Management of Osteoarthritis

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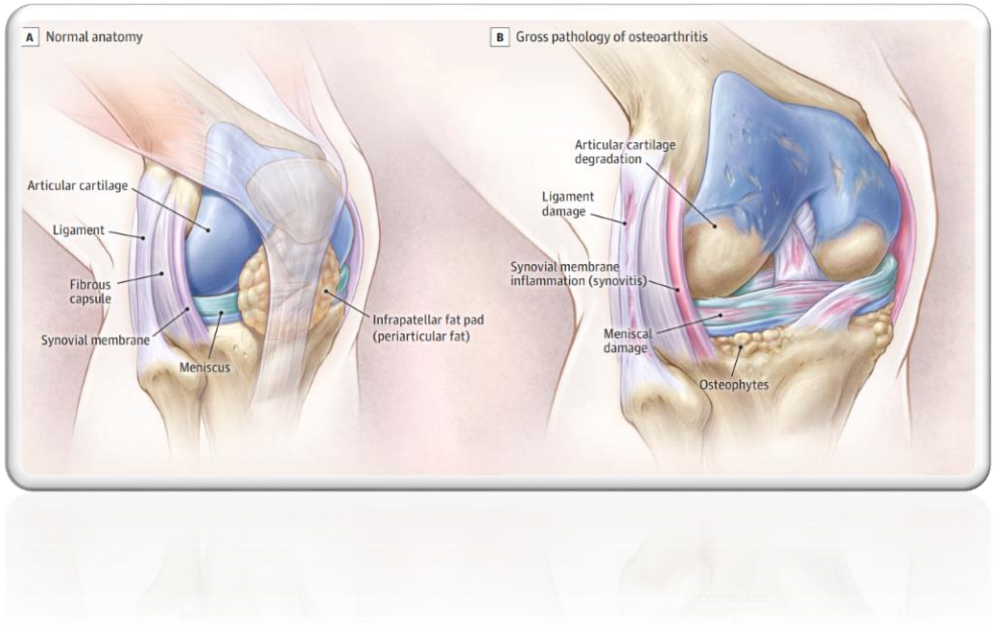


Learning Outcomes

At the end of this session, the learner is expected to:

- ❑ Know the Non-pharmacologic and pharmacologic management of OA
- ❑ Provide best patient education & counselling
- ❑ Be aware of the role of nutritional supplements and alternative medicines in management of OA

INTRODUCTION

- Osteoarthritis (OA) is the commonest form of arthritis and possesses marked variability of disease expression. It affects an estimated more than 240 million persons worldwide and an estimated more than 32 million persons in the US.

- Although most patients present with joint pain and functional limitations, the age of disease onset, sequence of joint involvement, and disease progression vary from person to person.

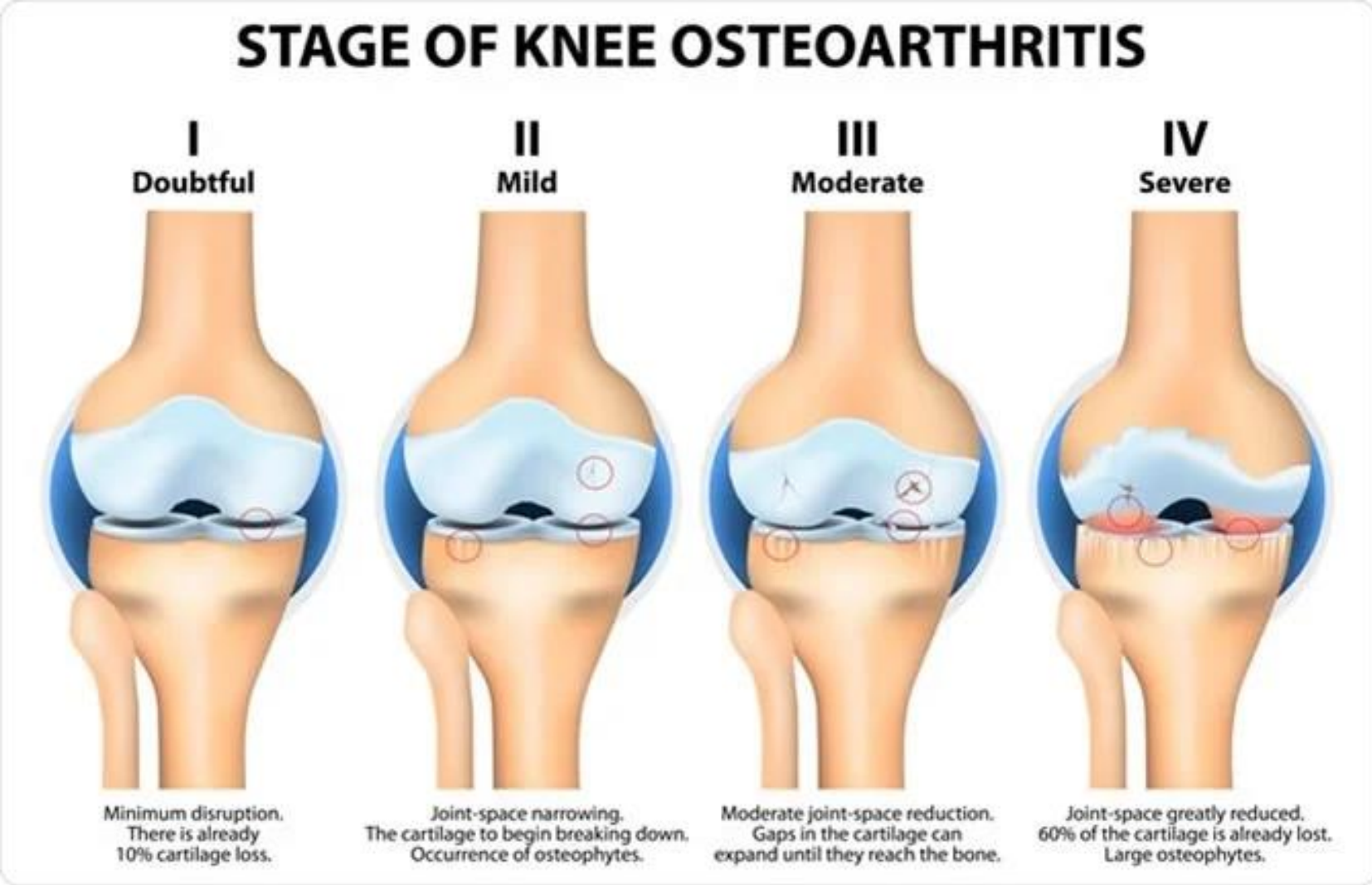
- OA ranges from an asymptomatic, incidental finding on clinical or radiologic examination to a progressive disabling disorder eventually culminating in "joint failure."

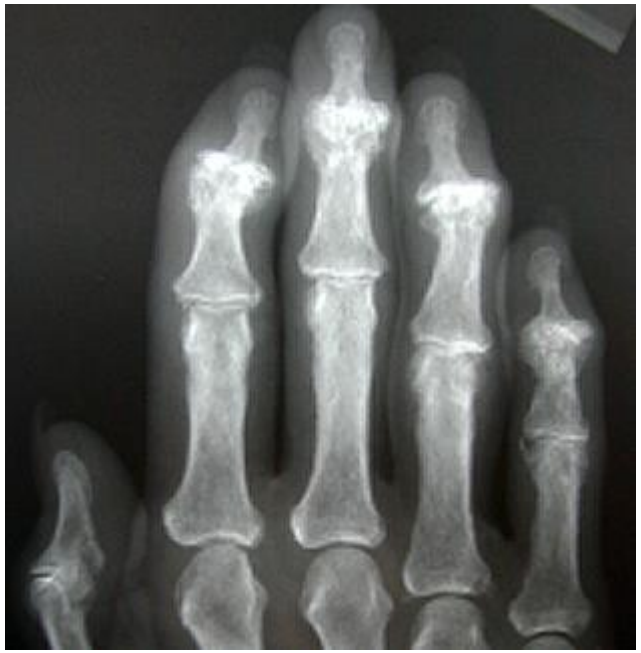
How Common Is OA?

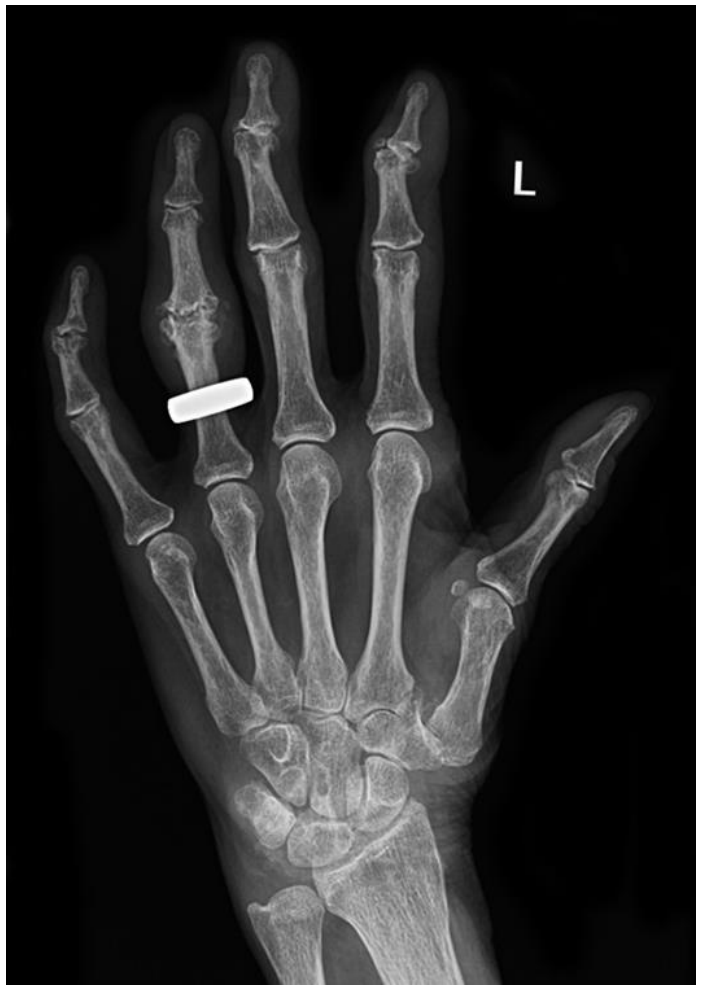
- The risk of OA increases markedly with age. One-third of individuals older than 75 years have symptomatic knee OA.
- Osteoarthritis is more common in women than in men.
- Other important risk factors of OA include obesity, prior joint injury, genetics, and malalignment of joints.

CLINICAL MANIFESTATIONS

- The primary symptoms of osteoarthritis (OA) are joint pain, stiffness, and locomotor restriction.
- Symptoms usually present in just one or a few joints in a middle-aged or older person.
- Other manifestations in patients with OA include sequelae such as muscle weakness, poor balance, and comorbidities such as fibromyalgia


STAGE OF KNEE OSTEOARTHRITIS
I
Doubtful
II
Mild
III
Moderate
IV
Severe
Minimum disruption.
There is already
10% cartilage loss.
Joint-space narrowing.
The cartilage to begin breaking down.
Occurrence of osteophytes.
Moderate joint-space reduction.
Gaps in the cartilage can
expand until they reach the bone.
Joint-space greatly reduced.
60% of the cartilage is already lost.
Large osteophytes.

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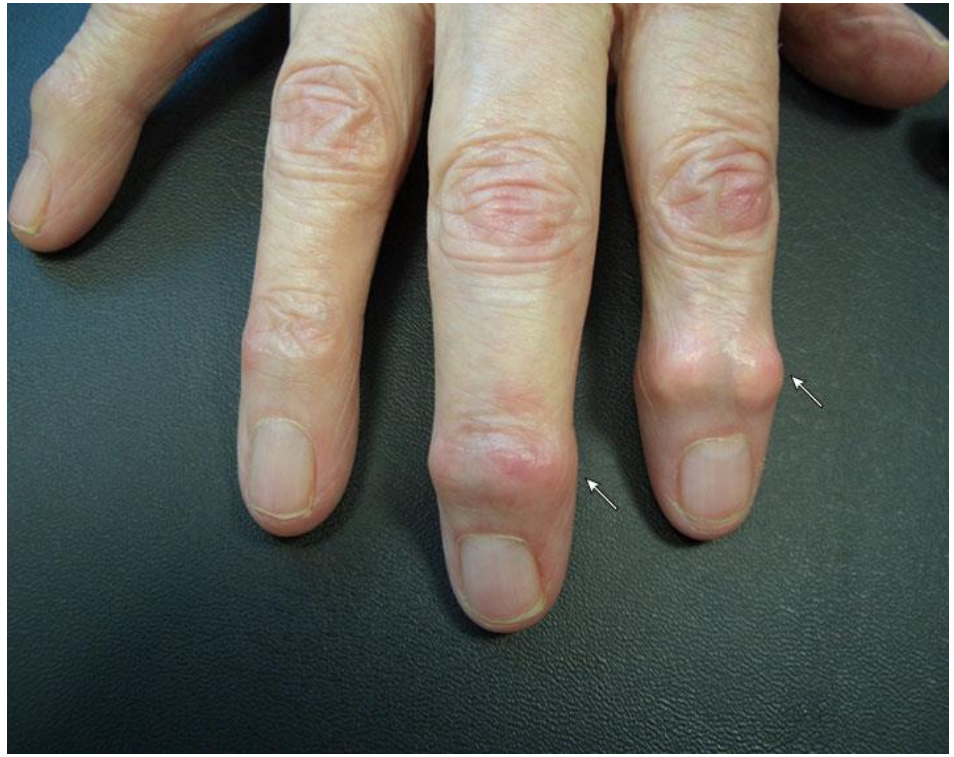
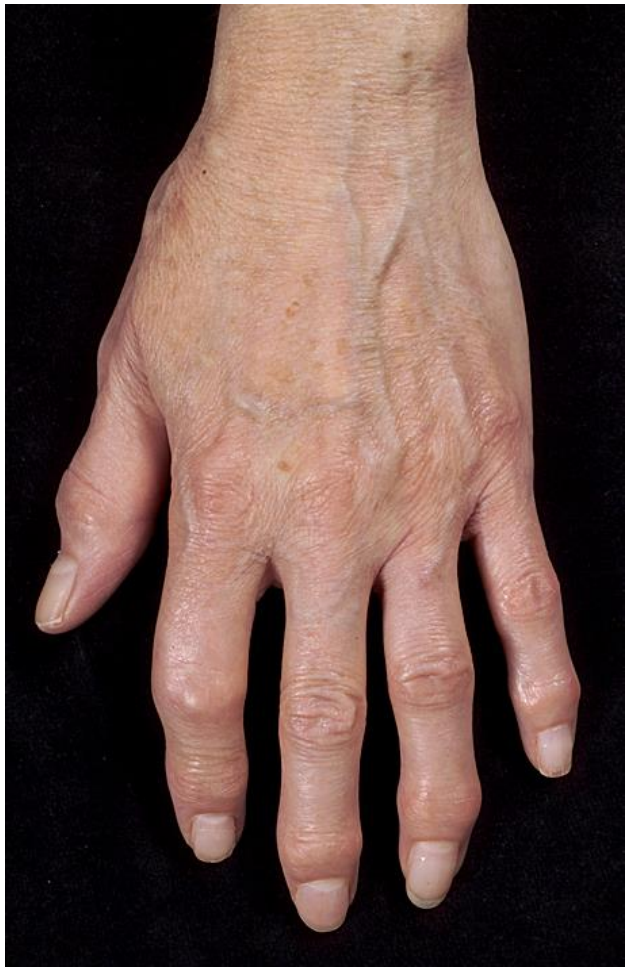


Heberden's nodes



Deformity
Heberden's nodes

Principal manifestations of osteoarthritis

Patient characteristics	
Age of onset	▪ >40 years*
Symptoms	
Pain	▪ Affects one or a few joints at a time ▪ Insidious onset - slow progression over years ▪ Variable intensity ▪ May be intermittent ▪ Increased by joint use and relieved by rest ▪ Night pain in severe osteoarthritis
Stiffness	▪ Short-lived (<30 minutes) and early morning- or inactivity-related
Swelling	▪ Some (eg, nodal osteoarthritis) patients present with swelling and/or deformity
Constitutional symptoms	▪ Absent
Physical exam findings	
Appearance	▪ Swelling (bony overgrowth ± fluid/synovial hypertrophy) ▪ Attitude ▪ Deformity ▪ Muscle wasting (global - all muscles acting over the joint)
Palpation	▪ Absence of warmth ▪ Swelling (effusion if present is usually small and cool) ▪ Joint line tenderness ▪ Periarticular tenderness (especially knee, hip)
Range of motion	▪ Crepitus (knee, thumb bases) ▪ Reduced range of movement ▪ Weak local muscles

Cardinal symptom.

OA: osteoarthritis.

* Major joint injury and certain rare conditions may predispose to OA before the age of 40 years.

Adapted from: OARSI Primer (http://primer.oarsi.org).

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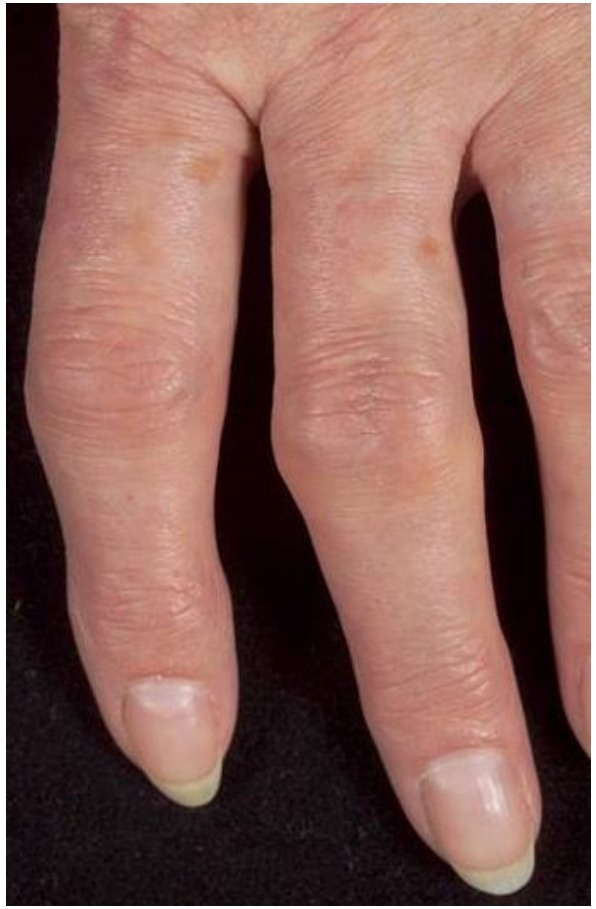
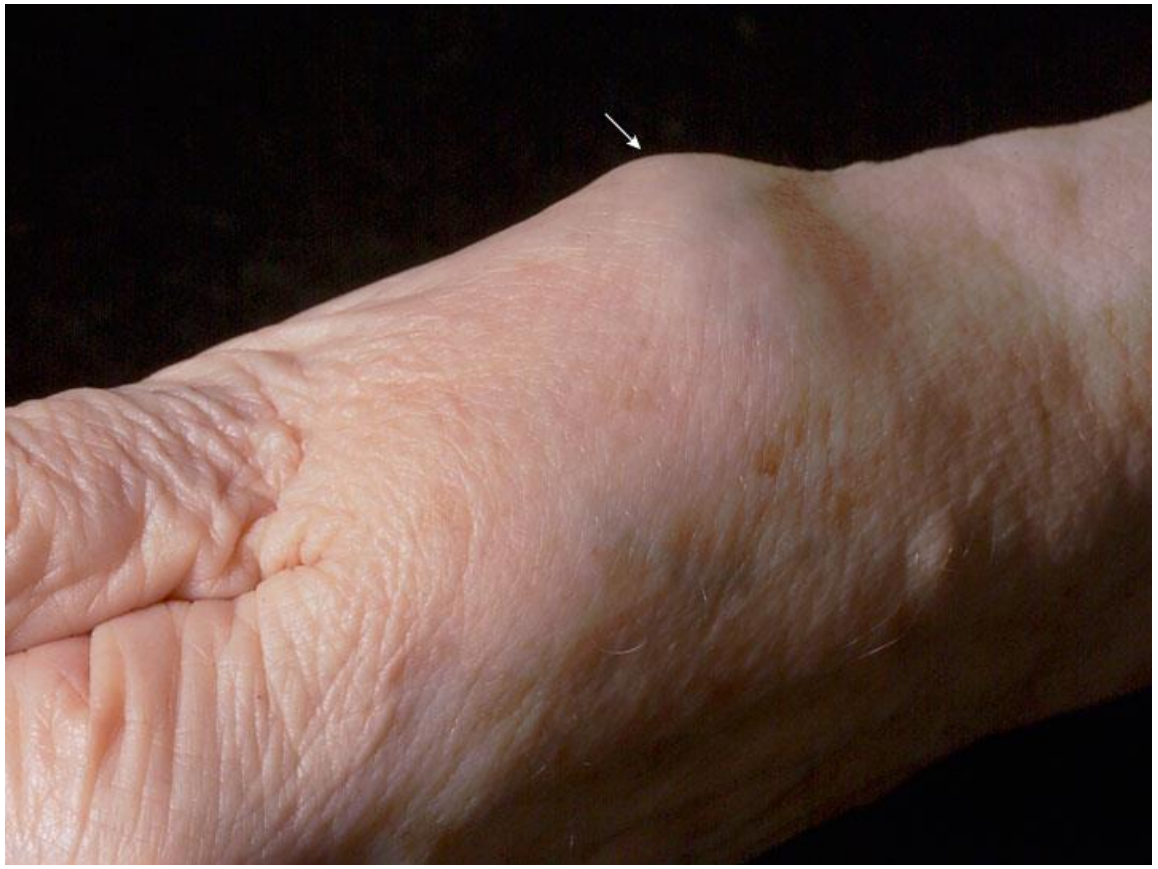
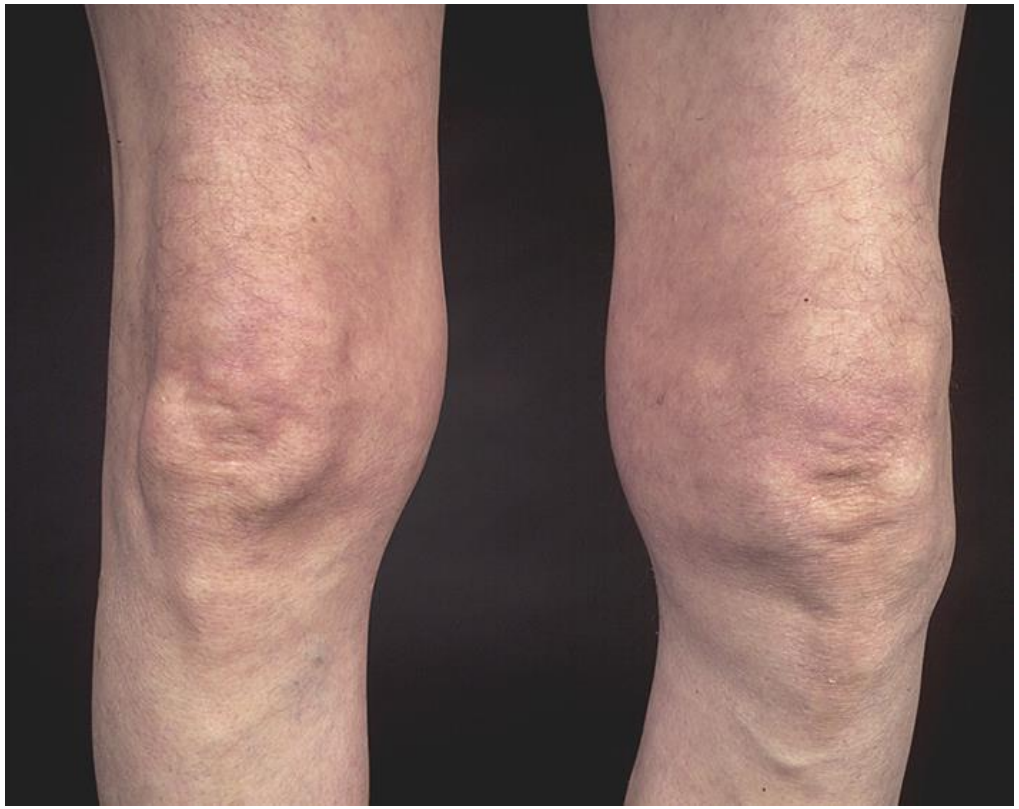


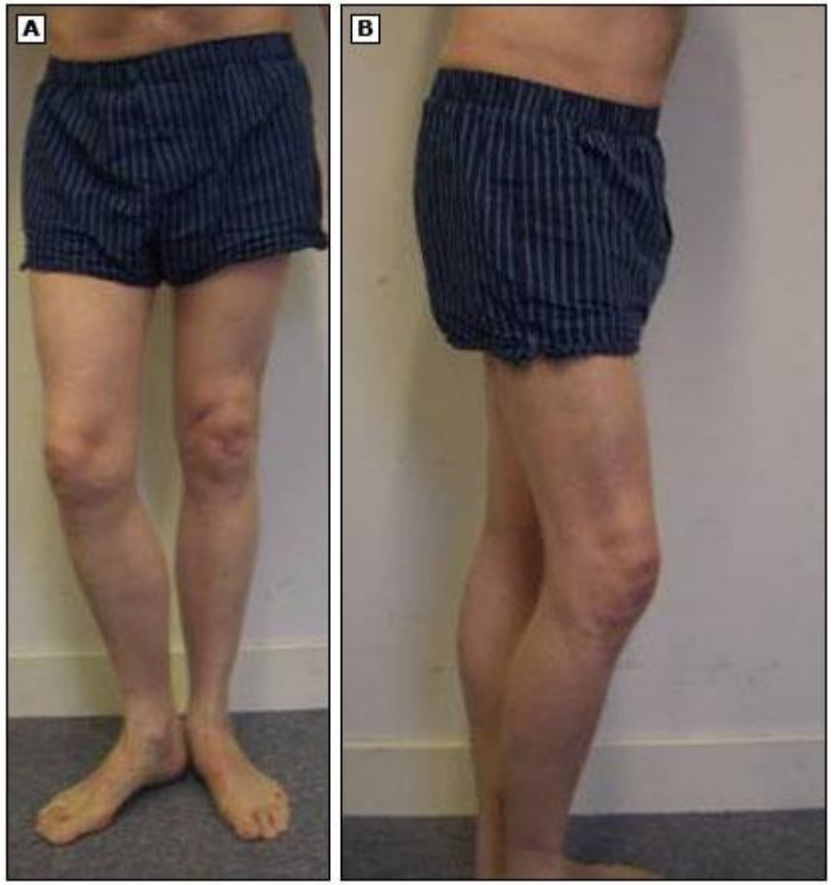
Erosive hand OA with marked radial deviation



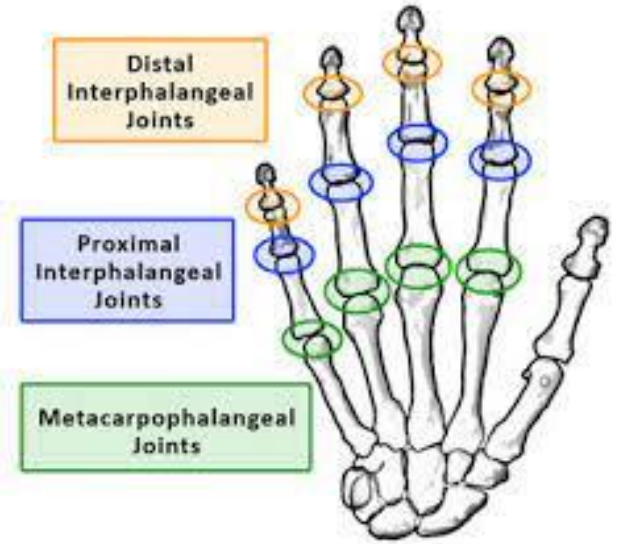
Thumb-base osteoarthritis



Unilateral knee OA



right hip OA, showing fixed flexion and external rotation deformity.

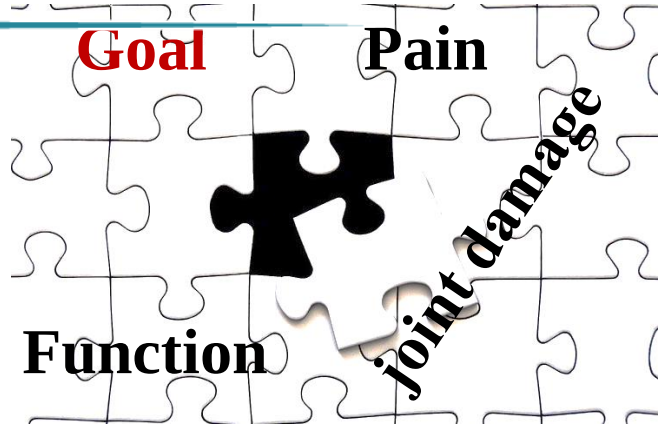


Clinical distinction between rheumatoid arthritis and osteoarthritis

Feature	Rheumatoid arthritis	Osteoarthritis
Primary joints affected	Metacarpophalangeal	Distal interphalangeal
	Proximal interphalangeal	Carpometacarpal
Heberden's nodes	Absent	Frequently present
Joint characteristics	Soft, warm, and tender	Hard and bony
Stiffness	Worse after resting (eg, morning stiffness)	If present, worse after effort, may be described as evening stiffness
Laboratory findings	Positive rheumatoid factor	Rheumatoid factor-negative
	Positive anti-CCP antibody	Anti-CCP antibody-negative
	Elevated ESR and CRP	Normal ESR and CRP

CCP: cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Goal of treatment



- **The goals of OA management are to**
  - Minimize pain
  - Optimize function
  - And beneficially modify the process of joint damage

Approach

- Due to the modest effects of the individual treatment options, a combination of therapeutic approaches is commonly used in practice and should prioritize therapies that are safer.

Non-pharmacologic therapy

- Non-pharmacologic interventions are the mainstay of OA management and should be tried first, followed by or in concert with medications to relieve pain when necessary.

Non-pharmacologic therapies include

- Weight management
- Exercises
- Braces and foot orthoses for patients suitable to these interventions

And use of assistive devices when required

Non-pharmacologic therapy for the management of OA

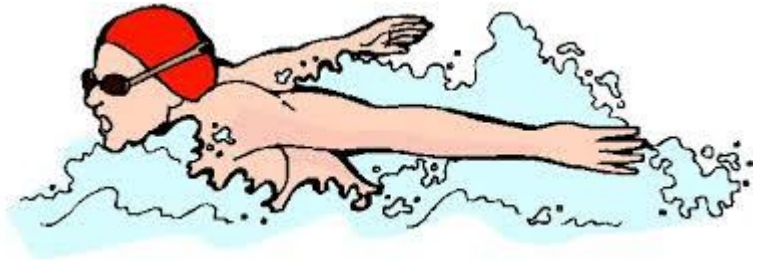
Weight loss

- Loss of at least 10 percent of body weight through a combination of diet and exercises has been associated with a 50 percent reduction in pain scores in overweight/obese patients with knee OA after 18 months.

Non-pharmacologic therapy for the management of OA

- Exercises have effects of similar magnitude on pain and function compared with NSAIDs.

A combination of aerobic, strengthening,isometric and aquatic exercises.



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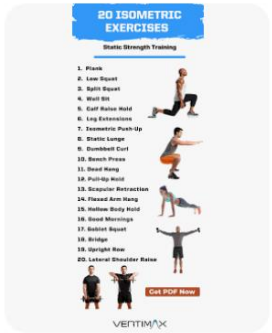

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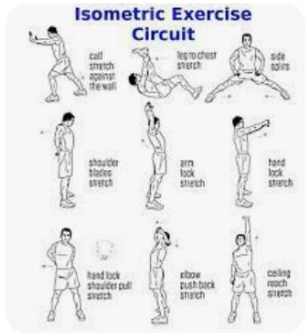

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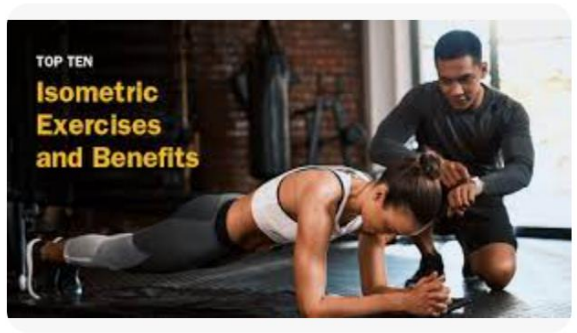
Isometric exercise ...



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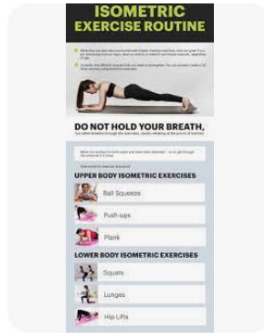

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Non-pharmacologic therapy for the management of OA
Equipment

Braces, foot orthoses, and assistive devices when required

Summary of Osteoarthritis Treatment Guidelines From Major Professional Societies

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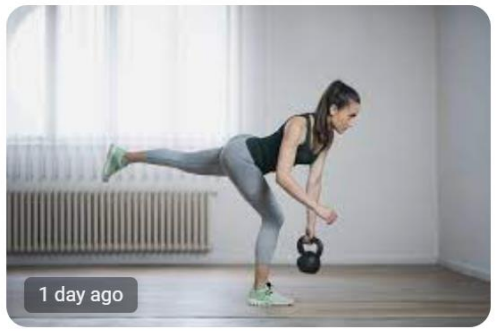

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Pharmacologic therapy

- Pharmacologic agents are used for patients with symptomatic OA who have not responded adequately to initial non-pharmacologic measures or concomitantly with these interventions.

- Pharmacologic therapy should only be used during periods when symptoms are present, since none of the interventions have been shown to be disease-modifying.

Pharmacologic therapy

The main medications used in the pharmacologic management of OA include:

- ❑ Oral and topical NSAIDs
- ❑ Topical capsaicin
- ❑ Duloxetine
- ❑ And intraarticular glucocorticoids & hyaloronate

General approach to pharmacotherapy

- In patients with one or a few joints affected, especially knee and/or hand OA, pharmacotherapy initiate with topical NSAIDs due to their similar efficacy compared with oral NSAIDs and their better safety profile.

General approach to pharmacotherapy

Topical NSAIDs

- The risk of gastrointestinal, renal, and cardiovascular toxicity is much lower with topical NSAIDs as compared with its oral formulation due to the reduced systemic absorption (5- to 17-fold lower)

- The tolerability profile is also better with topical NSAIDs, with mild skin rashes being the most commonly reported side effect.

Administration

Topical Diclofenac

- Lower extremity (eg, knee):

Gel 1% (OTC or Rx): Apply 4 g to each affected area up to 4 times daily; maximum dose per joint: 16 g/day; maximum total body dose (all combined joints): 32 g/day.

- Upper extremity (eg, hand):

Gel 1% (OTC or Rx): Apply 2 g to each affected area up to 4 times daily; maximum dose per joint: 8 g/day; maximum total body dose (all combined joints): 32 g/day.

Administration

- Apply to clean, dry, intact skin; do not apply to open wounds, eyes, or mucous membranes.
- Do not cover with occlusive dressings or apply heat, sunscreens, cosmetics, lotions, moisturizers, insect repellents, or other topical medications to affected area.
- Showering/bathing should be avoided for ≥1 hour following application. Wash hands immediately after application (unless hands are treated joint, then wait ≥1 hour to wash hands).
- Avoid sunlight to exposure areas.
- Avoid wearing clothes or gloves for ≥10 minutes after application.

General approach to pharmacotherapy

Capsaicin

- Topical capsaicin is a treatment option when one or a few joints are involved and other interventions are ineffective or contraindicated; however, its use may be limited by common local side effects.

General approach to pharmacotherapy

Oral NSAIDs are used in patients with:

- ❑ Inadequate symptom relief from topical NSAIDs
- ❑ Symptomatic OA in multiple joints
- ❑ And/or patients with **hip OA.**

Oral NSAIDs

- The use of NSAIDs in most patients is limited by the increased risk of serious gastrointestinal, cardiovascular, and renal complications.

- **The lowest effective dose should be used to control the patient's symptoms on an as-needed basis.**

Recommended doses

Diclofenac acid 35 mg is approximately equivalent to 38.5 mg of diclofenac salts

Drug	Usual analgesic dose (oral)	Maximum dose per day	Selected characteristics
Diclofenac	50 mg every 8 to 12 hours	150 mg for RA, labeling in United States permits up to 200 mg	•Dosing for free-acid preparation differs from doses listed here for sodium or potassium salts;
Indomethacin	25 to 50 mg every 8 to 12 hours	150 mg For rheumatologic conditions, labeling in United States permits up to 200 mg	More frequently associated with CNS side effects (eg, headache, altered mental status) compared with other NSAIDs
Meloxicam	7.5 to 15 mg once daily	15 mg	•Long duration of effect; relatively slow onset •Relative COX-2 selectivity and minimal effect on platelet function at lower daily dose of 7.5 mg
Piroxicam	10 to 20 mg once daily	20 mg	• Long-acting alternative for treatment of chronic pain and inflammation poorly responsive to other NSAIDs • **Prescribing generally limited to specialists with experience in treatment of chronic pain and inflammation**

Recommended doses

Drug	Usual analgesic dose (oral)	Maximum dose per day	Selected characteristics
Ibuprofen	400 mg every 4 to 6 hours or 600 to 800 mg every 6 to 8 hours	3200 mg (acute), 2400 mg (chronic)	•Shorter-acting alternative to naproxen; useful in patients without cardiovascular risks
Naproxen	Base: 250 to 500 mg every 12 hours or 250 mg every 6 to 8 hours	Base: 1250 mg (acute); 1000 mg (chronic); may increase to 1500 mg during a disease flare	•Often preferred by for treatment of acute or chronic pain and inflammation in patients without relevant comorbidities or risks •Higher dose (eg, 500 mg base twice daily) may have less cardiovascular toxicity than comparable doses of other NSAIDs; •Naproxen sodium has a faster onset than naproxen base
Celecoxib	200 mg daily or 100 mg every 12 hours	400 mg	•Less risk of GI toxicity relative to nonselective NSAIDs; benefit negated by low-dose aspirin, which may require concurrent gastroprotection •No effect on platelet function **•Cardiovascular and kidney risks are dose-related and may be similar to nonselective NSAIDs** •May be tolerated by patients with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis) who cannot take other NSAIDs

Gastritis and Gastroduodenal Ulcer Associated with NSAIDs

- For traditional NSAIDs, low and medium doses were associated with a lower risk than were higher doses.
- These adverse effects are less common with selective COX-2 inhibitors.
- Several NSAIDs had a far higher than average risk, including ketorolac and piroxicam.
- Drugs with a long half-life or slow-release formulation were associated with higher risk, even accounting for dose.

Cardiovascular Effects of NSAIDs

- The largest meta-analysis of observational studies available to date also clearly demonstrates that higher doses of NSAIDs, with the exception of naproxen, increased the risk of serious cardiovascular events.

- The effect of dose and slow-release formulation demonstrated that risk was a direct consequence of prolonged drug exposure.

- These adverse effects are more common with selective COX-2 inhibitors.

General approach to pharmacotherapy

Duloxetine

- Duloxetine is used for patients with OA in multiple joints and concomitant comorbidities that may contraindicate oral NSAIDs and for patients who have not responded satisfactorily to other interventions.

- 30 mg once daily, max dose 60 mg

General approach to pharmacotherapy

Acetaminophen

- Due to safety concerns pertaining to the use of acetaminophen (paracetamol) and increased awareness of its negligible and non-clinically significant effects on pain, this medication is no longer considered the first-line analgesic for the treatment of knee and hip OA by clinical guidelines.

General approach to pharmacotherapy

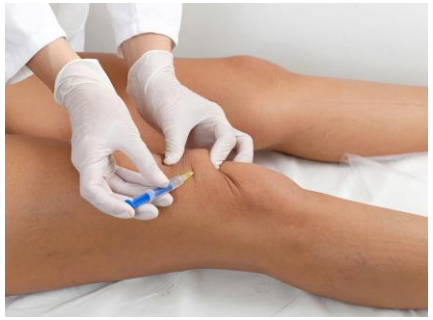
Acetaminophen

- Although its occasional use for treatment of mild OA with occasional pain is recommended, its lack of substantial efficacy suggests that it should not be a primary treatment for moderate to severe OA.

General approach to pharmacotherapy

Intraarticular glucocorticoid

- Intraarticular glucocorticoid injections do not routinely used due to the short duration of its effects.



Intraarticular glucocorticoid

Choice of glucocorticoid preparation

- Depot formulations are designed to stay at the injection site and display mostly local effects, although systemic effects can occur.

- **The most commonly used depot glucocorticoids**
  - Methylprednisolone acetate
  - Triamcinolone acetate
  - And triamcinolone acetonide

Intraarticular glucocorticoid

Variation of dose by anatomic location

- **Glucocorticoid doses should vary with the structure injected.**
- **The UpToDate authors use triamcinolone acetonide**
  - At standard doses of 40 mg for a large joint (knee, shoulder),
  - 30 mg for medium-sized joints (wrist, ankle, elbow)
  - And 10 mg for small spaces

Intraarticular glucocorticoid

Frequency of injection

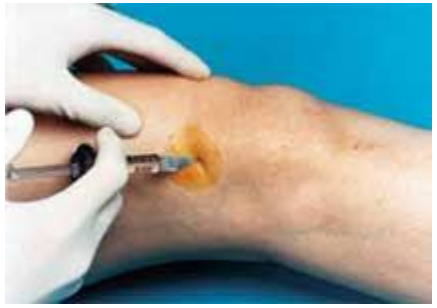
- Intra-articular steroids are expected to result in clinical improvement of arthritis for short duration.
- Therefore, if arthritis recurs, joint injections can be repeated as many as three times in a 12-month period.

General approach to pharmacotherapy

Hyaluronate

- The use of any intraarticular hyaluronic acid (HA) formulation is not recommended due to the lack of robust evidence demonstrating benefit.

- Moreover, intraarticular HA is associated with high costs and potential side effects such as pain flare-ups and joint infection, although the latter is a rare complication.



Platelet-Rich Plasma

Conclusions and Relevance Among patients with symptomatic mild to moderate radiographic knee OA, intra-articular injection of PRP, compared with injection of saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months. **These findings do not support use of PRP for the management of knee OA.**

2019

Platelet-Rich Plasma

Therapeutic Advances in Chronic Disease Review

Platelet-rich plasma in osteoarthritis treatment: review of current evidence

Lucía Gato-Calvo, Joana Magalhaes, Cristina Ruiz-Romero, Francisco J. Blanco and Elena F. Burguera

Ther Adv Chronic Dis
2019, Vol. 10: 1–18
DOI: 10.1177/2040622319825567

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At present, results from randomized clinical trials seem to favor PRP used over other IA treatments such as HA injections, to improve pain scales in the short and medium term (6–12months).

Concluding, at present the therapeutic potential of PRP products in OA remains unfulfilled and without further standardization its clinical efficacy will remain an open debate.

Additionally, RCTs in which OA patients were stratified suggest that PRP is more effective in those with lower degree of cartilage degeneration or OA grade. Therefore, careful patient stratification should be considered.

2021

Platelet-Rich Plasma

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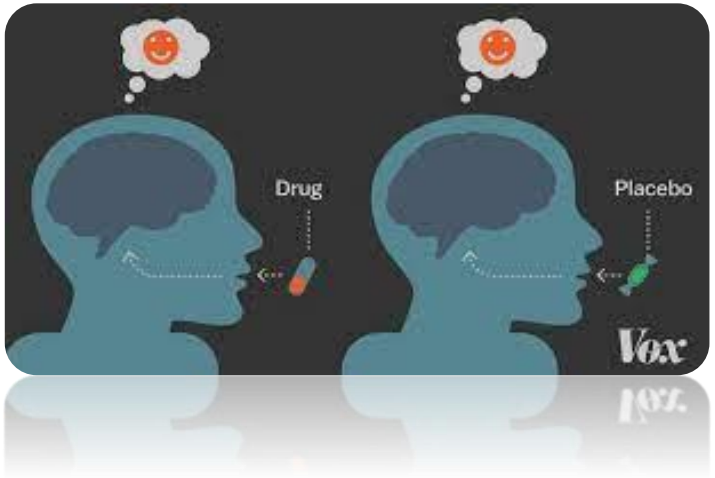
Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy

Despite encouraging results reported with regards to Platelet-rich plasma (PRP) application in osteoarthritis (OA) knee, still critical issues like conclusive structural evidence of its efcacy, standard dose and good manual method of preparation to obtain high yield remains unanswered.

Study demonstrated that an absolute count of 10 billion platelets is crucial in a PRP formulation to have long sustained chondroprotective efect upto one year in moderate knee OA.

Role of placebo effect

- According to a meta-analysis of trials including a placebo group, the overall effect size estimate of placebo for pain (defined as change from baseline to endpoint) was 0.51 (95% CI 0.46 to 0.55) for all trials, though there was significant variation among distinct types of placebo.



Role of placebo effect

- A number of determinants are able to evoke a placebo response. Among them, there are factors related to the intervention such as:
  - The route of delivery
  - Frequency of administration
  - Color and cost
  - How new the intervention is
  - And others related to the health professional-patient relationship (context effect).

Role of placebo effect

>>>

- Interventions delivered by invasive routes (ie, intraarticular injections and acupuncture) were associated with more robust placebo effects compared with oral or topical placebos.

- In addition to alleviating pain, improvements in other common clinical OA outcomes have also been observed with placebo such as stiffness and joint function.

Nutritional supplements in management of OA

- Glucosamine and chondroitin
- Avocado soybean
- Fish oil
- Curcumin

Nutritional supplements in management of OA

- These nutritional supplements are not routinely recommend due to lack of clear evidence demonstrating a clinically important benefit from these supplements.

- However, may have small effects on symptoms, and patients with mild disease who may benefit more from these therapies.

Nutritional supplements in management of OA

- Some meta-analyses also suggested that glucosamine sulfate (1500 mg/day) and chondroitin (800 mg/day) may have small effects in delaying structural progression of OA with long-term use (two to three years).

Be careful about serving size

Glucosamine Sulphate vs hydrochloride

Sulphate

- Needs to be stabilised with NaCL(salt) or KCL
- Can contain up to 30% salt if stabalised with NaCL
- Typically contains around 75% glucosamine
- Glucosamine 2KCL does not contain salt
- Sourced from shellfish

Hydrochloride

- A more concentrated
- Typically contains around 83% glucosamine
- Far lower in salt
- More naturally stable
- Doesn't require added salt
- Doesn't require preservatives
- Sourced from vegetables


NATURAL WORLD
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BioPerine
OptiMSM
Helps Cartilage Health and Joint Flexibility
60 CAPLETS


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Puritan's Pride
GLUCOSAMINE HYDROCHLORIDE
1000 mg
(Shellfish Free)
60 Tablets
DIETARY SUPPLEMENT


Health Aid
VEGAN
Glucosamine
Sulphate 500mg
2KCl
With Vitamin C which contributes to the normal function of cartilage
ONE-A-DAY
30 Tablets
VEGAN


NATURES AID
Glucosamine
Sulphate 2KCl

Glucosamine & diabetes

- Glucosamine is likely safe in patients with well-controlled diabetes (HbA1c less than 6.5%) taking one or two oral antidiabetic medications or controlled by diet only.

- In patients with higher HbA1c levels or those taking insulin, monitor blood glucose levels closely/more frequently.

Nutritional supplements in management of OA

- With role of placebo effect in mind and in line with the prerequisite of "do no harm," it is likely that patients with OA pain would benefit from clinicians who are able to optimize and use the placebo effect in clinical practice in the favor of their patients.

- Finally :we do not recommend these supplements routinely to all patients; however, we do not discourage their use for patients who are keen to take them, especially if symptomatic benefit is achieved with their use.

How Effective Is Total Joint Replacement? What Are the Risks? How Long Does the Implant Last?

- About 90% of recipients of total hip replacement and about 80% of recipients of total knee replacement report substantial improvement in pain.
- Mortality following these procedures is less than 1%, and serious problems such as pulmonary embolus, myocardial infarction, pneumonia, and infection of the implant occur in less than 5%.
- The implants are durable, with about 90% of knee implants and 80% of hip implants lasting 20 years.

Summary of Osteoarthritis Treatment Guidelines From Major Professional Societies

Recommendations	ACR		EULAR		AAOS		OARSI	
	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip
Pharmacologic treatments								
Oral NSAIDs	Strongly recommended	Strongly recommended		Strongly recommended	Strongly recommended	Strongly recommended	Strongly recommended	Conditionally recommended
Topical NSAIDs	Strongly recommended				Strongly recommended	Strongly recommended	Strongly recommended	
Acetaminophen (short-term relief only)	Conditionally recommended	Conditionally recommended			Inconclusive		Conditionally recommended against	Conditionally recommended against
Tramadol	Conditionally recommended	Conditionally recommended			Strongly recommended			
Nontramadol opioids	Conditionally recommended against	Conditionally recommended against					Conditionally recommended against	Conditionally recommended against
Duloxetine	Conditionally recommended	Conditionally recommended					Conditionally recommended	Conditionally recommended against
Glucosamine or chondroitin	Strongly recommended against	Strongly recommended against			Strongly recommended against	Conditionally recommended against	Conditionally recommended against	
Hyaluronic acid injection	Conditionally recommended against	Strongly recommended against			Strongly recommended against	Strongly recommended against	Conditionally recommended	Conditionally recommended against
Glucocorticoid steroid injection	Strongly recommended	Strongly recommended			Inconclusive	Strongly recommended	Conditionally recommended	Conditionally recommended
Growth factor injections and/or platelet-rich plasma	Strongly recommended against	Strongly recommended against			Inconclusive			

Strongly recommended
Conditionally recommended
Conditionally recommended against
Strongly recommended against
Inconclusive

PRP >>> IA hyaloronate

AAOS: American Academy of Orthopaedic Surgeons, **ACR**: American College of Rheumatology, **EULAR**: European League Against Rheumatism, **OARSI:** Osteoarthris Research Society International.

Take home message

- Non- pharmacologic interventions are mainstay of osteoarthritis management.
- 10 percent weight reduction ➡ 50% pain reduction.
- None of medicines are disease modifying and their use is limited to symptomatic conditions.
- Topical NSAIDs demonstrate similar efficacy with lower toxicity compare to Oral NSAIDs.

Take home message

- Acetaminophen is not recommended anymore.
- NSAIDs with a long half-life or slow-release formulation were associated with higher risk, even accounting for dose.
- The use of any intraarticular hyaluronic acid (HA) formulation is not recommended due to the lack of robust evidence demonstrating benefit.
- Use of supplements is not routinely recommended for all patients.

References

1. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014; 22:363.

1. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis care & research. 2012;64(4):465-74.

2. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43:701.

3. Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). Annals of the rheumatic diseases. 2017;76(9):1537-43.

4. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatology international. 2010;30(3):357-63.

Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA. 2021;325(6):568–578. doi:10.1001/jama.2020.22171