

CT is the choice of investigation for looking at bony changes and calcification of cartilages and preoperative assessment of the joints. The facet joint arthropathy can be better assessed. Drawback of CT scan is high ionizing radiation and its insensitivity to pick up cartilage changes of OA.

Nuclear medicine

The metabolism of skeleton, site of pathology and its severity OA can be made out by nuclear scan. The osteoplastic activity is noted by increased uptake of tracer of TC- 99 radioisotope, and it can be seen well before radiologically picked up. As per the study, there are good agreement between MRI and nuclear scan in demonstrating pathologic identification of bone marrow

lesions (BML) MRI and radionuclide uptake by scintigraphy.

Positron emission tomography (PET)

Like nuclear scan, PET by using fluoro deoxy glucose, we can identify the metabolic changes and areas of inflammation of the joints. PET in addition to high cost, and rarity, it too has high ionizing radiation.

Diagnostic Arthroscopy

The yield of tissue diagnosis of OA is much easier after an arthroscopic intervention. In addition to macroscopic diagnosis, we can do biopsy, and therapeutic wash and debridement of damaged joints.

In a small study from an Ireland and The Netherlands has compared with the synovial immuno-histologic features of early and late OA. They have selected early OA of less than 1 year duration and who are fulfilling the ACR criteria for OA knee with normal radiographs and synovial biopsy carried out by arthroscope at the point of maximum hypertrophy and degeneration and with late OA synovial tissue. These studies have shown that cellular infiltration, formation of neo-vessels and mediators of inflammation are less than what described in other inflammatory conditions like RA.

Synovial biopsy

It is not a common practice of doing synovial biopsy in OA. Pathogenetically, synovial inflammation can occur in early and late phases of OA, and again synovitis per se can cause clinical symptoms and thus targeting synovial cell inflammatory mediators, may alleviate symptoms of disease and perhaps also prevent structural progression. Therefore, synovial biopsy may occasionally be done in OA and by the way, it also helps us not to miss other autoimmune inflammatory arthritis. Synovial biopsy can be done either by open method or under arthroscopic guidance.

What Common Mistakes Happen During the Diagnosis of Osteoarthritis?

How to Differentiate Primary from Secondary Osteoarthritis?

One should not forget the medical dictum of “diagnosis precedes treatment” that is always must be right and never ever be wrong. If we miss, absolutely patient may miss right diagnosis and medications or else, it miserably leads to unnecessary stress to physicians and patients.

We often make mistakes in misinterpreting the patient's signs and symptoms. The pain: whenever patient complains of pain, it does not always mean an inflammatory arthritis. Just one question will help you to know whether we are dealing a case of inflammatory

arthritis or osteoarthritis, that is whenever, your patient's expresses his or her pain as "worsened by rest and relieved by work" it is an inflammatory arthritis whereas "worsened by work and relieved by rest" and it is surely and invariably due to osteoarthritis. When there is pain and swelling in DIP joints, don't jump to diagnose as OA, but it can be due to psoriatic arthritis, reactive arthritis, gonococcal arthritis, sarcoidosis, JIA, late onset RA (LORA), multicentric reticulohistiocytosis, tuberculosis, pachydermoperiostosis and including OA etc. Periarthritis, flexor tenosynovitis, tophaceous gouty arthritis, chickungunya arthritis, puffy hands of early scleroderma, MCTD, and RS₃PE syndrome can also present with arthritis, but everyone have its own peculiar clinical features and therefore one must pick up its own specific signs and reach diagnosis.

Sometime CPPD arthritis is mistaken for OA hand, RA, LORA, or mere OA being treated as RA, just because, he or she has PIP arthritis, clue for you to exclude RA by absence of MCP arthritis and bony hard DIP and PIP than usual doughy feel of RA synovitis. Adjacent structure of anserine bursa and trochanteric bursa can be inflamed by osteoarthritis of knee and hip, respectively. Hip disease with referred pain to knee, may end up with needless work up on knee joints.

People with cervical spondylosis with C3, C4 and C5 root pain, may be sitting as next candidate for an angiography. Spurling's test is clinically enough to waive from an invasive procedure. From my experience, many patients, in fourth, fifth and through sixth decades, present with shoulder pain and it is one of the indirect clues for an uncontrolled diabetes, thus proper treatment of diabetes can give immense relief from pain and thereby we can avoid unnecessary treatment as supraspinatus tendonitis, acromioclavicular or glenohumeral OA. Chronic non tophaceous gouty arthritis of 1st MTP, often wrongly diagnosed as OA or vice versa.

During diagnostic work up, unfortunately, in all cases of OA, some clinician's and many labs are doing useless tests like "arthritis panel's, autoimmune diseases panel's", and uric acid, ASO, CRP, ANA, anti-ds DNA, C3, C4 & erroneously ordering Rheumatoid Factor as RA Factor etc. (there is nothing like **RA Factor** and it is only **RF**). But I do not know, what is the rationale of doing these like arthritis panels or autoimmune diseases panels without knowing relevant clinical diagnosis and to my surprise, I don't know that what way all these type investigations are going to help them to treat OA. I humbly state that all immunological tests are maximum exploited by non-rheumatologist for no visible reasons.

Another noticeable common mistake is in ordering X-rays for diagnosing OA. Better to avoid ordering for X-rays of one limb, even when patient has pain one in limb, because unless, opposite joints X-rays are not there for comparisons, then there will be difficulty in arriving at diagnosis. Likewise, don't take X-rays in lying posture for weight bearing joint osteoarthritis of knee and hip. One limb X-rays might be useful for fracture cases but not for OA. As a clinician, always order X-ray knee in standing

posture in AP, standing with 15° flexed AP & PA view, sitting with 90° flexion and 30° knee flexion (skyline) view for looking tibiofemoral and patellofemoral joint spaces, respectively. Unless, bilateral joint views with weight or load bearing are available, we cannot know the real joint spaces, varus, valgus deformities and then, difficulties can arise in designing braces and footwear with medial or lateral insole elevation for reducing or preventing IA stress to tibiofemoral joint compartments.

Whenever any joint pain cases come, it is the duty of the clinicians to take proper history, clinical examinations and relevant work up to find out, whether they are having primary OA or secondary OA, because fundamentally, the management protocols are completely different one from another.

Treatment of Osteoarthritis

Non Pharmacologic Therapy

Education and Group Discussion

Symptoms of OA are often crippling and depends on somebody for day to day life thereby, they become frustrated and depressed. Therefore, patient education is considered an integral part of self management programme. When they know about their OA, available treatment options with care provider and availability of support group and group awareness programme, they can better involve themselves on their care. There are studies have documented that psychological and tender loving verbal and physical cares can give immense relief than real symptomatic drugs.

Patient education should be done in their regional languages without jargon of medical terms. Patient can get required information for making changes in life, how best to adapt and live with this debility or to prevent future debility and take decision on his or her work management. During this, patient can articulate with the fellow patients, share their views and expectations. They can discuss with care provider for the available treatment options, availability of resources in government or in private organisational health cares, how best they can control the symptoms with everyday domestic life, they acquire knowledge about self management and the risk and benefits. Mass exercise programme, sometimes reaches to patients very well than by individual teaching. The poor adherence to drugs and treatments defaults are very much less among patients who regularly come for group discussion. Instead of mere verbal discussion, audiovisual communication can easily reach public. We can give hand outs with an image explanation about the ways of exercise, how to stand, walk and sit can be helpful.

Physical Rest

Typically OA symptoms are worse by work and relief by rest but complete rest can give only negative results like muscle wasting and atrophy and functional loss or restriction of mobilities of joints. If patient presents with flare of OA with significant pain and inflammation,

returning to work after 12 to 24 hours of rest, is helpful to the patient. But they should be asked to do some form of passive physiotherapy at home.

Weight Loss

The obesity is directly linked to the development of OA on weight or load bearing joints, and also indirectly can affect non weight bearing joints by the cytokine (adiponectin). Therefore even modest weight loss, appears to lower the risk of OA knee and hip.

Exercise – Aerobic versus Resistance

Both aerobic versus resistive exercises can improve the power, endurance and range of movements of the structural components of joints. The strengthening or resistive exercise can be performed by bearable weight or with an inexpensive device. Whereas aerobic exercises like brisk walking, cycling, swimming or other low impact aerobics, help their heart and lungs get vitalized. The real benefits of exercise programme can be noted in patients who practice daily and definitely, they can perform well their routine works with meagre pain, and without morning gelling of joints, giving way than inactive counterpart.

Hot and Cold Therapy

Hot therapy

The joint stiffness, range movements and relief from fixed flexion deformity can be reduced by hot compression over the diseased joints. Though there are many practical methodology of heat therapy, simple home remedies like warm bath and showers can give better symptomatic improvements by lessening stiffness and resorption of swelling by venodilation. Care should be taken to avoid burning skin while doing heat therapy.

Cold therapy

Cold compresses can be of use in OA pain after a period of an exertion. It can be done easily at home itself. It gives excellent benefits in crystal induced arthritis.

Therapeutic Ultrasound

Osteoarthritis of knee, CMC, acromioclavicular, ankle and elbow joint OA can be dealt by US therapy using high energy sound waves, producing heat within the tissues, thereby it reduces pain and it is helpful for cartilage repair.

We can apply rubefacient gel while doing US therapy, and it is helpful in transdermal delivery of NSAIDs to the affected joint.

Life Style Modification for Joint Protection and Disability Prevention

Almost all people living with OA experiences some form of difficulty for their day to day activities, and including jobs, recreations, active physical relationship with their family members and close allies. Once patient understand the disease, and art of living with OA can be easily explained for care of joints, vocational activities to enable them to lead their life. Use mental exercises to relieve stress. Ask them to talk about the changes happened in OA pain and share their feelings with family and friends.

Family members also can help the disabled patients for reaching cane, walker, providing easy accessible racks for storing their files, keeping utensils and cooking commodities at reach. While sleeping, ask them to use cervical pillow. They can teach some tips for sitting, standing and walking with proper posture of body to avoid stresses on load bearing joints. The art of standing, one should keep the foot apart and one foot at front to have proper equilibrium. They can lean against the wall to have good spine support. One should not get up from bed quickly, but actually, they must roll, get up and sit up with hanging legs and do small waving moments of joints before standing and initiate walking to avoid postural falling of BP related issues and getting relief from gelling of joints. Likewise, whenever walking up in stairs, ask them to use stable limb first and while coming down, best to use diseased leg first, and if possible, holding the handrails gives an additional support. When they wanted to carry weight, they should equally spread the load to both sides or to have excessive weight on stable and non diseased joint side. The hand and elbow OA patients can easily handle purse with shoulder strap model than conventional one. There are art of lifting weight from floor by flex the knee and get up without stress to spine.

Orthotics- Footwear Modification, Braces and Knee Taping

Best results can be reached with orthotic devices, when they wear best designed and properly aligned one to suit the need of disabled osteoarthritic patients. There are many different types of orthotics like foot wear modification with medial and lateral insoles, adjusting limb height, splints and braces and application of patellar taping, etc are available for the needy patients. (vide. Figure 1.22 & 1.23)



Figure 1.22 Dynamic patella taping applied for recurrent dislocation of patella and in sports injuries.

Figure 1.23 Knee taping applied for soft tissues injuries following sports and running.

Footwears with insoles

When patients present with medial tibiofemoral OA, providing them with foot wear with lateral insole elevation, they feel comfortable and walk without pain, likewise medial insole elevation can be helpful for lateral tibiofemoral OA. Don't just jump in to advise foot wear modification, but clinical tricks play a role before suggesting foot wear modification, because many patients may have flat foot (pes planus) or differences in arches of foot, collapse of ankle mortise. My humble advice, always examine the feet in standing (straight), look for the presence or absence of arches (medial longitudinal and transverse), and its height, position of

medial and lateral maleollus, and then look at the knees for varus or valgus deformities and alignment of spine while they stand and during forward flexion. Normally, medial arch of foot must admit 3 fingers in its gap, and modification of insole chappals may not be decided by foot arches alone, sometimes, it should be changed according to the medial and lateral tibiofemoral joints spaces after ascertaining with x-rays of both knee in standing. Unless the foot wear matches with tibiofemoral joint spaces, there will be worsening of knee pain and gait. Without getting all these into consideration, just by advising foot wear modification, we are bound to fail in getting symptomatic improvement. The height of insole is decided by sizes of tibiofemoral joint spaces, sides of insoles depends on which side elevation is required to align the knee and foot is important, because knee is the utmost weight or load bearing joint and it is the only joint that evenly transmit the weight of our body to the ground. (vide. Figure 1.24 to 1.26).



Figure 1.24 Look at the image, this was taken before footwear modification, showing bilateral medial tibiofemoral joint space narrowing and intercondylar spike displacement

Figure 1.25 Look at this image again, it was taken after lateral insole footwear modification. Note the intercondylar spike, it become realigned well into the notch and good improvement in medial tibiofemoral joint space of left knee and both knee valgus reduced.

PLAN: Right medium size lateral insole. Left medium size medial insole footwear

Figure 1.26 X-ray both knees anteroposterior in standing position. Images were taken before insole footwear modification. Look, virtually there is no medial tibiofemoral joint space on right side and there is reduced joint space on left lateral TF joint.



Figure 1.27 X-ray both knees anteroposterior in standing position. Image was taken with insole footwear; there is notable improvement in joint space on right side. Even by this small improvement in the joint space, his walking is better and free from pain. (Courtesy: Samikrishnan Perumal).

FIGURE 1.28 & 1.29 showing bilateral collapse of ankle mortise, valgus of ankle and foot deformity and collapsed medial longitudinal and transverse archs of foot. This patient can have life, by foot wear modifications.

When there is collapse of ankle mortise, medial hind foot elevation or wrapping and cushioned elevation of medial malleolus is vital to give strength to ankle joint.

Splints and Braces

There are various splints with different sizes for all small and large joints are available to immobilize or to mobilize with the joints for maintaining normal anatomical position and their eventual function with an aim of aborting pain and deformity. Teach them to use the splints in proper position to achieve the results and that should be worn for longer period of time. Braces are useful in stabilizing the unstable joints and to align condylar displacement and with varus and valgus deformity of OA knee, shoulder braces may be useful in acromioclavicular and glenohumeral OA and acute Milwaukee shoulder with an effusion. Dorsolumbar braces for reducing discovertebral and root pain in spondylosis of DL spine. Cervical collar and cervical pillows are useful in cervical spondylosis. CMC joint OA pain can be reduced by full splint covering both thumb base and wrist than partial splint which covers only base of thumb.

Walking Aid, Cane and Crutches

Walking aids can reduce pain in OA by relieving direct impact on damaged joints. Always, we should teach them to use the sticks, cane, etc on side opposite to diseased legs to have additional load bearing capacity to normal side to carry forward the painful limb. The height of walker, sticks and cane should be at flexed elbow level. Adjustable aids are better to suit all the individual. Weightless walkers, canes and crutches with good bottom grip with suitable non slippery model of footing are useful in OA of hips, knees, ankle and including the dorsolumbar

spinal OA with kyphoscoliosis and cervical spondylosis with disturbances of gaits. By the use of sticks or cane, biomechanically, adduction movements across the medial tibiofemoral compartments and mechanical loading on hip joints are reduced, thereby we are preventing the main risk factor for progression of OA. Frames and wheeled walkers is preferable for those with bilateral diseases. Adjunctive assistive devices like enlarged grips on pens, electric can openers in kitchen, and bath room accessories like high level western commode, auto elevation model of seat cover, side bars in tub or wall mounted stainless steel clutches can be of use for the OA patients to perform daily chores. Sometimes, non slippery slippers or anklet or sandals and crepe model chappals may find useful in all elderly OA individuals.

Knee and Patellar Taping

Taping of knee's are important in preventing knee injuries during skiing, rugby game, healing of injured knees, and patellar taping is required in cases of patellofemoral OA, chondromalacia patellae, anterior knee pain syndrome, recurrent dislocation of patella and to align patella in cases of condylar displacement with patellar notch malposition.

Transcutaneous Electrical Nerve Stimulation (TENS)

It is yet another safe and effective adjunctive treatment modality for OA. In this modalities, small electrical impulses are passed to the skin and it stimulate the underlying pain receptors over the areas of interest and thereby it appears to work through inhibiting the nociceptive pain transmission via pain gate at spinal cord level and thereby it modify or reduce the pain.

Fascia manipulations

This is one type of manual chirotherapy practiced to manipulate the fasciae of the various joints and bodily parts by physiotherapist. It was developed by Luigi Stecco, an Italian physiotherapist. There are three types of fasciae, namely superficial, deep and subserous or visceral, which are intricately wrap and weft with its underlying structures. These fasciae contains thick undulated collagen and elastic fibres and these are arranged and aligned in different direction, and it can stretch. When the inflammatory focus or site is identified, an assisting, accurate, organized, unidirectional movements of the richly innervated fasciae can give myofascial and tensional rearrangements of the underlying structures, and it can give immense and lasting

pain and stiffness relief. It can be of use for spinal mechanical back pain, muscles spasm, the periarticular muscles weaknesses, periarthrititis, adhesive capsulitis, tendonitis, enthesitis, ligamentous laxicity and it can reduce the fixed flexion deformities of joints.

Yoga and Recreations

For millions of years, yoga is being practiced in India. It is a practice of exercise, breathing technique and meditation, and it being taught as a way to boost physical and mental health. Studies have proven that regular yoga can help people with arthritis, and It reduces the joint pain, improve joint flexibility and function, lowers the stress and tension, and promote sleep.

Acupuncture

Whenever conventional treatment fails to provide satisfactory relief, patient may seek alternative medical treatment. Acupuncture is an ancient chinese traditional practice and it has multiple potential benefits to diseased people.

In acupuncture, the qualified specialist of this field, uses the circulating Yang and Yin energy meridians the body. General belief that when these meridians get blocked, and eventually result in diseases. They usually identify the defined meridian of the suspected organ disease and stimulate it by pins and needles and thereby that acupuncture pins and needles may stimulate the nervous system and its neurohormonal secretions, including endorphins, endogenous opioids, and etc, which can influence the recovery of the affected organ and in addition, the pain sensitivity can be reduced through stimulation of sensory areas of brain. Berman et al, demonstrated the cascade of events and release of neurotransmitters like enkephalin and the release of cortisol which can reduce the pain and inflammations.

Tai Chi

Tai Chi is a graceful form of exercise. Chinese, call it as meditation in motion. It is being practiced as hours of sessions at once or twice a weeks. They should do gentle, slow and flowing series of bodily movements and simultaneous in depth breathing. Continuous practice of Tai Chi, can give relief to pain and sense of well being and desired strength to the arthritic patients. The role of Tai Chi on OA knee have been published in Arthritis Rheumatism states that 12 weeks of twice a week sessions with 4 stages of 10 minutes self massage, 30 minutes of Tai Chi, 10 minutes of deep breathing and 10 minutes of relaxation of body have given them reduced pain, improved physical mobilities and sustained benefits for a year (Chenchen Wang et al, 2009).

Mud –Pack Therapy

This is a cost effective management of osteoarthritis, where mud pack being applied to the painful joints. It can retain the cold compression effect for prolonged period than ice. The dark and greasy soil is suitable because it can form as paste, and can be easily applied. Due to its long retaining capacity of water, it can relieve stiffness, and control inflammation and it is found useful in sports related injuries and its effects was confirmed by reductions in the proinflammatory mediators like tumour necrosis factor α , interleukin- 1β , prostaglandin E2 and leukotrine B4 etc. Sometimes, it can absorb toxin from skin and simultaneously deliver its natural minerals, thereby it can vitalize body.

Pharmacologic Treatment

Topical Agents- NSAID and Capsaicin's Rubefaciants

It is a form of topical medication applied to the skin over the joints, available in the form of creams, gels, lotions and ointments. When applied to the skin, it causes irritation and reddening of the skin due to underlying vascular dilation with an increased blood flow. Various kinds of analgesic agents are being prepared for the use in acute and chronic musculoskeletal diseases. There are number of randomized and double-blind studies on topical uses of analgesic agents on acute and chronic painful conditions for a period for 7 to 10 days and 14 days of external application for acute and chronic conditions, respectively. Primary outcome was assessed in both groups of patients. But the results were not robust. Studies have not shown any evidence of pain relief with salicylate containing rubefacient gel.

However, as per CDC reports, diclofenac (1 & 1.5%) gel is effective in OA knee¹ and it can be applied to all the peripheral joints but rubefacient is not recommended for OA hip. There are number of other preparations from different classes of analgesics being used as rubefaciants like ibuprofen, ketoprofen, piroxicam etc. Often these rubefaciants contain various compositions of capsaicin, menthol and thiocolchicoside for the additive benefits. Addition of capsaicin (0.025%) with NSAIDs, with an aim to deplete the substance P, thereby the pain is controlled well. Therefore, rubefaciants can be of use in mild and moderate OA of peripheral joints and this is to be tried before initiating any form of oral NSAIDs.

Indication:

As per OARSI (Osteo-Arthritis Research Society International) EULAR and NICE (National Institute for health and Clinical Excellence), have incorporated topical NSAIDs into their OA management guidelines and before imitating oral NSAIDs as adjunctive agents. So, we can try in mild to moderate OA of peripheral joints, spine, age > than 70 years and, patients with cardiorespiratory diseases or GIT intolerances for NSAIDs, and in those who are using corticosteroids or anticoagulants.

Caution, Contraindications and usages

Known histories of drug allergy to any group of NSAIDs are contra indicated. The general advice, it is first to be applied over volar aspect of forearm and look for any allergy, if there is no evidence of allergic manifestations, and then it can be applied to joints with gentle massage and against the skin crease for at least twice a day. Do not apply rubefacient gels over non-intact skin or over ulcer areas.

Transdermal NSAIDs and Opioid Patches

Transdermal NSAIDs and opioid patches that provide continuous and systemic release of medicine by delivery system (TDS) are found to be effective and safe. The patches are provided with leak proof membrane on the top by polymer matrix. This should be fastened to cleaned and hairless or hair removed areas of the interest, and that be changed every 24 hours.²Comparative studies on diclofenac transdermal patches and oral diclofenac on tooth extraction results have shown that transdermal patch provided potent analgesia as that of oral agent and added advantages of better patient compliance (Hemant Bhaskar et al, 2010). Agarwal et al, 2006, on venous cannulation pain, Alessandri F et al, 2006 on post laparoscopic gynec surgery, Roth SH et al, 2004 on primary OA knee etc, have shown promising results as compared to oral or parenteral NSAIDs.

Acetaminophen (Paracetamol)

Acetaminophen is a relatively safe, low cost and it is a COX 3 inhibitor, gentle to stomach and it can be used in mild form of OA as a first line agent. It possesses weak anti-inflammatory, but efficient analgesic and antipyretic activity. It can be given as 1 gm divided doses and should not exceed 4 gm per day due to fear of hepatotoxicity, which get worsened when they use alcohol. Paracetamol may cause renal papillitis.

Opioids

Opioids should be considered when topical NSAIDs and paracetamol are found to be ineffective in relieving symptoms of OA. Opioids can be given by oral and transdermal (fentanyl) patch and it is acting through endogenous opioid receptors. There are number of side effects on using opioids, therefore, now it is restricted to codeine and modified release tramadol for OA treatment. Due to more incidence of addiction, codeine is banned from market.

Yet another European Union licensed novel therapeutic agent from opioid group, and it was designed to avoid nausea, vomiting and constipation by combining naloxone with oxycodone. Naloxone act as antagonist for oxycodone in the gut, thereby side effects of opioid is almost negligible.

Tramadol

It is a synthetic centrally acting opioid and the pain modulation caused by inhibiting the reuptake of norepinephrine and serotonin. As it is a water-soluble

agent, it can be given with or without food. The onset of action after oral administration is about an hour and its analgesic effect persists for six hours and it get metabolized in the liver by cytochrome P 2D6 and cytochrome P 3A4 enzyme conjugation. Because of its metabolism and its elimination occur via liver and kidney, dose adjustments are required in cirrhotic and in moderate to severe renal failure and likewise, tramadol dose to be reduced in older age, due to age related decreases in renal clearance and another co-existing organ dysfunction.

Vorsanger G et al, in 2007 is carried out study on geriatric OA patients with extended release tramadol and found that there was a significant improvement in pain and physical function and routine side effects of opioid like constipation, nausea, dizziness and headache.³

Dosage

Start with 50mg and slowly titrate the dose up to 300 to 400mg in four divided doses. Never give more than 400mg/day.

Drug Interactions

Whatever drugs get metabolized by cytochrome P 2D6 can have drug interaction, like fluoxetine, paroxetine and quinidine, can reduce the metabolism of tramadol, result in plasma concentration of tramadol increased whereas carbamazepine increases metabolism of tramadol, hence analgesic effect it reduced, and tramadol may precipitate seizure. There are chances of serotonin syndrome with seizures, if they consume MAO and serotonin re-uptake inhibitors along with tramadol.

Tramadol plus Paracetamol (Tramadol and Acetaminophen)

Across the world, this combo drug has satisfied many clinicians and millions of patients with moderate and moderately to severe pain of musculoskeletal systems without fear of known and unknown complications of NSAIDs and more so, it is quite often useful in certain comorbid conditions. In these fixed dose combinations, the individual drug dosage is lesser than, what is given separately to achieve the similar clinical benefits and in additions, the chances of side effects of each drugs are minimized.

Various RCT with this combo drug on OA patients have shown that significant reduction in symptoms and signs, and there was no haematemesis and renal complications.

Norman et al, evaluated the safety and efficacy of tramadol (37.5mg) and paracetamol (325mg) in 308 elderly OA patients with OA flare in 30 outpatient centres.⁴ In his observations, this combo drug was significantly superior to placebo for average daily pain intensity and relief. These combination drugs proved to be helpful in elderly OA patients, who had inadequate pain relief from either from selective or non-selective CO2 inhibitors.

Dosages

This combo tramadol plus paracetamol drugs are available in different doses, vary from 18.75mg +162.5mg, 37.5mg+375mg, 50mg+500mg, respectively. Start low and go-slow slogan is suits well for this combo drugs for getting better patient compliance.

Indications of Tramadol plus Paracetamol

As per the routine guidelines of ACR & AAOS (American Academy of Orthopaedic Surgeons), tramadol, tramadol plus paracetamol is the choice of initial treatment for OA of hand, knee and hip. Always start with low dose and slowly build up to avoid fore said opioid side effects.

Osteoarthritis and Co-morbid Conditions

There are few conditions, where NSAIDs cannot be issued due to some underlying comorbid diseases but tramadol plus paracetamol can be given without fear of NSAIDs complications or with dose reductions in the following situations such as- upper GI complications- Gastritis, Gastroduodenal ulcer, mild to moderate renal failure, mild cirrhosis or liver cell failures, ages less than 70 years, allergic to common NSAIDs, coexisting malignancy with MSK symptoms or with OA, salt and fluid volume over load patients, osteoporosis with mechanical back pain, Paget’s disease of bone, bone secondaries with or without pathological fractures and of course, patients preferences.

Common Rationale of Prescription of Non-Steroidal Anti-inflammatory Agents

Generally, in order to minimize potential side effects all types of NSAIDs, one should use low dose for the minimum duration and as well as, for the known side effects of NSAIDs, some amount of tolerable pain is safe than aiming for complete resolution of pain. GI side effects are common with NSAID use, dyspepsia, serious peptic ulcers, perforations and concealed or revealed GI bleeding. If NSAID is combined with paracetamol, GI

side effect will be high. Therefore, we can minimize upper GI complication by using gastroprotective agents and addition of proton pump inhibitor. Likewise, all NSAIDs can cause fluid retention, so care should be exercised while issuing in hypertensive and with existing renal and cardiac compromised patients. Both non-selective COX1 and selective COX2 inhibitors are associated with cardiac mortality by increased incidence of arterial thrombosis, but naproxen has lower risk profile. Long acting extended or sustained release formulations and other NSAIDs having enterohepatic recirculation’s can cause small and large bowel erosion, ulcers, concealed bleeding, perforation and rarely strictures. In all cases of total hip replacement, addition of NSAIDs in post-operative periods, found to prevent heterotopic new bone formation, raising concerns over possible effects on bone remodeling and osteophytes in OA (Larid Harrison et al, 2015). Alcoholic, if they continue to consume, they are at increased risk for NSAIDs induced upper GI ulcers. (Box.1.2)

BOX: 1.4

Risk factors for the development of GI ulcer in NSAID users	
established risk factors	Older the age
	Previous history of ulcer
	Person already on steroid
	One who on maximum dose of NSAID
	One who receiving more than one NSAID
	Patients already with anticoagulant
	Infection with H. Pylori
Possible risk factors	cigarette smoking
	Alcohol

While administering NSAIDs, it is vital to know about the disease chronobiology, because the pain of OA is worsened during work, as against inflammatory arthritis, worse at rest. Therefore, NSAID for OA patients preferably be administered in daytime as against, in RA and SpA, best to be administered at night.

Box: 1.5

Classification of Common Non-Steroidal Anti-inflammatory Agents

Salicylic acid derivatives	Aspirin	Not in routine use for OA	
	Diflunisal		
Heteroaryl acetic acids	Diclofenac,	25, 50, 75& 100 SR	TDS, SR- BD
	Aceclofenac	100mg, SR	BD
	Ketorolac,	10mg	TDS
	Tolmetin	200, 400mg	TDS
Propionic Acid	Ibuprofen	200, 400	TDS
	flurbiprofen,	50mg, 100mg	TDS
	Ketoprofen	50, 75mg, 100SR	TDS, SR- BD
	Fenoprofen	200, 400 mg	BD
	Naproxen	250, 375, 500mg	BD
Indole acetic acids	Indomethacin	25, 50mg, 75SR	TDS, SR- BD
	Etodolac	200, 300, 400mg	TDS
	Sulindac	150, 200mg	BD
Anthranilic acids (Fenamates)	Mefenamic acid	50, 100mg	TDS
Enolic acids Oxicams	Piroxicam	10, 20 mg	OD

	Tenoxicam		
	Meloxicam	7.5, 15 mg	OD
Non Acidic Compounds	Nabumetone	500, 750 mg	OD
Pyrazolidinediones	Phenylbutazone	Not in routine use for OA	

Ibuprofen

When patients are not responding to topical agents and paracetamol, we can suggest Ibuprofen, preferably with small dose. Ibuprofen appears to be safe to GIT but carefully avoid using high-dose ibuprofen (2400mg or higher per day) in patients with established CAD, PVD, CCF with NYHA class II-III and with uncontrolled hypertension. Theoretically, ibuprofen can be given as 200mg, 400mg, 600mg (3 times daily), but a single 200mg dose in the morning can give tremendous relief and better mobility to OA patients.

Diclofenac & Aceclofenac

Diclofenac and aceclofenac are commonly prescribed drugs for OA. The efficacy of it is largely unchallenged and as effective as newer COX 2 inhibitors. Better to administer with PPI or cytoprotective agent misoprost. There are reports that aceclofenac has chondroprotective and cartilage repairing properties and it has better tolerability than diclofenac. Usual precaution to be exercised in hepatic, cardiac and renal compromised diseases (Akimoto H et al, 2000, Reginster JY et al, 2001).

Indomethacin

Indomethacin is 20 times potent analgesic and anti-inflammatory than diclofenac. There are reports that indomethacin may cause joint space narrowing and cartilage degeneration in OA knee (Huskiison et al, 1995). However, when patient is allergic to diclofenac, ibuprofen and COX2 (contain sulpha) inhibitors, indomethacin can be tried and in addition, crystal arthritis like CPPD and Milwaukee shoulder arthritis responds better with this agent. Indomethacin has enterohepatic circulation; therefore, the chances of intestinal ulcer, perforation and stricture complications of small and large bowel can occur.

Naproxen

Among available NSAIDs, naproxen has better cardiac safety profile. Due to long half life, it can be given on twice daily basis. It is contraindicated in known cases of porphyria. American Academy of Orthopaedic Surgeon (AAOS) recommends naproxen 500mg BD with PPI for the cases of osteoarthritis (Alfred F. Tallia et al, 2016).

Ketorolac & Etodolac

Ketorolac is found to have more analgesic effect than anti-inflammatory, so it finds well in post-operative periods whereas etodolac has both analgesic and anti-inflammatory effect. It can be used in all cases of OA, inflammatory arthritis and crystal arthritis etc.

Piroxicam

It is a long acting NSAID, given as once daily dose. Ritonivir inhibits the metabolism of piroxicam increasing its toxicity. Lornoxicam is intermediate acting, this can be administered twice daily. ACE inhibitors and frusemide effects are reduced by piroxicam and if patient is already taking fluoxetine (SSRI drugs), do not give oxycam group of drugs, because it precipitates gastric bleed.

Nabumetone

Non-acidic compound derivative and it is relatively safe to stomach as this agent is a prodrug and it has no local prostaglandin inhibitory effect. Nabumetone may be taken during 2nd trimester of pregnancy but like any other NSAIDs, it is always better to avoid during 1st and 3rd trimester of pregnancy.

COX - 2 Inhibitors

Prostaglandins are synthesized by cyclooxygenase-1 and 2 (COX-1 & 2) enzymes. Each one has its own different effects on the body. COX-2 inhibitors are that selectively block the COX-2 enzyme, thereby generation of prostaglandins are reduced, as a result, pain and swelling of inflammatory signs disappear. As against COX2, COX-1 is an enzyme and it exist in number of tissues, including sites of inflammation and in the GIT and this COX-1 is known to protect the mucosal layers and maintain the blood flow of the gastrointestinal tract. Non-selective NSAIDs like aspirin, ibuprofen and diclofenac can block both COX-1 and COX-2. Thus, COX-1 inhibition helps in controlling inflammation, whereas the protective effect on the mucosal lining of the GIT is lost and these leads gastrointestinal upset, erosions, ulcers, bleeds and ensue in related complications of haematemesis, melena, blood loss and hypovolemic shock.

Patients who already on anticoagulant, to prevent coronary events, care must be taken while initiating COX2 blockers because it is associated with increased risk of MI, likewise, check BP, as there may be rise in blood pressure due to alteration in prostaglandin mediated renovascular pressure regulation and sodium and water retention.

Celecoxib & Etoricoxib

There are two molecules available in the market, celecoxib (100mg & 200mg) and etoricoxib (60mg & 120mg). Celecoxib alone is available in America. It can be prescribed to arthritis and OA patients with an evidence of gastro duodenal ulcers. But there are reports that high doses of COX2 per se, can cause gastrointestinal erosions and ulcers. Care should be taken in initiating in elderly individual with comorbid conditions like hypertension, ischemic heart disease and renal compromise with volume overload. It should not be prescribed prior to angioplasty due to higher chances of thrombosis and its related

morbidity. All coxibs are sulpha based compound; it cannot be given in individuals with sulpha allergy.

Nutraceuticals and Symptomatic Slow Acting Drugs for OA (SYSDOA)

There are wide range of natural products and food stuffs thought to have health benefits, so they are called as nutraceuticals. These nutraceuticals are claimed to have pain relieving effects and or it retard the structural damages of OA joints, and so it's further referred as SYSDOA. Since they are food products and there is no compulsory quality control, it can be purchased at OTC (over the counter) and in supermarkets. The mode of action and in vitro or in vivo studies on these molecules are controversial.

Glucosamine and Chondroitin Sulfate

(Glucosamine Sulfate derived from shell of shellfish and hydrochloride from crustacean chitin and chondroitin derived from cow cartilage).

Aggrecan of cartilage is a compound of glycosaminoglycan and it consists of glucosamine and chondroitin. Biomechanically, these negatively charged glycosaminoglycans are forced into close proximity during intraarticular stress (IAS) by compression at and at the end of compression or release from IAS, the predominant electrostatic force of these aggrecan molecules, move away from each other, and ultimately cartilage resume back its original thickness. Therefore, the chondroitin and glucosamine are the one, which contribute to biomechanical compressive stiffness of cartilages. Matter of fact, glycosaminoglycans are not synthesized from intact glucosamine or chondroitin molecules, and therefore, it is unlikely that ingested glucosamine or chondroitin could be assimilated or taken into intact cartilage. When we ingest glucosamine salt (either of HCL or sulfate form), this molecule dissociates into glucosamine and its one of salt. Thus, the anion accompanying glucosamine does not have therapeutic effect of glucosamine.

Various RCT have shown its efficacy in OA knee and hip by the patient global and physician's global assessment and by WOMAC index. Likewise, animal studies also have proven anti-inflammatory effect by glucosamine and chondroitin sulfate. Others have postulated the effect of these kinds of food supplements, indirectly on the bone and joints via its direct effect on the liver.⁸⁹ Despite over two decades of research, the efficacy of glucosamine for osteoarthritis is still unclear.

Diacerein

Diacerein, a cathartic, obtained from rhubarb species like *Rheum undulatum*, *Rheum palmatum* and *Cassia reticulata*. The review of literature discerned that diacerein found to be slightly, but significantly, effective than placebo in OA knee and hip by reduction in both pain and progression of disease.

Diacerein, specifically blocking the actions of interleukin-1 beta, thereby inflammation can be reduced. In vitro and in animal model showed that, diacerein found to have anti-OA and cartilage repairing effects. The studies have shown that, in patients with OA knee treated with diacerein dosages of 50 mg, 100, and 150 mg/day as BD doses in three different group of patients are found to be effective and it conclude that minimum required doses are 100mg twice a day.^{5,6}

Glucosamine and Diacerein

The evidence from meta-analysis shows that in symptomatic relief of OA hips and knees, both glucosamine and diacerein are appears to be same. However, side effect profiles are more with diacerein.

Univestin

It is derivative of plant flavonoids from *scutellariabaicalensis* and *acacia catechu*. Since it is food supplement, it can be sold at OTC without the prescription.

Univestin acts by modulating the COX and LOX enzymatic pathways and reduces the proinflammatory cytokines while simultaneously increasing antioxidant activity and regulating gene expression. Univestin has been clinically proven to provide fast acting relief of joint discomfort and stiffness by alleviating discomfort, stiffness, and improve joint mobility.

Comparative study using univestin and naproxen was carried out for about week duration in OA knee and laboratory work up was done for proinflammatory cytokines like IL1 β , IL6, TNF μ and hyaluronic acid and clinical evaluation was recorded for Pain, knee range of motion, and physical activity at initiation and at the end of study period. Univestin group had marked reduction in pain and appreciable increase in range of motion whereas stiffness of knee was found to be equally reduced in both group and it was statistically significant.⁷

Similar study by Lin et al have found that univestin containing flavonoids can inhibit the expression and activation of the proinflammatory cytokines and reduces synovial fibroblasts MMP enzymes and it increases inhibitor of MMP like TIMP and therefore, univestin have anti-inflammatory effect on osteoarthritis.

Oxaceprol

The oxaceprol is acetylated form of hydroxyproline. As hydroxyproline is a part of articular cartilage, its ingestions, found to have cartilage protective property and with better safety profile. It acts on articular cartilage by inhibiting the neutrophilic infiltration, adhesion and migration, stimulates synthesis of collagen and glycosaminoglycans and by its anti-inflammatory effects.

A comparative study was conducted with oxaceprol 400mg TID and diclofenac 50mg TID in two group of patients of OA knee and hip joints for about 3 weeks

period. The end point analysis proved that both group of patients the pain, stiffness significantly improved, and mobility and pain free walking distance have been increased. Oxaceprol effect on OA is equivalent to diclofenac and tolerated well than diacerein and diclofenac in OA management.⁸

Epigallocatechin -3- O –gallate

Recent studies have found that, the polyphenols, and its compound epigallocatechin gallate of green tea are known to reduce the proinflammatory mediators, production of nitric acid and PGE2, and as a result, it can prevent the progression of OA. Administration of green tea polyphenol to mice led to a decreased incidence of arthritis with an associated decrease in COX2, IFN γ and TNF. In addition, an epidemiological study showed that older women who were drinking more than 3 glasses of green tea per day had a significantly lesser incidence of rheumatoid arthritis than those who drank no tea.⁹

Aflapin (Boswellic Acid)

This is a gum resin extract from a tree *Boswellia*, its active molecule is boswellic acids and can be used as drug and it acts through inhibition of LOX5 and NF-KB. There was a significant reduction in pain and definite improvements in their mobilities are seen and in addition, it has added advantage of weight reduction in OA patients. Its usage was found in ayurvedic, Chinese medicine, and its benefits have also been appreciated in Middle East and tropical countries.

Rosehip extract

Richard Alleyne et al of Danish research revealed that, rose-hip powder supplement has anti-inflammatory effect on osteoarthritis. Recent scientific experiences showed that powder extract from rosehip, *Rosa canina*, is found to be good than glucosamine in management of OA. The fruit of rose hip plant believed to give relief for 2 million and more sufferers of OA.

Dr Rod Hughes, a Consultant Rheumatologist at St Peter's Hospital in Chertsey, Surrey, expressed that "He recommends rose hip extract for OA if any patients wish to take natural remedy for OA" in addition to any other prescribed drugs.

Vitamin – D3

We have learnt that vitamin D3 deficiency is one of the factors for the onset of OA and its progression. Nowadays, we have vitamin D3 available in the form of capsules or sachets. Generally, ask the patient to take 60 million units of one capsule or sachets, every day for 2 weeks, every week for 2 to 4 weeks, and then monthly once for correcting the deficiency. But in chronic conditions like RA, SLE, osteoporosis, OA and any other conditions on steroids, can be continued for prolonged period. Always assess for serum parathormone, as it correlates directly with normalization of vitamin D deficiency, but alkaline phosphatase normalization may take long time. Over

dosages of vitamin D3 may cause headache, nephrocalcinosis or renal stones.

Intraarticular Procedures

Injection of Corticosteroid

Intraarticular long acting steroids are useful for the osteoarthritis of 1st CMC, knee, hip, ankle, acromioclavicular, and occasionally in elbow joints. It can be given even in facet joint and at MTP joints. Numerous RCT have justified the uses and benefits of steroid in OA. This simple and sterile OP procedure gives quick and tremendous relief than placebo lasting for about 8 weeks to 6 months. Whenever, OA patients clinically have large effusions, synovial thickening, high CRP and in suspected cases of CPPD arthritis, they will respond well to steroids. Synovial fluids to be aspirated before giving steroids for the real maximum effect and they should be asked to take rest 6- 8 hours before ambulation. It is always best to administer under guidance of US or under C- arm, at least in hip and facet joint procedure.¹⁰ Minimum periods of six months are necessary for second doses of steroid, but many of our patients don't require second doses.

Injection of Hyaluronic Acid – (HA) (Viscosupplementations)

Hyaluronic acid is a normal constituent of any joints, and it is essential for joints to move without friction. There are various strength and weight of (10, 000 to 60, 000 Daltons) hyaluronic acid are commercially available and these can be administered intra-articularly into knee, hip, glenohumeral joints. I have enrolled 358 patients (104 males and 254 females) of osteoarthritis of knee with radiological Kellgren and Lawrence (K&L) grades 2 to 4 based on X-rays of knee taken in AP in standing view.(Fig.3) Pain was evaluated by VAS, and performance was assessed by 50 foot walk time.

I have categorized the patients into KL grade 2 (M 24 & F 82); KL grade 3 (M 41 & F 112) and KL grade 4 (M 39 & F 60). We have randomly picked up and formed into group-A & B. 178 cases are kept in group-A with KL grade-2 (M22 & F37), KL grade-3 (M27 & F52) and KL grade-4 (M21 & F19). In group- B, we have selected 180 cases from KL grade-2 (M24 & F44), KL grade-3 (M29 & F40) and KL grade-4 (M 19 & F 24). In group- A (n-178), 85 cases allotted for low (M32 & F53) and 93 cases for high (M40 & F53) molecular weight viscosupplement without steroid and it was kept as control for Group-B. In group-B (n-180), 86 cases have been selected for low (M32 & F54) and 94 cases for high (M40 & F54) molecular weight viscosupplement with steroid. The low molecular weight HA was given as weekly once for five weeks and high molecular weight viscosupplement was given as single dose. From group- A and B, we randomly selected 211 (60.75%) cases (37 & 52 from group- A and 40 & 82 from group- B) for assessing the role of C- arm in delivering viscosupplements into knee joint cavity, because knee joint cavity is well away from sub-patella and in KL grade 3 and 4, joint cavity is narrow or asymmetrically present with valgus and varus deformity

and thus, viscosupplement was given under the guidance of C-arm for appropriate target delivery.

After intra-articular HA, OA patients can experience relief of pain and the regained mobilities can last for several

months. There are various RCT studies are available to support long lasting pain relief in OA knee and hip than by simple IA steroid alone.(vide. Figure 1.30 to 1.32)

Group-A and Group-B cases categorized for Low and High MW viscosupplement.

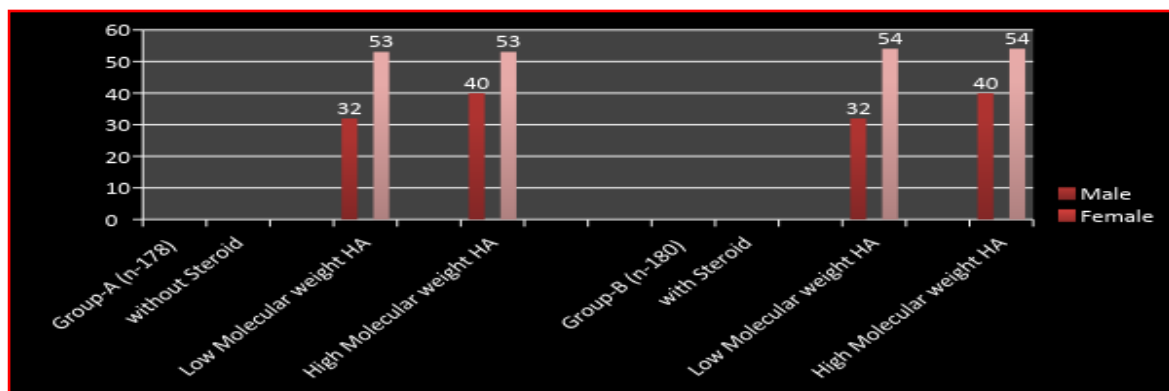


FIGURE 1.30 to 1.32 Viscosupplement and steroid was given into joint cavity under C-arm guidance.

(Sarah R Kingsbury et al, 2013 & Jacqueline Detert et al, 2014).

I preferred to give HA under C-arm guide and it was given into the joint cavity of hip and knees than by routine blind approach. Interestingly, CPPD arthritis patients responded well with HA with steroid and on radiography review after 3 months, the CPPD calcifications of the cartilages have disappeared.¹¹

Disease Modifying OA Drugs (DMOADS)

Doxycycline

Doxycycline and tetracycline which are MMP 7, 9, and 13 inhibitors, the potential to slow the cartilage degeneration and some symptomatic improvement can be seen. But RCT with doxycycline, the benefits are yet to get confirmed than placebo.

Hydroxychloroquine

Hydroxychloroquine is not a routine drug for OA, but it can be given in erosive hand OA where synovitis is prevalent. As per the HERO study (Hydroxychloroquine Effectiveness in Reducing symptoms of hand Osteoarthritis and OA TREAT trail) of RCT, they have proposed to give HCQ in moderate to severe hand OA

Colchicine

Colchicine is known to reduce MSU and CPPD crystals induced inflammation. The enzymes like MMP and elastases can play role in OA inflammation and cartilage losses. Therefore, colchicine effect is extrapolated into OA as one of DMOAD. In a study among 58 patients, one group of 31 cases were issued with colchicine, and other group was instituted with placebo and if required, patients can take acetaminophen for the pain, and the clinical improvement was assessed after about 3 months. Symptomatic improvement was noted in colchicine group than in placebo and it was statistically significant and acetaminophen intake was less in colchicine group.

Inhibitor of Nerve Growth Factor

Studies have shown that, expression of nerve growth factor (NGF) is increasingly noted in the OA joint, and tanezumab, that is inhibitor of NGF, have proved analgesic efficacy and an improvement in symptoms of 450 people with knee OA, compared to placebo. Recently FDA committee voted to continue anti NGF in OA treatment, till certain safety criteria are observed. In future, anti NGF may have role in reducing OA symptoms.

Fibroblast Growth Factor

Intraarticular injection of recombinant human fibroblast growth factor (rhFGF) -18 is found to have adult cartilage regenerative capacity. In an animal study, once a week injection of rhFGF-18 at 10 µg/ week for 3 weeks, have shown that there was an upregulation of TIMP1 and inhibition of aggrecan release (Y Mori et al, 2014). Another human study on OA knee by Eckstein F et al, 2015 with rhFGF (Sprifermin) with 10, 30 and 100µg and placebo by intraarticular injection as weekly once for 3 weeks was given and treatment response was assessed by MRI of knee, and it has shown that Sprifermin not only increased the cartilage thickness, but also reduced the cartilage loss.

Bradykinin B2 Antagonist

Another innovative molecule in the management of OA is bradykinin β2 antagonist (Icatibant), and it is given as intraarticular injection and it produces long lasting analgesic effect by countering the inflammatory and vasodilatory role of BK (Meini S et al, 2008). Song IH et al, did case control comparative study and he assessed response of disease with contrast enhanced US and contrast enhanced MRI of knee after 3 doses of icatibant in two group of patient with 500 microgram (Group B) and 2000 microgram (Group C) and suitable placebo (Group A). He has found appreciable analgesic response after icatibant in high dose group C. However, he could not find anti-inflammatory effect by CE-US and with CE-MRI of knee.

TNF α Inhibitors

The cytokines like TNF α and IL 1a are also said to have involved in OA pathogenesis. Therefore, across the world, various studies are carried out on the usefulness of infliximab and IL 1a inhibitor in OA. Güler-Yüksel M et al of The Netherland, during 2010 used infliximab in RA patients and who have osteophytes in DIJ and PIPJ and he evaluated them for 3 years for secondary OA of hand. He found that, there was reduction in further progression secondary OA of PIPJ. He advised; further studies are needed to confirm its effects on primary hand OA.¹²

Antonella Fioravanti et al in 2016, did pilot study on hand OA with intra-articular injection of infliximab into PIPJ (0.2ml) and DIPJ (0.1ml) in one hand and in another hand with used as control with saline injection. There were followed up and clinical efficacy was assessed after 6 and 12 months and their radiological images are compared with base line X-ray and with at the end of 6 and 12 months. Almost all patients had relief from their signs and symptoms at 6 months itself and the radiological progression was reduced, and its effects persist for 12 months.¹³

IL- 1Ra Therapy

The IL-1a receptor (IL-1Ra) antagonist as IA injection and its efficacy in OA knee have been proved by both In vitro and experimental studies. They all tolerated well and there

was no rebound inflammation. Carroll MB et al, used Canakinumab (IL1a inhibitor) given as single subcutaneous injection in erosive hand OA, and they were followed up weeks, but there was no appreciable response.¹⁴

Platelet Rich Plasma

It is a form of treatment, where the well-known disease entities and its pathogenesis are being extrapolated to obtain the beneficial effect of platelet on OA management. Platelet has significant number of inflammatory cytokines and growth factors and it can stimulate cell regeneration, proliferation, neovascularization, and collagen synthesis. In this, minimally invasive procedure, centrifuged small volume of concentrated, autologous plasma containing high numbers of platelets are delivered into site of injured areas of tendon and cartilage at specific interval of two weeks and they must be monitored for the clinical improvements of signs and symptoms of OA. Platelet rich plasma therapy appears to be theoretically sound, and it is another form of optional treatment for osteoarthritis. Though, there are many studies have been conducted, yet there were no convincing reports and further studies are required to validate the importance of these procedures. (Gulis Kavadar et al, 2015).¹⁵

Cartilage Gene Therapy

The research in the field of osteoarthritis not yet developed as tremendous progresses as witnessed in rheumatoid arthritis. As far as cartilage gene therapy for OA is concerned, we are on infantile stage. Though, synovial cell is not primarily involved OA pathogenesis, the first attempt was made by transducing synovial cells, with an expectation that products of protein from these cells might be helpful for repairing cartilage and bone. The possible therapeutic strategies are, over expression of growth factors, inhibition of proinflammatory cytokines, and the prevention of chondrocyte apoptosis. Cartilage repair can be achieved by increasing the synthesis of cartilage matrix and by suppressing cartilage degradation. Basically, in gene therapy, the cytokines which are elsewhere plays as pathogenic molecules, and that same cytokines, should be extrapolated in some other diseases to suppress or to prevent the pathogenesis of another disease by using ad transduction (ad- adenovirus as vector). Thus, transforming growth factors β, etc could act as chondrocyte stimulating factors, and it has therapeutic benefit as these are all involved in cartilage homeostasis.

IL- 1 is a known proinflammatory cytokine in degradation of cartilage, whereas invitro study using IL 1 Ra demonstrated to have an antagonist effect on cartilage. These findings are in favour of developing IL-1 blockade in the treatment of OA. Likewise, in another study, rabbit OA model has shown promising results by using FGF combined with IGF-1 and IL-1 Ra as gene therapy. In rat model of OA, when angiogenesis is inhibited by over expression of thrombospondin-1 (TSP-1) with an ad vector, there is reduction in cartilage inflammation and the progression of disease. Another rat model OA study has found that controlling chondrocyte apoptosis by nitric acid

synthase and with treatment with hyaluronan, can enhance the life of chondrocyte. Likewise, transduction of chondrocytes and chondroprogenitor cells can be achieved using another vector.

Currently in America and Korea, two ongoing trials are under investigation on the efficacy and safety of allogenic human chondrocytes expressing TGF- β 1. Results are awaited.

Stem Cell Therapy

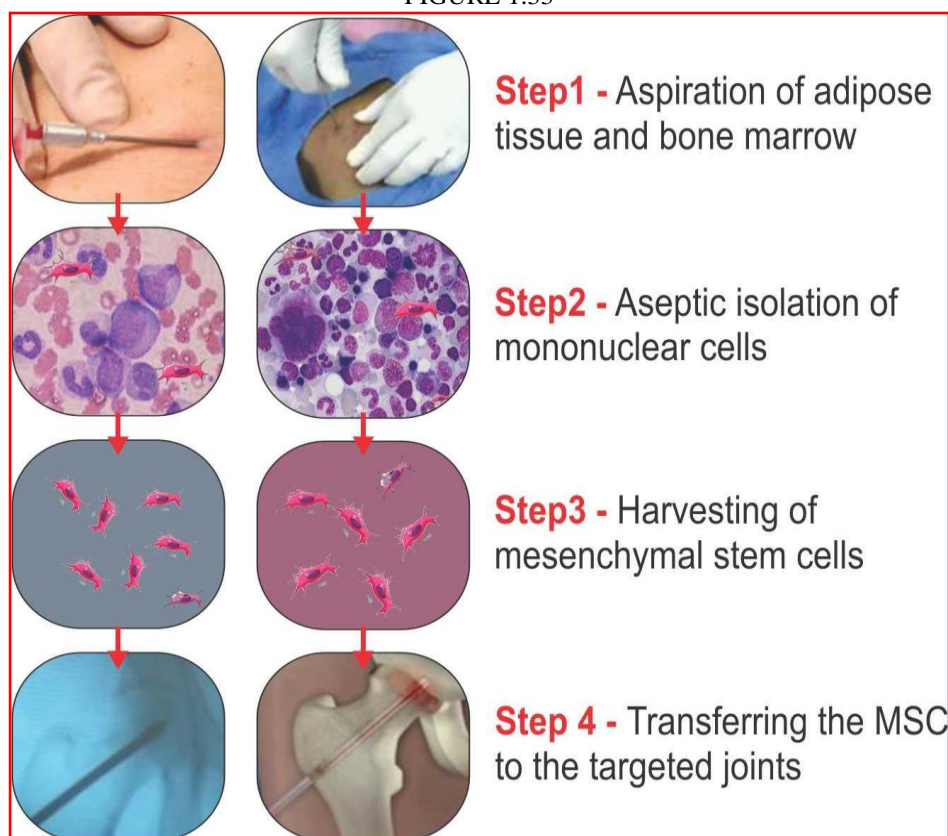
This new modality of stem cell therapy is hopeful of giving life to enormous number of people with OA. Harvested MSC (mesenchymal stem cell) is administered intraarticularly and it gets differentiated into cell of interest and repairs the damaged chondrocytes, cartilages and the bone. Jo CH et al have studied in 3 groups of 18 patients with low, mid and high dose categories (1.0×10^7

cells, 5.0×10^7 and 1.0×10^8 respectively) and his results showed that high dose category patients had improvement in function, pain and cartilage regeneration as proven by arthroscopic study.

As we aware, as the world population swells and aging population and increasing OA incidence and prevalence's are being recognized. Therefore, OA will continue to impose an increasing burden on these populations. It is a real urge to design new methods of treatment to meet out the increasing demand for surgical management of OA. Stem cell therapy can fill the gap and as in this, intra-articularly administered mesenchymal cell can differentiate into cell of interest and repair the already damaged articular cartilage and bone. (Figure 1.33)

Techniques for MSC collection, separation & isolation from bone marrow and adipose tissue and transplantation to the damaged joints.

FIGURE 1.33



In a routine practice, the aspirated, harvested and separated autologous mesenchymal cells (MSCs), which are obtained either from bone marrow or from adipose tissue, have to be administered intra-articularly in a single sitting and further improvement following stem cell therapy can be monitored by MRI or by arthroscopy.^{16, 17}

Bisphosphonate

Osteoporosis, bone marrow lesions, cartilage damages are inherent pathological features of OA. Antiresorptive,

bisphosphonate have overall benefit in pain, cartilage and bone marrow lesion by limiting the activity of osteoclast and thereby the imbalance between osteoblast and osteoclast is maintained. Studies are there to prove the effect of bisphosphonate either by intraarticular (clodronate) or by parenteral (zolindronic acid) routes on womac pain score, and reduction of bone marrow lesions and which was confirmed by MRI. Alendronate, risedronate 35 & 70mg given as weekly oral dose, and ibandronate orally can be given as monthly once whereas Palmidronate, zolindronic acid 5mg is adequate to be administered at yearly once. While giving oral bisphosphonate, care must advise to take sips of water for

about an hour and ask them not bend forward for about an hour, to prevent GERD symptoms or best to give them prokinetic agent along with oral bisphosphonate. There are reported adverse effect of bisphosphonates are avascular necrosis of jawbone or TMJ and oesophagitis and occasionally oesophageal growth after prolonged use for five years and more.^{18, 19}

Calcitonin

Calcitonin appears to slow down or counteracts cartilage damage and subchondral bone lesions of OA. Published report of Carol Eustice et al, found that calcitonin is able to control rapid cartilage degeneration and prevent erosions of bone and cartilage. But yet another study by Manicourt D. H et al, pointed out that calcitonin can be preventive than therapeutic and of course, it is of great use at an early initiation in OA.²⁰

Strontium Ranelate

The Strontium structure is like calcium; hence strontium can be taken up by bone. When it is mixed as salt to ranelic acid, strontium can boost the bone formation by osteoblast and simultaneously prevent resorption of bone by osteoclast. In addition, it also has cartilage regenerative capacity. Study has conducted on two groups of patient with 1 gm and 2 gm dosages in OA patients with KL grade 2 and 3 and they were followed up for 3 years. It found that people using 2 gm daily, had improved health status, overall WOMAC score and WOMAC pain score was reduced well, and with significant reduction in progression of radiographic joint space width. The dosage is, 1-2 gm daily.²¹

Role of Yttrium -90 Radiation

Chatzopoulos D et al has used intra-articular Yttrium- 90 radiation in 97 cases of OA, who are not responding to systemic or local treatment. He followed up the cases at 6th and 12th month after the procedure and assessed the outcome of his study. There was improvement in pain in 71.1% at 6 month and 72.5% at 12 months (P=0.0002). In addition, there was a considerable improvement in resting and nocturnal pain, knee movements and the articularswelling.²²

Duloxetine

Recent studies have shown that this centrally acting serotonin noradrenaline reuptake inhibitor is having significant improvement in pain and function of OA knee (Chappell AS et al, 2011) especially in patients having no symptomatic relief from any one of the above modalities of treatment. Recently, OARSI has recommended duloxetine in management of multiple joints OA (McAlindon et al, 2014).

Muscle relaxants

Either centrally or peripherally acting muscle relaxants (methocarbamol, thiocholchicoside and tolperizone, etc.) can give tremendous relief in cases of inflammatory and osteoarthritic patients where stiffness of muscles around

the large joints and spine can cause troublesome pain and restriction of range of movements.

Tapentadol

It is yet another novel centrally acting mu- opioid drug for the management of OA. Placebo controlled comparative studies on 1000 people have noted, sustained pain relief and better safety profile when compared with oxycodone. Side effects of opioids remain major disadvantages and concerns for the continuing use (Wild JE et al, 2010 and Friedmann N et al, 2011).

Amitriptyline and Imipramine

Large number of patients with chronic refractory painful OA is found to be depressed and become sleepless. This holistic approach of issuing low dose antidepressant like amitriptyline and imipramine, appears to improve sleep and it is successful in relieving depression, improving pain and disabilities (Fernandes et al, 2013).

Prevention

Osteoarthritis is a disease that is quietly coming along with your age and only to manifest when your joints quiescence is broken. The truth, we are the one, and the only one responsible for losing of quiescence of our joints. Therefore, the prevention of osteoarthritis must start from within. No one can change the risk factor of age, but certainly we can control or reduce our weight. Studies have shown that obese women and men are four and five times at risk for OA, respectively. Weight loss of 5% is known to decrease the risk of OA by 50%, and if you are already obese with OA, losing weight dramatically improves symptoms. So, if you are overweight, losing weight is your best edge of advises against OA.

Daily exercises like bicycling, swimming, isometric movements, and wall sliding is enough to keep your muscles strong at your joints and prevent weight gain. If you have weak thigh muscles, there is a chance for bucking and fall, leads to painful OA. Try to avoid repeated injuries to the joints because injured knee is four times at risk for future OA. Injured joints should get prompt treatment and take steps to avoid further damage, by reducing the high impact movements, using braces and proper positional rest to the joint.

Dietary intake of omega-3 fatty acids containing fish, walnut, canola, soybean, etc and likewise, intake of vitamin D is known to decrease knee OA. You must be aware about how to protect your joint and must be mindful of proper movements of joints, adopting good postures and stance is best one to have healthy joints.

Always listen to your pain, it seems so awkward, but many do not listen to it, hence suffer. When body sense pain, it is a signal that you are overdoing, therefore definite rest required for it. So, learn your limit and do not overuse it, and consider pain is the stop sign.

Certain occupations are the reasons for OA. If applicable, and if there is a chance of getting another job or alternative job, we can advise them to have alternative job modification. Professional athletes and other sports-related injuries require timely intervention and rest and repair of soft tissue may negate the onset of OA.

Ultimately, if nothing could be done to prevent, go ahead and blame your mother. Researchers recognized that about 20–35% of knee osteoarthritis and about 50% of hip and hand osteoarthritis may be determined by genetics.

We all know, OA is a yet another crippling and mobility-limiting disease but many of us, still unaware that OA per se is a killer disease in about 6% of osteoarthritis population and it may be quite high, if we add those unknown clear data of nonsteroidal anti-inflammatory drugs induced morbidity or mortality of all OA cases, and it is difficult to arrive at the correct figures, because, osteoarthritis are being managed by patients themselves by over the counter drugs, all kinds of medical practitioners and including by quacks.

Common Rationale for the Prescription of NSAIDs

Everyone thinks that it is easier to treat pain, but it may be true for milder pain but not for severe, crippling and debilitating prolonged pain. When we have rights to prescribe, the patients too are having their basic rights to know about their pain management drugs. Pain management requires an individualized approach, and it is mostly based on each patient's needs. Certainly, sufferer words are important, because he can only tell you whether your interventions are working on him or not.

Better to explain all our chronic musculoskeletal and articular joint pain patients, neither to expect 100% relief from chronic pain, and nor aim for total pain free life. If we do so, it may really worsen the life. Ask them to use the analgesics and NSAIDs as prescribed and request them to incorporate non-pharmacological measures to enhance the overall analgesic effect. Make them understand that these two can work hand in hand to achieve a level of pain control and it is superior to that of either approach used alone. Always, best to start with safest drugs at first and with upward titration until the patient's goal for pain relief are achieved and adjust the pain management plan as needed. If one set of interventions doesn't work, try another. Sometimes, multidisciplinary approach is needed, including psychotherapy.

Care should be taken to prevent or minimize side effects and adverse effects of NSAIDs, by wisely using clinical and laboratory monitoring. Best to educate the patient, his family and friends about the pain and pain management, thereby chances of importance of his treatment continuity is ascertained.

There are no ideal NSAIDs. Though many drugs are available to relieve pain and choosing the right one or right combination to relieve a patient's pain can be a rigorous clinical task. Often, trial and error is involved to find the best NSAID with fewer and most tolerable

adverse effects. Just because one agent works well, it doesn't mean that it will continue to be the best agent for that given patient.

In fact, yet no NSAIDs are shown to prevent or delay the progression or reverse the pathologic changes of OA. As everyone knows that, the GI side effects of NSAIDs are seen, even with PPI. So, no NSAIDs are superior or inferior with respect to intolerance or side effect profile. The so called, COX2 inhibitor per se can cause GI ulcer when we give for prolonged period or it may cause cardiac complications. Studies have proved that, patients on chronic NSAIDs with PPI have increased incidences of osteoporosis and fractures.

Care should be exercised, while giving NSAIDs to old age, hypertensive, cardiac failure, diabetic, nephropathic and in allergic asthmatic bronchitis patients, because one way or other, it can precipitate acute or chronic morbidity.

As I have mentioned in the etiopathogenesis itself that, OA is not just a disease of old age, quite often, even the young and obese male and females are coming with OA. When female become pregnant, NSAIDs are usually contraindicated in early and late pregnancy for the fear of congenital anomaly and premature closure of ductus arteriosus, respectively.

Though, there are many pharmacologic treatment options are available, it does not mean that all kind of drugs are necessarily to be given. Every patient is different, and each one's response to drugs also different. It is an art to prescribe to OA individual, because they are often old and they have co-morbid conditions. Ask them to give "pain killer holiday" that is whenever, there is no pain, less or tolerable pain, it is better to bear pain and stop NSAIDs. Therefore, we can prevent or delay the onset of drug related complications. The future of OA patients are looks bright, due to availability of new modalities of treatment and by that, we can give just "not pain free but disease-free life".

Generally, one should not have a fixed idea about the available NSAIDs and each one has its own effects and reported, under reported or else, yet to get reported side effects. Choice of NSAID is purely individual patient choice and should consider the trade-off between benefits and adverse effects. Always, the patient age, comorbidity, concomitant drugs are key considerations in everyday practice of medicine.

AHRQ (The Agency for Healthcare Research and Quality)- comparison study shows that paracetamol is inferior to any other NSAIDs in reducing pain, but with lower risk for GI ulcer. On the other hand, it poses higher risk for liver injury. The GIT risk with selective NSAID has low risk than non-selective like Naproxen, ibuprofen, diclofenac. The partially selective NSAIDs like meloxicam, etodolac has lower risk of GI ulcer related complications. Risks of serious GI adverse effects are higher with naproxen than ibuprofen. Celecoxib and non-selective NSAIDs, such as Ibuprofen & diclofenac increased risk with CVS complication than placebo but

not with naproxen. Of course, all NSAIDs can cause HT, CCF, impaired kidney function. Use lowest dose, intermittent use. If patient has highly resistant pain, then use tramadol. In OA knee, if patient has persistent pain, duloxetine, selective serotonin- nor epinephrine reuptake inhibitor- effective in knee OA.

2. Conclusion

Osteoarthritis is a worldwide disease and is the second leading cause of disability. Osteoarthritis is not only seen after fifth decade of life, is quite often seen in third and fourth decades too, by the increasing prevalence of plump and belly's population. The true prevalence of OA, however, varies greatly depending on the kind of definition used, age, sex, and geographical area studied. When we apply the radiographic criteria, the prevalence of OA can be very high. To stress, OA is the failure of repair of damage that has been caused by excessive mechanical stress on the joint tissues. Without attempting to contain or correct the mechanical insult, whatever attempt at healing will fail. The early OA can be asymptomatic, but only to precipitate with profound symptoms after some time. Osteoarthritis is a very basically treatable and, at times, it can be a preventable disorder. An appropriate nonpharmacological and pharmacological treatment can have improved and disability-free life. Pain control is often inadequate when OA progresses to severe stage. The identification of individuals at high risk for OA and an early detection and intervention are essential for the improved management of the disease, or else in future, across the globe the medical and surgical caregiver for these ailments are going to be more demanding.

In near future, newer treatment options like growth factors, stem cell therapy, genetherapy, and cartilage transplantations are going to be the promising mode of therapy for OA and surely, we can see marked improvement in the functional activities of this huge suffering population of the globe.

References

- [1] Predel, et al. Topical diclofenac patch in patients with knee osteoarthritis: A randomized, double blind, controlled clinical trial. *Clinical and Experiment Rheum*; 21(2): 193-8,2003.
- [2] Agarwal A et al. evaluation of a diclofenac transdermal patch for the attenuation of venus cannulationpain: A prospective, randomized, double blind, placebo-controlled study. *Anaesthesia*; 61(4): 360-362, 2006.
- [3] Vorsanger G et al. Randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clin Ther*; 29Suppl: 2520-35, 2007.
- [4] Norman R. Rosenthal et al. Tramadol/Acetaminophen Combination Tablets for the Treatment of Pain Associated With Osteoarthritis Flare in an Elderly Patient Population: *J Am Geriatr Soc*: 52(3), 2004.
- [5] Jatupon Kongtharvonskul et al. Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis: *Eur J Med Res*; 20(1): 24; 2015.
- [6] Pelletier JP et al. Efficacy and safety of diacerein in osteoarthritis of the knee: a double-blind, placebocontrolled trial. *Arthritis Rheum*: 43(10): 2339-48, 2000.
- [7] Bahram H. Arjmandi et al. Combination of *Scutellaria Baicalensis* and *Acacia Catechu* Extracts for Short-Term Symptomatic Relief of Joint Discomfort Associated with Osteoarthritis of the Knee: *J MedFood*. 17(6): 707–713, 2014.
- [8] Herrmann G et al. The therapeutic equivalence and safety of treatment for 21 days with 400 mg t.i.d.oxaceprol (n = 132) and 50 mg t.i.d. diclofenac (n = 131) were assessed in a multicentre, randomised, double-blind study of a mixed population of patients with osteoarthritis of the knee and/or hip. *Clin Rheumatol*: 19(2): 99-104, 2000.
- [9] Shen CL et al, Dietary polyphenols, Epigallocatechin -3-O -gallate in osteoarthritis. *J NutrBiochem*; 23(11): 1367-77, 2012.
- [10] Arroll B, Goodyear-Smith F. "Corticosteroid injections for osteoarthritis of the knee: meta- analysis".*BMJ*. 328 (7444): 869, 2004.
- [11] Jevsevar D, Donnelly P, Brown GA, Cummins DS. "Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review of the Evidence." *The Journal of bone and joint surgery, American volume*.97 (24): 2047–60, 2015.
- [12] Güler-Yükselx M et al, Osteoarthritis Cartilage Treatment with TNF- α inhibitor infliximab mightreduce hand osteoarthritis in patients with rheumatoid arthritis; 18(10): 1256-62, 2010.
- [13] Antonella Fioravanti et al. A pilot study: Treatment of erosive osteoarthritis of the hands by intraarticular infliximab injections: *Rheumatology International*: 29(8): 961-5, 2016.
- [14] Calich AL et al. Osteoarthritis: can anti-cytokine therapy play a role in treatment? *Clin Rheumatol*; 29(5): 451-5, 2010.
- [15] Gulis Kavadar et al. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: a randomized prospective study: *J Phys Ther Sci*. 27(12): 3863–3867, 2015.
- [16] Jo CH et al. intra articular injection of MSCs for the treatment of OA of knee: proof of concept trail: *Stem cells*; 32(5): 1254-66, 2014.
- [17] Pers YM et al. Adipose Mesenchymal Stromal cell based therapy of the OA knee; stem cells *Transl Med*: 5(7): 847-56, 2016.
- [18] Wysowski DK et al. Reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360: 89–90, 2009.
- [19] Green J, Czanner G, Reeves G, Watson J, Wise L, et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. *BMJ*341: c 4444, 2010.
- [20] D-H. Manicourt et al. Rationale for the potential use of calcitonin in osteoarthritis: *J Musculoskelet Neuronal Interact*; 5(3): 285-293, 2005.
- [21] Kevin Deane MD, Reginster JY, Badurski J et al. Efficacy and Safety of Strondium Ranelate in the treatment of osteoarthritis: results of a double blind randomised placebo controlled trail. *Ann RheumDis*; 72: 179-186, 2003.
- [22] Nucl Med Commun. Yttrium-90 radiation synovectomy in knee osteoarthritis: a prospective assessment at 6 and 12 months; 30(6): ch-11.indd 100 01-02-2017 15: 45: 03