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UNIVERSITÀ DEGLI STUDI DI ROMA

Chondrotoxicity of intra-articular injection products

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Author has nothing to disclose

BACKGROUND

- **Intra-articular (IA) injections** are common in **osteoarthritis** to **reduce pain and improve function**

biomedicines
MDPI

Article

Long-Term Efficacy of Carboxymethyl-Chitosan in Advanced Knee Osteoarthritis: A Twelve-Month Follow-Up Study on Non-Responders to Hyaluronic Acid

Nicola Manocchio [1], Carmelo Pirri [2], Concetta Ljoka [1], Andrea Sorbino [1], Nicolò Piacentini [1], Cristiano Monello [1], Giulia Vita [1] and Calogero Foti [1,*]

ELSEVIER
Osteoarthritis and Cartilage
Volume 13, Issue 12, December 2005, Pages 1126-1127

Letter to the Editor

Repeated ultrasound-guided intra-articular injections of 40 mg of Hyalgan® may be useful in symptomatic relief of hip osteoarthritis

A. Migliore M.D. †, S. Tormenta M.D. ‡, U. Massafra M.D. †, E. Carloni M.D. †, C. Padalino M.D. †, F. Iannessi M.D. ‡, A. Alimonti M.D. †, L.S. Martin Martin M.D. §, M. Granata M.D. ||

ELSEVIER
Maturitas
Volume 78, Issue 3, July 2014, Pages 188-198

Review

Chondrocyte and mesenchymal stem cell-based therapies for cartilage repair in osteoarthritis and related orthopaedic conditions

Ali Mobasheri [a b c d e], Gauthaman Kalamegam [e], Giuseppe Musumeci [f], Mark E. Batt [b g]

Intraarticular injection of anakinra in osteoarthritis of the knee: A multicenter, randomized, double-blind, placebo-controlled study

Arthritis Care and Research • Article • *Open Access* • 2009 • DOI: 10.1002/art.24096

Chevalier X. [a, k]; Goupille P. [b]; Beaulieu A.D. [c]; Burch F.X. [d]; Bensen W.G. [e]; +5 authors

BACKGROUND

Bucharest 2-4 October 2025

The most used compounds for IA injections are:

- Corticosteroids
- Local Anaesthetics
- Hyaluronic Acids (HA)
- Platelet-rich Plasma (PRP)
- Nonsteroidal Anti-inflammatory Drugs (Nsaids)
- Collagen Medical Devices
- Bisphosphonates

Like all substances used as drugs, these compounds can also have **side effects**

Brown, G.A et al. AAOS Clinical Practice Guideline: Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline, 2nd Edition. J. Am. Acad. Orthop. Surg. 2013

BACKGROUND

Articular cartilage is a delicate, avascular tissue reliant on chondrocytes for matrix synthesis and repair

- balanced tissue of 2–4 mm-thick hyaline cartilage
- no nerves and blood or lymphatics vessels
- complex extracellular matrix (ECM) and specialized cellular elements

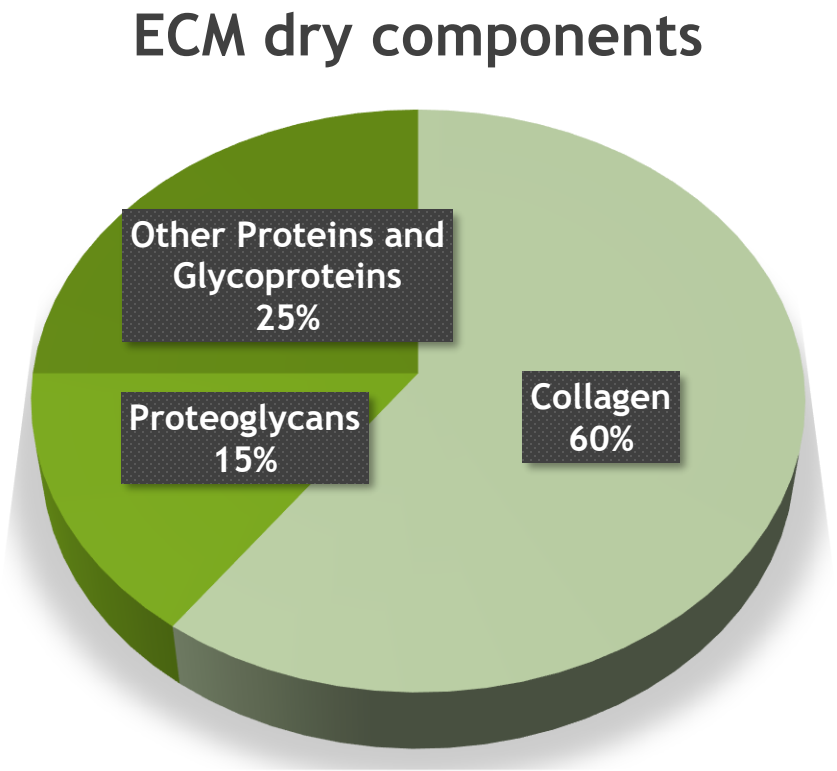
This sophisticated composition confers the capacity to endure substantial compressive forces while enabling smooth, frictionless articulation of the joints

Sophia Fox AJ et al. The basic science of articular cartilage: structure, composition, and function. Sports Health. 2009 Nov;1(6)

BACKGROUND

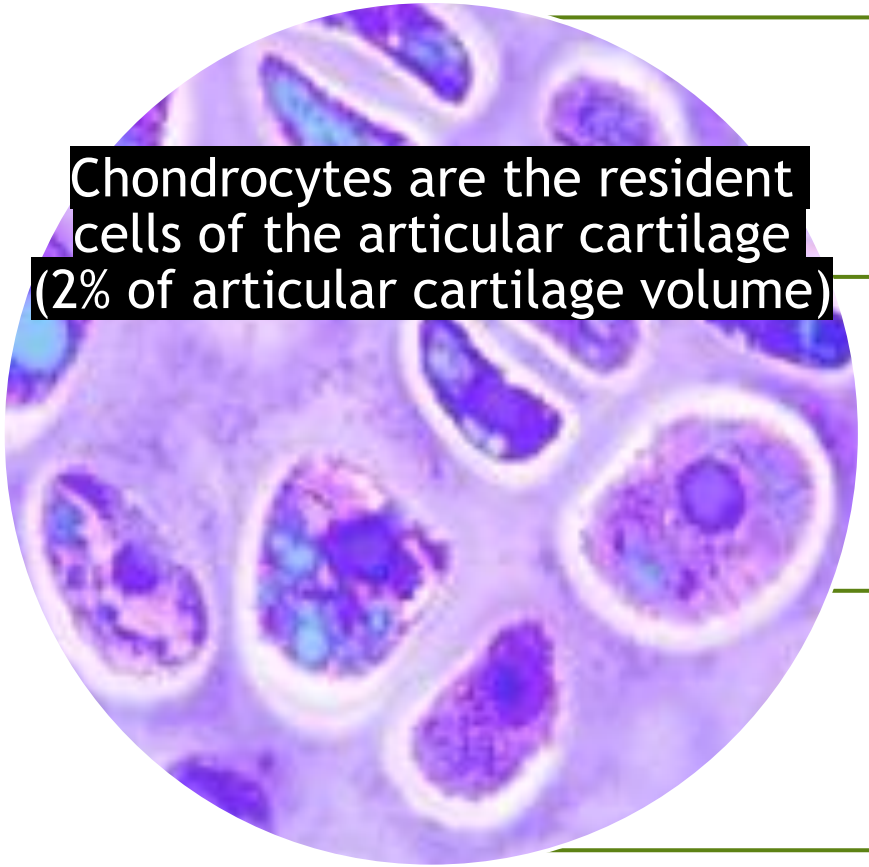
- ECM is the main structure of articular cartilage
  - **Water**, **collagen**, **proteoglycans**, other **non-collagenous proteins and glycoproteins** are the main ECM constituents

- **Type II collagen fibers (90%)** are stabilized by other less frequently appearing collagen types



Buckwalter, J.; Mankin, H. Articular Cartilage: Part I. J. Bone Jt. Surg. 1997, 79, 600

BACKGROUND

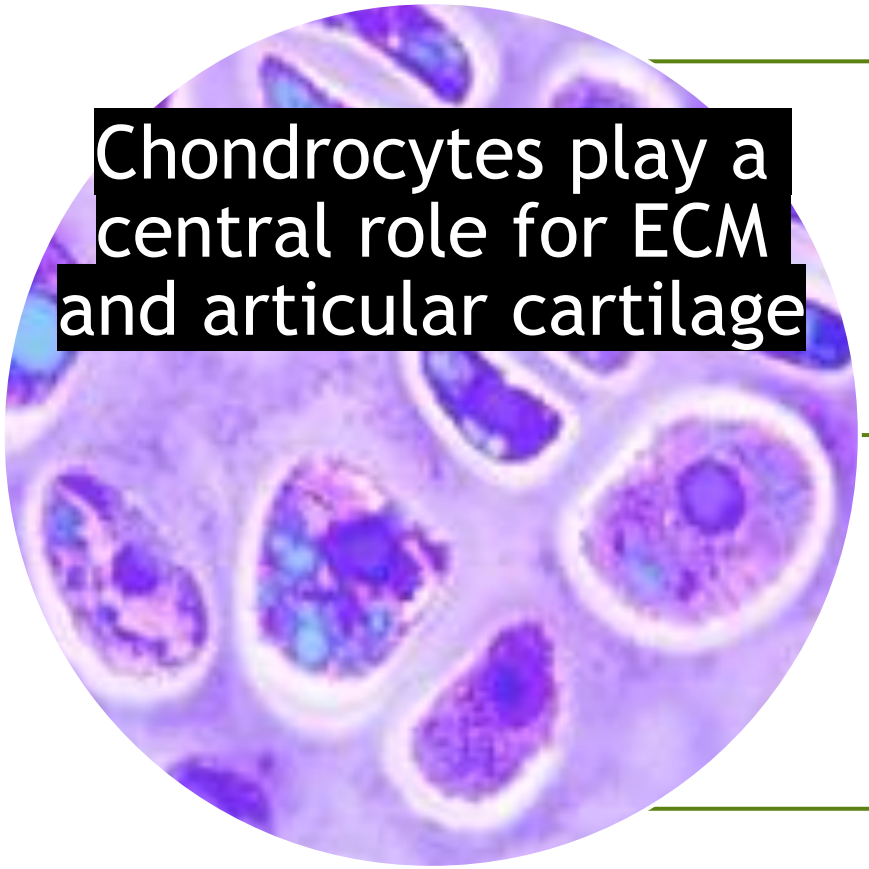


Chondrocytes are the resident cells of the articular cartilage (2% of articular cartilage volume)

- **Highly specialized** and metabolically active cells
- Derived from **mesenchymal stem cells**
- Involved in **formation, upkeep, turnover and restoration** of the ECM
- Create **specialized microenvironments**

Buckwalter, J. et al. Articular Cartilage: Tissue Design and Chondrocyte-Matrix Interactions. Instr. Course Lect. 1998

BACKGROUND



Chondrocytes play a central role for ECM and articular cartilage

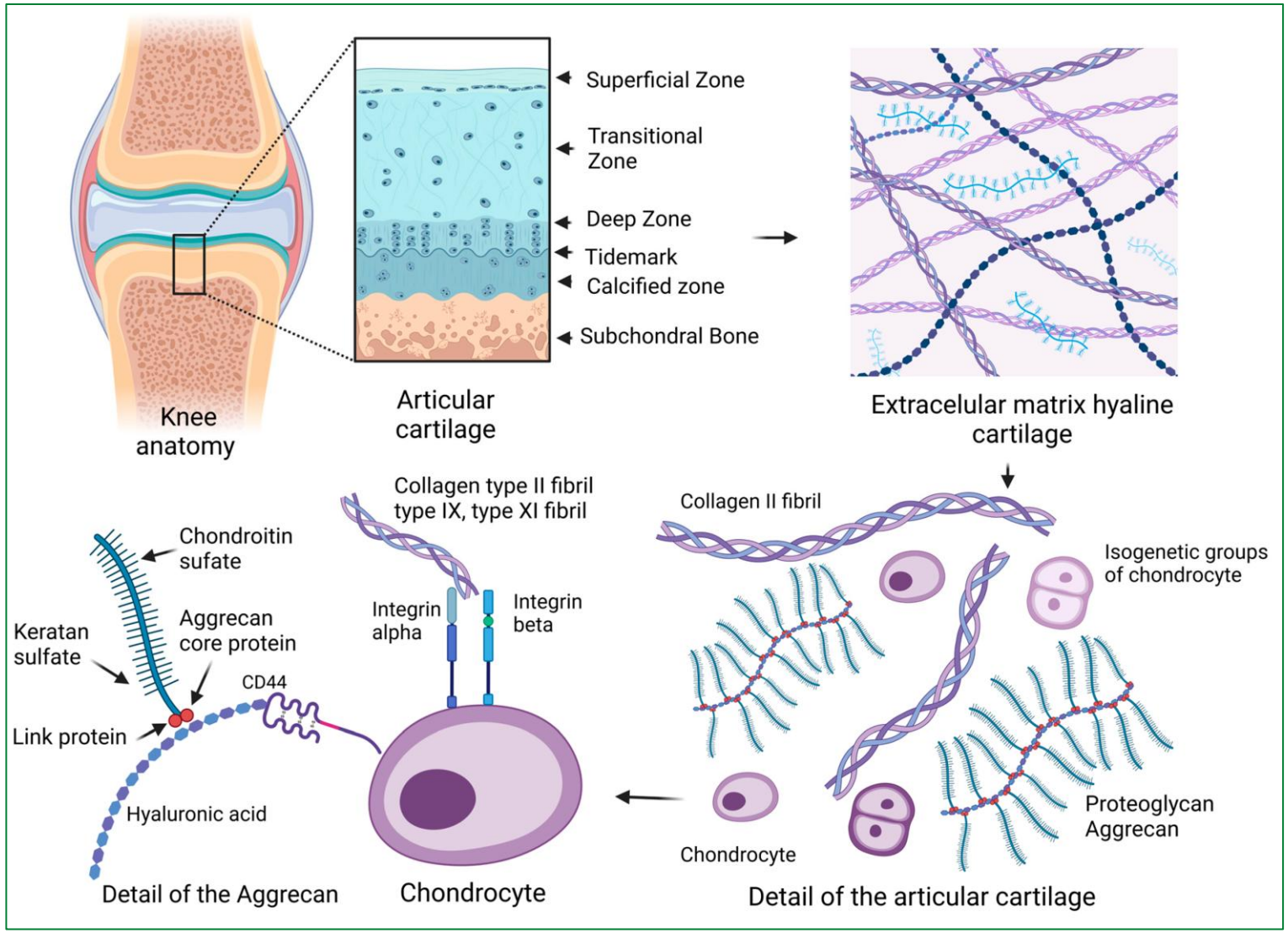
Synthesize **ECM components** and several **enzymes** responsible for its remodelling

As vascularization is lacking: primarily **anaerobic metabolism**

Metabolic activity can be altered by cytokines, growth factors, regulatory peptides, **joint motion and load**

Buckwalter, J. et al. Articular Cartilage: Tissue Design and Chondrocyte-Matrix Interactions. Instr. Course Lect. 1998

BACKGROUND


Knee anatomy
Superficial Zone
Transitional Zone
Deep Zone
Tidemark
Calcified zone
Subchondral Bone
Articular cartilage
Extracelular matrix hyaline cartilage
Collagen type II fibril type IX, type XI fibril
Chondroitin sufate
Keratan sulfate
Aggrecan core protein
CD44
Link protein
Hyaluronic acid
Integrin alpha
Integrin beta
Detail of the Aggrecan
Chondrocyte
Collagen II fibril
Isogenetic groups of chondrocyte
Proteoglycan Aggrecan
Chondrocyte
Detail of the articular cartilage

BACKGROUND

ARTICULAR CARTILAGE IS A PARTICULARLY DELICATE TISSUE, VERY DIFFICULT TO REPAIR

CHONDROCYTES HAVE A CENTRAL ROLE FOR ECM SYNTHESIS AND REPAIR

CONCERN EXISTS ABOUT **DRUG-INDUCED CHONDROTOXICITY** COMPROMISING CARTILAGE INTEGRITY AND LONG-TERM OUTCOMES

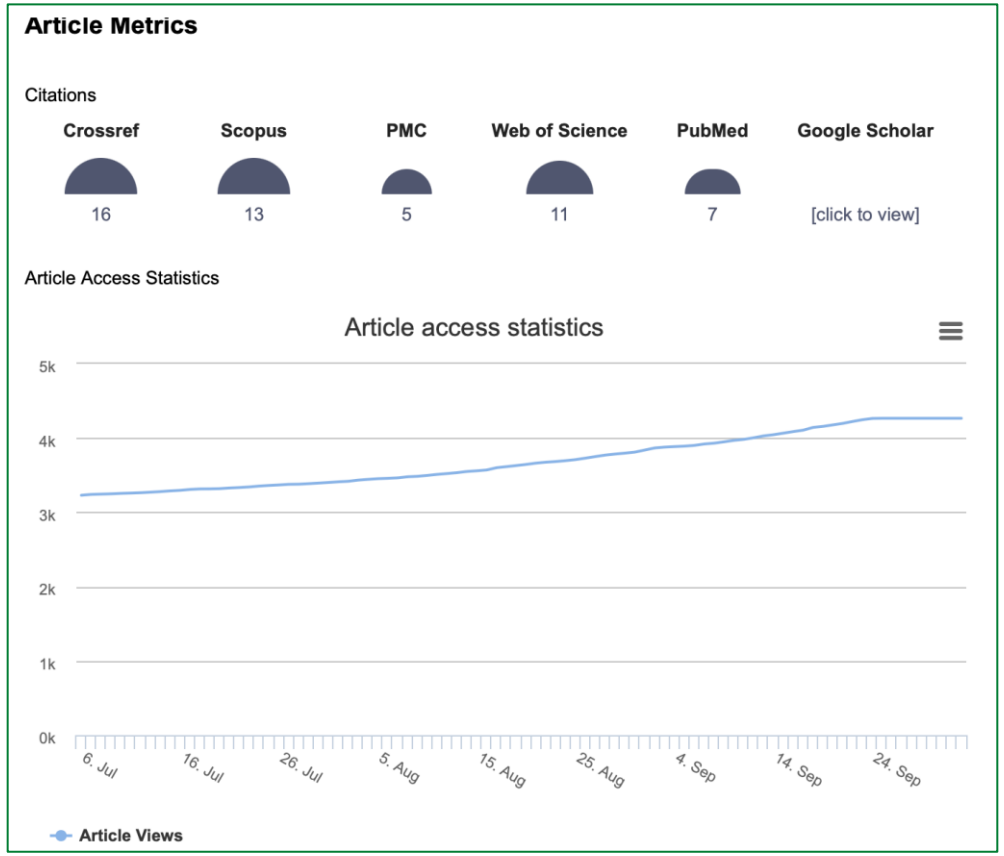
To review chondrotoxic effects of the most used IA products

International Journal of *Molecular Sciences*
MDPI

Review

Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review

Carmelo Pirri [1], Andrea Sorbino [2], Nicola Manocchio [2], Nina Pirri [3], Antonio Devito [4], Calogero Foti [2] and Alberto Migliore [5,*]



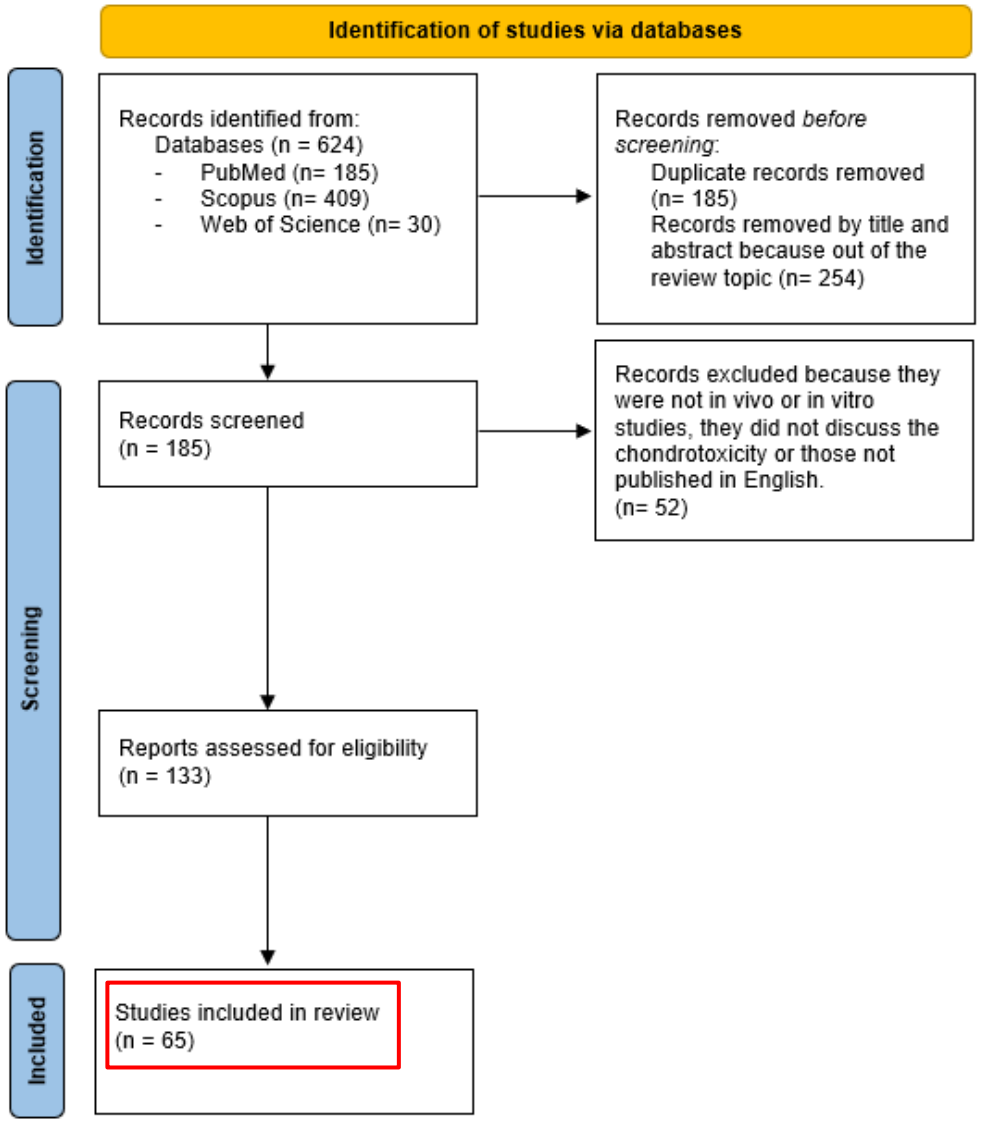
- **Paper available here**

METHODS

- An extensive literature search was performed using the following MeSH terms on **PubMed, Scopus and Web of Science**:
  - "chondrotoxicity", "intraarticular injection", "corticosteroids", "steroids", "hyaluronate or hyaluronic acid", "non-steroidal anti-inflammatory drug", "anaesthetic", "platelet rich plasma", "collagen medical devices" and "bisphosphonates".

Studies were **included** if	in vivo or in vitro
	evaluated chondrotoxicity
	published in English

RESULTS


Identification of studies via databases
Identification
Records identified from:
Databases (n = 624)
- PubMed (n= 185)
- Scopus (n= 409)
- Web of Science (n= 30)
Records removed *before screening*:
Duplicate records removed (n= 185)
Records removed by title and abstract because out of the review topic (n= 254)
Screening
Records screened (n = 185)
Records excluded because they were not in vivo or in vitro studies, they did not discuss the chondrotoxicity or those not published in English. (n= 52)
Reports assessed for eligibility (n = 133)
Included
Studies included in review (n = 65)

RESULTS

In total

65 studies

were included in the review

- Corticosteroids: 33
- Local Anesthetics: 18
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): 5
- Hyaluronic Acid (HA): 7
- Platelet-Rich Plasma (PRP): 2

No paper was retrieved regarding collagen medical devices or bisphosphonates

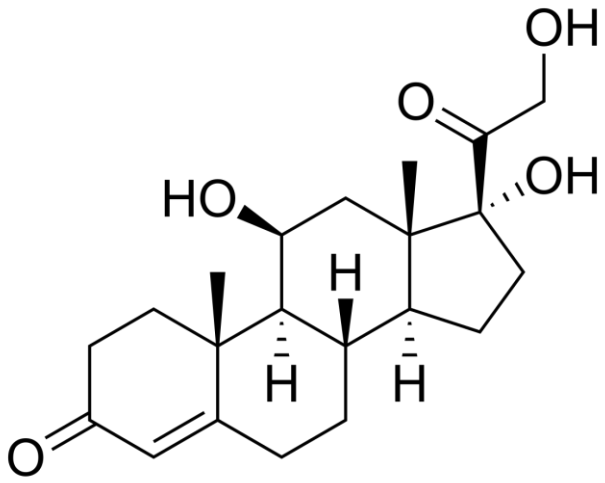
Manocchio N et al. Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review. Int J Mol Sci. 2024 Jun

RESULTS – Corticosteroids (n = 33)

A total of 33 papers regarding corticosteroids were retrieved

14 on human subjects, 17 on animals, and 2 comparisons (humans and animals)

16 in vivo studies, 16 in vitro and 1 ex vivo



Explored drugs: Betamethasone, Methylprednisolone, Triamcinolone, Dexamethasone, Hydrocortisone

19 (58%) studies expressed evidence about corticosteroids' potential chondrotoxicity

RESULTS – Corticosteroids (n = 33)

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Corticosteroids are frequently used due to their anti-inflammatory effects

Dose- and frequency-dependent chondrotoxicity (except for **triamcinolone**)

Corticosteroids can improve **functional outcomes and quality of life** in painful conditions

Both in vitro and in vivo studies in humans and animals showed **variable but concerning cartilage damage**

Manocchio N et al. Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review. Int J Mol Sci. 2024 Jun

RESULTS – Local Anaesthetics (n = 18)

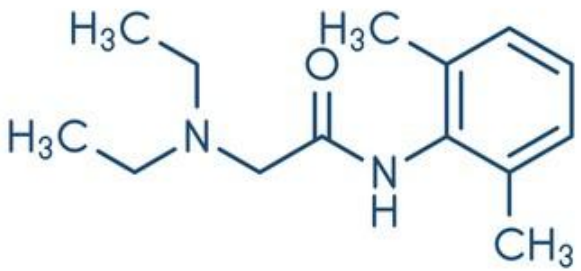
A total of 18 papers regarding local anaesthetics were retrieved

4 on human subjects, 14 on animals

6 in vivo studies, 12 in vitro

Explored drugs: Bupivacaine, Lidocaine, Ropivacaine, Mepivacaine

17 (95%) studies expressed evidence about local anaesthetics' potential chondrotoxicity



lidocaine

RESULTS – Local Anaesthetics (n = 18)

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Widely used to achieve analgesia (often combined with corticosteroids), crucial for the success of an IRP

Ropivacaine and liposomal formulations of bupivacaine appeared less toxic

Bupivacaine, lidocaine, and ropivacaine showed dose- and time-dependent chondrotoxicity

Vitamin C may mitigate chondrotoxic effects

Importance of limiting dose and frequency

Manocchio N et al. Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review. Int J Mol Sci. 2024 Jun

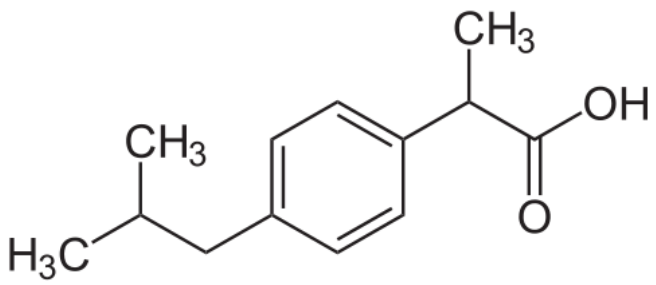
RESULTS – NSAIDs (n = 5)

A total of 5 papers regarding NSAIDs were retrieved

3 on human subjects, 2 on animals

1 in vivo studies, 4 in vitro

Explored drugs: Dexketoprofen, Ketorolac, Naproxen, Ibuprofen, Aceclofenac, Diclofenac



4 (80%) studies expressed evidence about NSAIDs potential chondrotoxicity

Manocchio N et al. Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review. Int J Mol Sci. 2024 Jun

RESULTS – NSAIDs (n = 5)

Widely used in OA for oral administration to reduce pain and functional impairments

Limited and inconsistent data on chondrotoxicity

Ketorolac and Naproxen showed potential cartilage damage

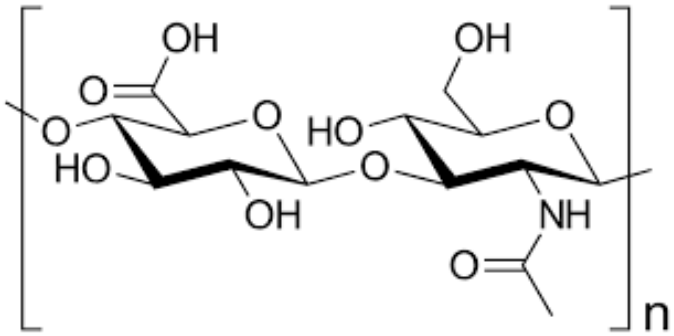
IA injections not common - this route might reduce systemic side effects and increase local efficacy

Aceclofenac showed potential positive effects on glycosaminoglycan synthesis

Ibuprofen showed limited toxicity

RESULTS – Hyaluronic Acid (n = 7)

A total of 7 papers regarding Hyaluronic Acid were retrieved



- 2 on human subjects, 5 on animals
- All the studies were conducted with in vitro models
- Focused on assessing HA efficacy in reducing chondrotoxicity caused by other drugs (carprofen, corticosteroids and anaesthetics)
- All the studies showed potential benefits by HA in reducing other compounds' chondrotoxicity

RESULTS – Hyaluronic Acid (n = 7)

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One of the most used compounds for IA injections in OA

HA promotes chondrocyte survival and function

HA appears safe and protective against the toxicity of other drugs

Only in vitro data about chondrotoxicity, limiting translation to real world scenario

Manocchio N et al. Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review. Int J Mol Sci. 2024 Jun

RESULTS – PRP (n = 2)

- 2 papers on PRP were retrieved, both on humans
- Beitzel et al. (2013) showed **increased cell proliferation and viability in tendon and cartilage after PRP**
- **Limited evidence available**, more research needed to clarify PRP effects (beneficial or harmful)
- PRP may represent a therapeutic option with low chondrotoxicity risk

Manocchio N et al. Chondrotoxicity of Intra-Articular Injection Treatment: A Scoping Review. Int J Mol Sci. 2024 Jun

CONCLUSION

- **Heterogeneity** in study protocols and methods **limits definitive conclusions**
- Chondrotoxicity seems influenced by **dose, frequency, and drug combinations**
- Corticosteroids (except triamcinolone), local anesthetics (except ropivacaine and liposomal forms), and some NSAIDs (ketorolac, naproxen) show higher risk profiles
- **HA and PRP show promise as safer options**, but more research needed in real world
- Standardized, larger studies are urgently needed

Thank you for your attention!

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Thank you for your attention!

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