Indian Journal of Orthopaedics Surgery 2021;7(2):95–99

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Orthopaedics Surgery

Journal homepage: https://www.ijos.co.in/

Editorial

Osteoarthritis knee decelerate joint damage time now to get them right

S S Jha[1,2,*]

[1] *Director, Harishchandra Orthopaedic Research Institute, Patna, Bihar, India*
[2] *Chief Consultant, Bharat Vikas Sanjay Anand Hospital for the Handicapped, Patna, Bihar, India*

ARTICLE INFO

Article history:
Received 22-05-2021
Accepted 24-05-2021
Available online 12-06-2021

1. Newer Horizons in Pathogenesis of Osteoarthritis

Osteoarthritis is a common heterogenous disease with multiple etiologies but primarily is considered to be a degenerative joint disorder that presents with pain, joint swelling and limited mobility in response to mechanical damage. This perception needs to be drastically changed that OA results from focal 'wear and tear' of articular cartilage and also the fact that the treatment options are limited. The current dogma is that both mechanics and genetics contribute to the development and progression of OA, depending on the anatomic location. OA is not a focal disease rather is a non-classical inflammatory disease of diarthrodial joints with presence of synoviocyte hypertrophy, pro-inflammatory cytokines and differentially affected sub-chondral bone compartments.

Degree of joint space narrowing is positively associated with subsequent total knee arthroplasty within 15 years. For each 1% rate of tibial cartilage loss there is 20% increased risk of undergoing total knee arthrtoplasty within 4 years.

2. OA Phenotypes

There is no generally accepted classification system for OA phenotypes. Dell'Isola et al. (2016) in their aim to identify the various phenotypes proposed several phenotypes. Osteoarthritis can be divided into subgroups of phenotypes on the basis of different dimension of disease: on aetiological phenotypes, structural/symptomatic presentation phenotypes, pain phenotypes, joint function related phenotypes, disability related phenotypes. Phenotypes are proposed differently also-

1. Chronic pain associated osteoarthritis with prominent central mechanism
2. Inflammation associated osteoarthritis
3. Metabolic syndrome associated osteoarthritis
4. Associated with joint – localized bone and cartilage metabolism
5. Mechanical load associated osteoarthritis
6. Osteoarthritis with minimal disease and low rate of progression

Disease phenotypes are meaningful, when they reflect differential treatment effects, prognosis or aetiology regardless of whether they are based on single factor or multiple factors.

3. Role of Pro-inflammatory Cytokines & Key Players

The pro-inflammatory cytokines IL-1β and TNF are produced ultimately leading to loss of tensile strength. Cytokines IL-1β and TNF inturn induces the expression of other cytokines (IL-6 and IL-8), chemokines (monocyte chemotactic protein 1 and granulocyte-macrophage colony-stimulating factor) and catabolic enzymes that are

* *Corresponding author.*
E-mail address: drssjhapatna@gmail.com (S. S. Jha).

https://doi.org/10.18231/j.ijos.2021.015

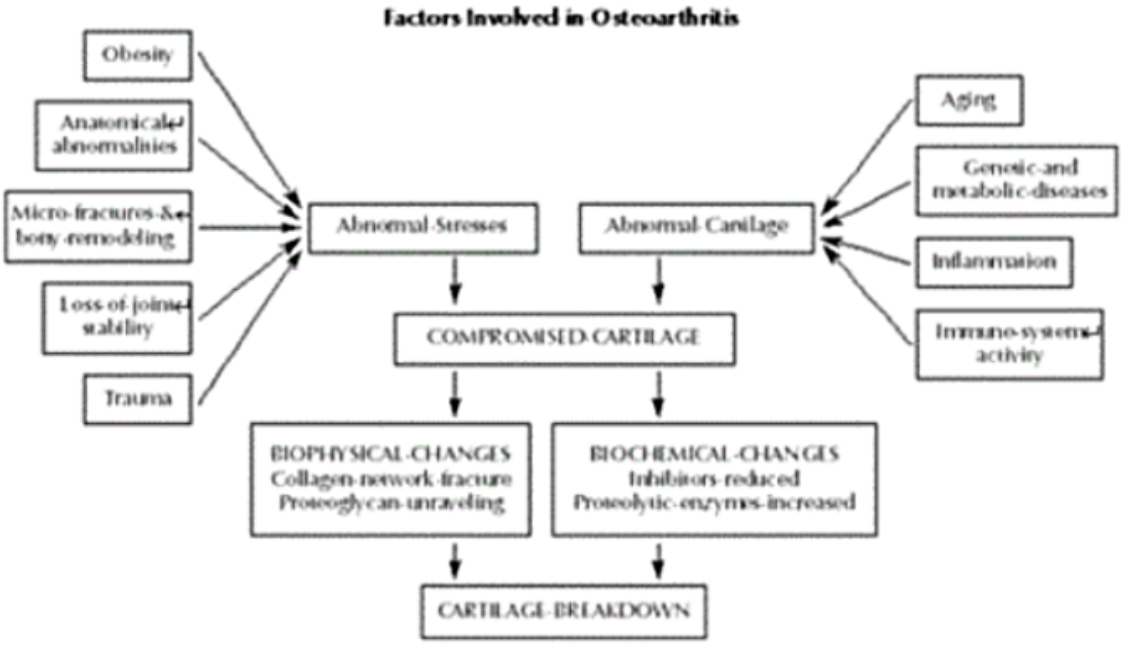

Fig. 1: Mandelbaum B, Waddell D. Etiology and pathophysiology of osteoarthritis. 2003;28 (suppl):S207-S214

responsible for breakdown of cartilage and proteoglycans (matrix metalloproteinases, the MMPs and aggrecanases).

Under healthy conditions synoviocytes produce synovial fluid to nourish and lubricate articular cartilage. Thereby contributing to cartilage homeostasis. In OA, the synovium contributes to articular cartilage catabolism by-products of breakdown of cartilage extracellular matrix such as fibronectin and collagen fragments, induce inflammation in extant chondrocytesand adjacent synovium. The activated macrophage-like synovial cells express TNF and IL-1β, which inturn induce fibroblast-like synoviocytes to secrete other chemokines and cytokines. Concommitently MMP-1, MMP-3, MMP-9 and MMP-13 are expressed by fibroblast like synoviocytes and further contribute to cartilage degradation. CX43 is increased in the synovium and articular chondrocytes of patients with OA, and is positively regulated by IL-1β in both fibroblast-like synoviocytesand chondrocytes. Over-expression of CX43 in fibroblast–like synoviocsytes increases the expression of MMPs aggreecanases and pro-inflammatory cytokines through a mechanism dependent of nuclear factor kB. It is noteworthy that in rheumatoid arthritis also CX43 is observed in all tissues of the joint highlighting its involvement not only OA but in RA also.

4. Management of Osteoarthritis

Plenty of guidelines have been developed for management of osteoarthritis but they do not correlate well with the required management of osteoarthritis. Hence, majority of patients do not get the right care. Health care cost also becomes an important factor. Now there is general awareness that glucosamine, paracetamol, opiods, viscosupplementation and arthroscopy-constitute palliative treatment, which frequently have no clinical benefit. They may be even harmful and not cost effective.

Efficacious evidence-based lifestyle behavior management strategies such as exercise and weight loss have never been fully emphasised. Inculcation of behavioral changes in the patient to perform exercise and undertake weight loss programme will initiate holistic approach at a minimal cost.

An early diagnosis of osteoarthritis enhances the opportunity to provide meaningful therapeutic benefit early in disease process.

5. Recent Advances in Management

Introduction of new therapeutic agents and introduction of evolution of sophisticated drug-delivery systems have been interesting advances in the past few years in the management of osteoarthritis. Consequences of long term use of conventional intra-articular glucocorticoids in the treatment of OA and evolution of a small-molecule inhibitor of the Wnt signaling pathway, sm04690 (Wnt pathway inhibitor) with possibilities of disease modifying OA, deserves attention for the management of OA. The Wnt signaling pathway stimulates the production of catabolic proteases that have been implicated in matrix degradation and modulates the differentiation of osteoblasts

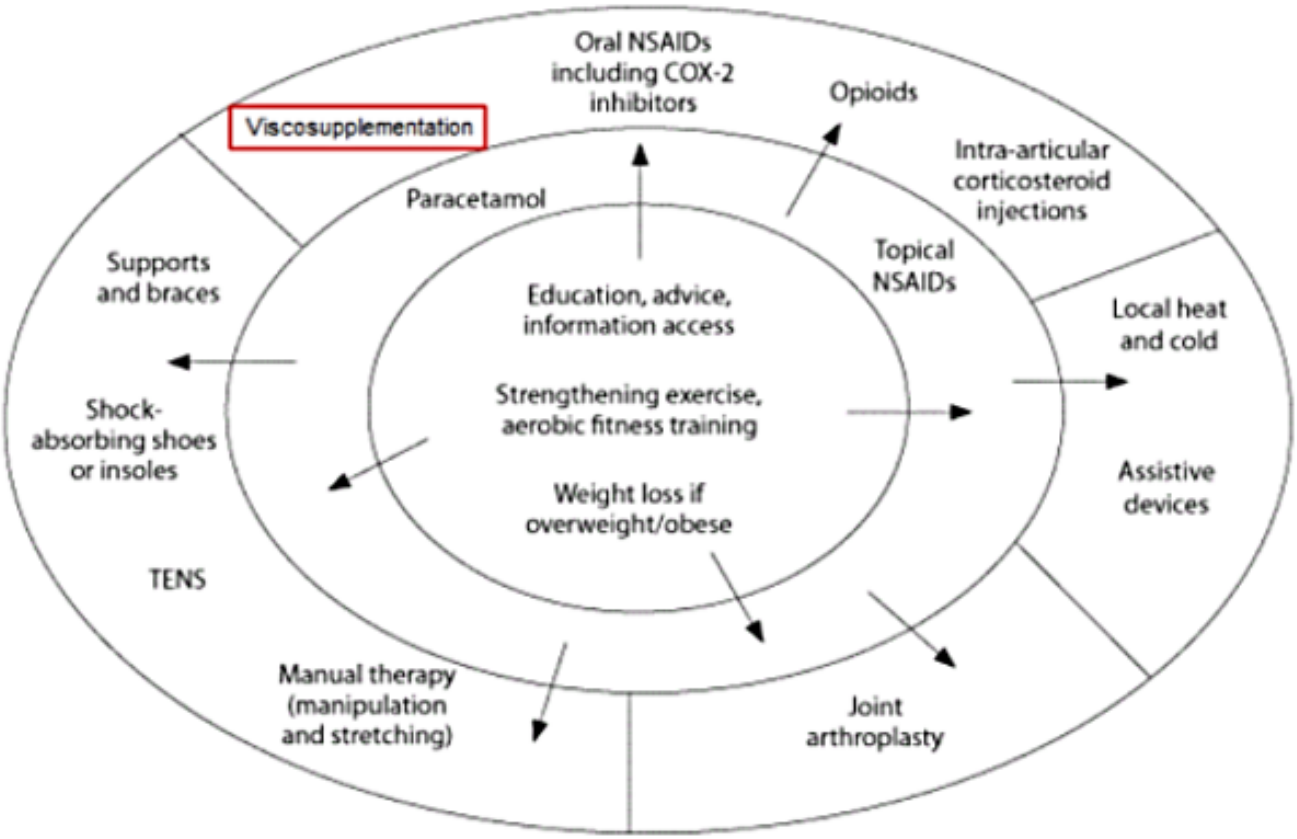

Fig. 2: Visco supplementation very weak evidence

and chondrocytes. Intra-articular SM04690 might cause cartilage regeneration and provide protection from cartilage catabolism. A significant difference in joint space width is claimed to be observed. A larger phase-2 trial is expected soon which will fully examine the effects of SM04690.

Clinical trials suggest declining analgesic effect of most widely recommended intra-articular glucocorticoid within 2-4 weeks. In an attempt to prolong the action of glucocorticoids, new delivery systems such as poly (PLGA:Poly Lactic–co-Glycolic Acid) microspheres have been introduced. An extended-release formulation of triamcelonone acetonide in PLGA microspheres, FX006 has been developed to maintain the concentration of this synthetic glucocorticoid in the joint for several months after a single dose. It claims to provide greater pain relief from 5 to 10 weeks. FDA approval was granted to FX006 for the management of knee OA. This approval represents a technological advance in providing a model for targeted delivery approach in treatment of OA.

6. Stem Cell: Mesenchymal and Hematopoetic

Role of mesenchymal stem cells (MSCs) in the repair of joint damage is too clearly understood. MSCs differ from bone marrow residing hematopoetic stem cells and are present in the joint in subchondral bone, cartilage, synovial fluid, synovium and adipose tissues. Migration of MSCs adjacent to the joint cavity becomes crucial for chondrogenesis–has been suggested in experimental models during embryogenesis. Synovium derived MSCs is advocated to be the primary drivers of cartilage repair in adulthood-is also suggested in experimental models. Joint-resident MSCs with access to superficial cartilage become key cells in adult cartilage repair and represent important targets for manipulation in chondrogenic osteoarthritis (OA) specially in the context of biomechanical correction of joints in early disease. Joint resident MSCs are abundant in vivo and are likely to occupy multiple nichs in the joint, thus enabling single-stage therapeutic intervention in osteoarthritis. Contrary to this, native bone marrow-resident MSCs are being linked with a nerve growth factor (NGF), CD271. This opens a gateway of vital role of neutrophils in OA pathobiology but the implications needs exploration because any anti-NGF therapy might worsen OA. Disease initiation and progression in pathogenesis of osteoarthritis is complex. In development of therapies for osteoarthritis specially for chondrogenic osteoarthritis,

abundant literature is available emphasizing the role of culture expanded cellular therapies and scapholds. In chondrogenic OA, disease initiation and progression seems to be essentially dependent on the articular cartilage. Role of subchondral bone, including the osteochondral junction becomes important in the pathogenesis of OA. Role of native bone marrow-resident stem cells, specially at sites of cartilage denudation needs to be further explored in advanced OA where such topographically localized cells can directly reach the joint cavity.

7. Total Joint Distraction Procedures and Osteotomies Promotes MSCs-mediated Repair

Spontaneous MSCs-mediated repair can happen in vivo has been realized. The mere fact that native MSCs are relatively abundant in the joint cavity, can be recruited to heal the cartilage defect. Remarkable structural repair of cartilage damage is demonstrated by total joint distraction procedures and osteotomies. Even topographic placing of MSCs at sites of injuries initiates the repair. These highlight, how intrinsic joint repair might be harmless. A window of opportunity is provided by removing the mechanical load and stopping the destructive forces on the damaged cartilage. It re-establishes joint haemostasis.

8. Gene Therapy

Intra-articular gene therapy was initially developed for overcoming the pharmacokinetic barriers in delivering biologics to the joints. It has great potential in the treatment of multiple diseases including OA (and RA also). After more than 25 years of development, arthritis gene therapy is finally entering in clinical practice. In 2017, the FDA approved three new gene therapeutics and the South Korean Ministry of Food & Drug Safety has approved the first Arthritis Gene Therapy: invossa.

Upon successful gene transfer & expression of the gene in the joint by residing cells, the therapeutic gene products are synthesized indigenously and continue to be synthesized for potentially extended period of time.

In vivo gene delivery to the joint by direct intra-articular injection is an alternative way to expedite the treatment. Adino-associated virus (AAV) has emerged as a popular vector for invivo delivery because the virus is safe, effective and less immunogenic. When injected into joints, recombinant AAV transduces synovial lining cells as well as chondrocytes throughout the thickness of the articular cartilage. This is a considerable advantage in OA in which chondrocyte dysfunction has a key role.

A faster approval is expected from FDA for these gene therapy new drugs. Invossa is only the fifth gene therapy product to be approved for anywhere in the world and the second for a non-lethal disease. Rapid future progress in genetic medicine for arthritis and other joint diseases is likely to be widely available in the coming years.

9. Silver Lining in Medical Management of Osteoarthritis: Sulfasalazine and Small Molecules

Effects of sulfasalazine and the small molecule, tofacitinib on the protein profile of articular chondrocytes have opened up a new vista in the management of osteoarthritis, whereas a small molecule claims to promote cartilage extracellular matrix generation thereby inhibiting osteoarthritis development.

The mode of action of sulfasalazine is inhibition of tumour necrosis factor (TNF)-alpha expression and may reduce the secretion of inflammatory cytokines such as interleukin (IL)-8 as well as may suppress B-cell function. Sulfasalazine has three mechanisms of action-

1. Antibacterial effects – Arthritic patients tend to have intestinal inflammation. Sulfasalazine reduces bacterial counts in the gut and possibly related to prostaglandin sparing effect through inhibition of PGDH activity
2. Anti-inflammatory effects- Sulfasalazine inhibits inflammatory reactions, superoxide production and enzyme secretion.
3. Immunomodulatory effects-Sulfasalazine decreases or increases the number or activity of one or more subsets of lymphocytes or other mononuclear cells.

Dose: Sulfasalazine in a dose of upto 2g/day is started in gradually increasing dose starting from 500 mg twice daily in osteoarthritis (in rheumatoid arthritis, if methotrexate cannot be used due to intolerance or contraindications).

Furthermore, tofacitinib increases the cellular levels of adenosine, which is known to have anti-inflammatory activity, through the down regulation of AMPD2. This would be a novel functional aspect of tofacitinib in osteoarthritis. Over and above, it has been demonstrated in experimental models that inhibition of TAK1 and/or JAK can rescue impaired chondrogenic differentiation of human mesenchymal stem cells in osteoarthritis-like conditions. Tofacitinib inhibits JAK 1 and 3 and Baricitnib inhibits JAK 1 and 2. Both the JAK inhibitors can be administered as monotherapy or in combination with methotrexate. Tofacitinib is taken orally wice daily with a dosage of 5 mg. Baricitinib is taken orally once daily. There are two dosages available: 4 mg or 2 mg.

Osteoarthritis knee from management point of view have several targeted therapy as above with either medical or even surgical procedures (distraction and various osteotomies) short of joint replacements. Thereby, it can effectively be concluded that progressive joint damage can definitely get decelerated, if not halted.

Use of small molecules apart from the very common DMARD, sulfasalazine with its three-dimensional antibacterial, anti-inflammatory & immunomodulatory effects, has opened up greater hopes of arresting the disease

at some stage before progressing to a stage, where joint replacement becomes inevitable. Future awaits gene therapy when it is likely to be widely available for clinical use in osteoarthritis.

In the meanwhile, sophisticated drug delivery system such as Poly Lactic-co-Glycolic Acid (PLGA) microspheres has been introduced. The extended release formulation of triamcelonone acetonide in PLGA microspheres will maintain the concentration of glucocorticoid in the joint for several months after a single dose. Evolution of intraarticular small molecule inhibitor of the Wnt signaling pathway provides strong possibilities of modifying osteoarthritis by causing cartilage regeneration and will also simultaneously protect the cartilage from catabolism.

The best development in surgical discipline has been the evolving indications, where surgery can be deferred or avoided by use of available therapeutic armamentarium or substituting it with joint preservation surgery. Future will only tell us that knee joint replacement goes in the history books by end of this century, if not earlier.

10. Further Reading

1. Cicuttini, F. M. et al. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. Ann Rheum Dis 2004;63:1124–27.
2. Deshmukh, V. et al. A small-molecule inhibitor of the Wnt pathway (SM04690) as a potential disease modifying agent for the treatment of osteoarthritis of the knee. Osteoarthritis Cartilage 2018;26:18–27.
3. Flexion Therapeutics Inc. Zilretta (triamcinolone acetonide extended-release injectable suspension), for intra-articular use [label] Food and Drug Administration https://www.accessdata.fda.gov/drugsatfda_docs/label/2 017/208845s000lbl.pdf (2017).
4. Homandberg, G. A. & Hui, F. Association of proteoglycan degradation with catabolic cytokine and stromelysin release from cartilage cultured with fibronectin fragments. Arch Biochem Biophys 1996;334:325–31.
5. Intema, F. et al. Tissue structure modification in knee osteoarthritis by use of joint distraction: an open 1-year pilot study. Ann Rheum Dis 2011;70:1441–46.
6. Koshino, T., Wada, S., Ara, Y. & Saito, T. Regeneration of degenerated articular cartilage after high tibial valgus osteotomy for medial compartmental osteoarthritis of the knee. Knee 2003;10:229–36.
7. US Food and Drug Administration. Approved cellular and gene therapy products. US Food and Drug Administration. FDAhttps://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm (2018).
8. Wiegant, K. et al. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis Cartilage 2013;21:1660–67.

Author biography

S S Jha, Member, IOA 2021 Rheumatology Subcommittee,
Patron & Founder President, Indian Orthopaedic Rheumatology Association,
Vice Secretary General, Asia-Pacific Society for Foot & Ankle Surgery

Cite this article: Jha SS. Osteoarthritis knee decelerate joint damage time now to get them right. *Indian J Orthop Surg* 2021;7(2):95-99.