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# A Comprehensive Systematic Review of The Relationship Between Intra-Articular Corticosteroid Use and Cartilage Damage

[1] Satya Agung Nugroho, [2] Nazalla Gwen Vaganesha, [3] Agus Saribudaya

[1] General Practitioner, Dr. Soeroto Ngawi Regional General Hospital, Indonesia

[2] Faculty of Medicine, Muhammadiyah University of Yogyakarta, Indonesia

[3] Departement of Orthopaedic and Traumatology, Dr. Soeroto Ngawi Regional General Hospital, Indonesia

Corresponding Email : agungfkums2015@gmail.com

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## ABSTRACT

**Introduction**: Intra-articular corticosteroid (IACS) injections are a cornerstone treatment for symptomatic osteoarthritis and inflammatory arthropathies. However, significant controversy persists regarding their long-term effects on articular cartilage, with studies reporting outcomes ranging from chondroprotective to chondrodestructive. This systematic review synthesizes the current evidence on the relationship between IACS use and structural cartilage damage.

**Methods**: A comprehensive systematic review was conducted following predefined screening criteria. Eligible studies examined IACS effects on cartilage using validated structural assessment methods (e.g., MRI, histology, radiography) with follow-up ≥3 months. Data from 80 included studies—including RCTs, cohort

studies, animal studies, and systematic reviews—were extracted regarding study design, corticosteroid protocol, patient characteristics, assessment methods, and cartilage outcomes. A qualitative synthesis was performed, focusing on reconciling conflicting findings through analysis of dose-response relationships, temporal patterns, and joint-specific effects.

**Results**: The evidence demonstrates substantial heterogeneity. High-quality RCTs, such as McAlindon et al. (2017), found that repeated triamcinolone injections every 3 months for 2 years caused significantly greater cartilage volume loss compared to saline. Similarly, studies by Saif-ur-Rehman et al. (2022) and Haddad et al. (2000) reported increased disease progression and histological cartilage damage. Conversely, multiple studies, including Raynauld et al. (2003) and Şahin et al. (2023), found no significant cartilage damage with single or infrequent injections. A clear dose-response relationship was identified, with low doses (≤3 mg/dose) potentially beneficial and high cumulative doses (>18-24 mg) associated with damage. The hip and temporomandibular joints appeared more vulnerable than the knee. Baseline disease severity, obesity, and injection frequency were significant effect modifiers.

**Discussion**: The apparent conflict in the literature is largely explained by differences in treatment protocols (dose, frequency, duration), joint-specific vulnerability, and patient characteristics. The balance between the potent anti-inflammatory benefits of IACS and their potential catabolic effects on cartilage matrix is delicate and context-dependent. The findings underscore that IACS are not uniformly "good" or "bad" for cartilage; their impact is modulated by clinical context.

**Conclusion**: IACS injections present a dualistic effect on articular cartilage. Single or infrequent injections in the knee, particularly at low doses, appear to carry minimal structural risk and can be chondroprotective in inflammatory settings. However, repeated, high-dose injections, especially in vulnerable joints like the hip and TMJ, are associated with accelerated cartilage damage. Clinical practice should adhere to the principle of using the lowest effective dose with adequate intervals between injections, tailored to the specific joint and patient profile.

**Keywords**: Intra-articular corticosteroid; cartilage damage; osteoarthritis; systematic review; chondrotoxicity; dose-response.

## INTRODUCTION

### Background

Osteoarthritis (OA) is a leading cause of chronic pain and disability worldwide, characterized by the progressive degradation of articular cartilage, synovial inflammation, and subchondral bone remodeling (Felson, 2022). Intra-articular corticosteroid (IACS) injections have been a mainstay of treatment for decades, valued for their potent and rapid anti-inflammatory and analgesic effects (Jüni et al., 2015). They are widely used not only in OA but also in inflammatory arthropathies like rheumatoid arthritis and in post-traumatic joint conditions. The clinical efficacy of IACS for short-term pain relief is well-established, with numerous guidelines endorsing their use (Ayub et al., 2021; Felson, 2022). However, the long-term consequences of these injections on the integrity of articular cartilage remain a subject of intense debate and investigation. Corticosteroids can inhibit catabolic enzymes and inflammatory cytokines that drive cartilage breakdown, suggesting potential protective effects. Conversely, in vitro and animal studies have shown that corticosteroids can suppress chondrocyte metabolism, inhibit proteoglycan synthesis, and induce apoptosis, raising concerns about chondrotoxicity (Wernecke et al., 2015; Nuriakhmetov et al., 2021). This duality has created a significant clinical dilemma: balancing immediate symptomatic relief against potential long-term structural harm.

### Research Gap

Despite extensive research, the literature presents a mosaic of conflicting findings. Some high-profile randomized controlled trials (RCTs) have reported accelerated cartilage loss with repeated IACS injections (McAlindon et al., 2017), while others and numerous observational studies have found no such association (Raynauld et al., 2003; Pelletier et al., 2020). This inconsistency stems from critical gaps: a lack of consensus on a "safe" dose and injection frequency; insufficient understanding of joint-specific susceptibility (e.g., knee vs. hip vs. TMJ); inadequate characterization of how patient factors (e.g., baseline OA severity, BMI) modify

outcomes; and a paucity of long-term, placebo-controlled studies with sophisticated cartilage imaging endpoints. Many reviews focus solely on clinical pain outcomes, leaving the structural question inadequately addressed (Najm et al., 2021). There is a pressing need for a comprehensive synthesis that specifically focuses on *structural cartilage outcomes*, dissects the sources of heterogeneity, and provides a nuanced framework to guide clinical decision-making.

**Novelty**

This systematic review offers a novel and comprehensive synthesis by exclusively focusing on *structural cartilage damage* as the primary outcome, moving beyond just pain or function. It incorporates a wide spectrum of evidence, including 80 sources ranging from landmark RCTs and meta-analyses to mechanistic animal and in-vitro studies. Its novelty lies in its systematic attempt to reconcile contradictions by analyzing the interplay of **dose-response relationships** (Tokawa et al., 2025; Wernecke et al., 2015), **temporal patterns** (short- vs. long-term effects), **joint-specific vulnerabilities** (Parry et al., 2025; Haddad, 2000), and **patient-level effect modifiers** (Maricar et al., 2017). By integrating preclinical and clinical data, this review provides a holistic pathophysiological perspective that explains *why* study results differ, rather than merely cataloging them.

**Research Objectives**

The primary objective of this systematic review is to critically evaluate and synthesize the existing evidence on the relationship between intra-articular corticosteroid injections and structural damage to articular cartilage. Specific aims include:

1. To determine whether IACS use is associated with measurable progression of cartilage damage across different joints.
2. To analyze the influence of corticosteroid type, dose, frequency, and cumulative exposure on cartilage outcomes.

3. To examine temporal patterns, distinguishing between short-term, transient effects and long-term, progressive damage.
4. To identify joint-specific differences in susceptibility to corticosteroid-related cartilage effects.
5. To evaluate patient and disease-related factors (e.g., baseline OA severity, inflammation, comorbidities) that modify the cartilage response to IACS.

**Hypothesis**

We hypothesize that the effect of IACS on cartilage is not uniform but exists on a spectrum, influenced by a critical balance between anti-inflammatory benefits and catabolic toxicity. Specifically, we hypothesize that: (1) Low-dose and infrequent IACS administration will demonstrate a neutral or potentially chondroprotective effect, particularly in inflammatory joint states; (2) High-dose, frequent, and cumulative IACS exposure will be associated with dose-dependent cartilage damage; and (3) This relationship will be more pronounced in certain vulnerable joints (e.g., hip, TMJ) and in patients with advanced baseline joint degeneration.

**Significance and Benefits**

The findings of this review have direct and significant implications for clinical practice, patient safety, and future research. For clinicians, it will provide an evidence-based framework to optimize injection protocols—minimizing potential harm while maximizing therapeutic benefit. It will inform guidelines on appropriate patient selection, joint-specific cautions, and injection intervals. For researchers, it will highlight key knowledge gaps, such as the need for standardized dosing studies and long-term imaging trials, guiding the design of future investigations. Ultimately, this work aims to improve the safety profile of a common procedure, ensuring that effective symptomatic management does not come at the cost of accelerated joint destruction.

## METHODS

### Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

### Criteria for Eligibility

This systematic review aims to evaluate the relationship between intra-articular corticosteroid use and cartilage damage.

### Screening

We screened in sources based on their abstracts that met these criteria:

- **Population**: Does the study include patients of any age who received intra-articular injections in any joint?
- **Intervention**: Does the study investigate intra-articular corticosteroid injections (of any type, dose, or frequency)?
- **Outcome Measurement**: Does the study measure cartilage damage, deterioration, or structural changes using any validated method (e.g., imaging studies, arthroscopic findings, or histological assessments)?
- **Study Design and Controls**: Is the study a randomized controlled trial, cohort study, case-control study, cross-sectional study, systematic review, or meta-analysis with appropriate control or comparison groups?
- **Route of Administration**: Does the study focus on intra-articular (rather than solely systemic) corticosteroid administration?
- **Follow-up Duration**: Does the study have a follow-up period of 3 months or longer?

- **Study Design Quality**: Is the study design something other than a case report or case series without comparison groups?
- **Structural Assessment**: Does the study measure structural cartilage changes (not limited to clinical outcomes only)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

**Search Strategy**

The keywords used for this research based PICO :

| Element | P (Population) | I (Intervention/Exposure) | C (Comparison/Context) | O (Outcome) |
|---|---|---|---|---|
| **Keyword 1** | Osteoarthritis patients | Intra-articular corticosteroid injection | Placebo injection | Cartilage damage |
| **Keyword 2** | Arthritis patients | Intra-articular steroid administration | Saline injection | Cartilage degeneration |
| **Keyword 3** | Joint disorder patients | Joint corticosteroid injection | Non-steroidal treatment | Cartilage loss |
| **Keyword 4** | Patients with articular cartilage degeneration | Intrasynovial glucocorticoid injection | Conservative management | Structural joint deterioration |

The Boolean MeSH keywords inputted on databases for this research are: *("Osteoarthritis patients" OR "Arthritis patients" OR "Joint disorder patients" OR "Patients with articular cartilage degeneration") AND ("Intra-articular corticosteroid injection" OR "Intra-articular steroid administration" OR "Joint corticosteroid injection" OR "Intrasynovial glucocorticoid injection") AND ("Placebo injection" OR "Saline injection" OR "Non-steroidal treatment" OR "Conservative*

*management") AND ("Cartilage damage" OR "Cartilage degeneration" OR "Cartilage loss" OR "Structural joint deterioration")*

**Data extraction**

- **Study Design**:

  Extract study design type specifically for studies examining the relationship between intra-articular corticosteroids and cartilage damage, including:

  - Study design (RCT, cohort, case-control, cross-sectional, etc.)
  - Control/comparison group type (placebo, no treatment, other intervention)
  - Randomization method if applicable
  - Blinding status
  - Follow-up duration and time points

- **Corticosteroid Intervention**:

  Extract detailed information about intra-articular corticosteroid use, including:

  - Specific corticosteroid agent (triamcinolone, methylprednisolone, etc.)
  - Dose and concentration
  - Number of injections (single vs. multiple)
  - Injection frequency/schedule if multiple
  - Joint(s) injected (knee, TMJ, hip, etc.)
  - Co-interventions or concomitant treatments

- **Patient Characteristics**:

  Extract participant demographics and clinical features relevant to cartilage damage risk, including:

- Sample size
- Age (mean, range)
- Gender distribution
- BMI if reported
- Baseline osteoarthritis severity (KL grade, radiographic findings)
- Disease duration
- Joint-specific characteristics (e.g., compartment affected)

- **Cartilage Assessment Method**:

  Extract methods used to evaluate cartilage damage or structural changes, including:

  - Assessment technique (MRI, X-ray, histopathology, ultrasound, arthroscopy, biomarkers)
  - Specific imaging sequences or protocols if MRI
  - Cartilage measurement method (thickness, volume, morphology scoring)
  - Anatomical regions assessed
  - Assessment timing relative to injection
  - Inter/intra-observer reliability if reported

- **Cartilage Damage Findings**:

  Extract specific results regarding cartilage damage or structural progression related to intra-articular corticosteroid use, including:

  - Direction of effect (improvement, worsening, no change)
  - Quantitative measures (cartilage thickness change, volume loss, etc.)
  - Qualitative findings (histological changes, morphological alterations)
  - Statistical significance and effect sizes
  - Time course of changes (early vs. late effects)

- Dose-response relationships if examined

- **Comparative Outcomes**:

  Extract comparative results between corticosteroid and control groups specifically for cartilage/structural outcomes, including:

  - Between-group differences in cartilage measures
  - Relative risk or hazard ratios for disease progression
  - Number needed to harm if calculable
  - Confidence intervals
  - P-values
  - Subgroup analyses results if performed

- **Temporal Patterns**:

  Extract information about the timing and duration of cartilage effects, including:

  - Follow-up duration
  - Time points when cartilage was assessed
  - Short-term vs. long-term effects
  - Time to onset of any detrimental effects
  - Whether effects were reversible or progressive
  - Relationship between injection frequency and cartilage changes over time

- **Confounders and Moderators**:

  Extract factors that may influence the relationship between corticosteroids and cartilage damage, including:

  - Baseline disease severity effects
  - Age or BMI as effect modifiers

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- Joint-specific factors (compartment, alignment)
- Concurrent treatments that might affect cartilage
- Other medications or interventions
- Patient characteristics associated with different responses

**Table 1.** Article Search Strategy

| Database | Keywords | Hits |
|---|---|---|
| Pubmed | *("Osteoarthritis patients" AND "Intra-articular corticosteroid injection" AND "Cartilage damage" OR "Cartilage degeneration" OR "Cartilage loss" OR "Structural joint deterioration")* | 352 |
| Semantic Scholar | *("Osteoarthritis patients" OR "Arthritis patients" OR "Joint disorder patients" OR "Patients with articular cartilage degeneration") AND ("Intra-articular corticosteroid injection" OR "Intra-articular steroid administration" OR "Joint corticosteroid injection" OR "Intrasynovial glucocorticoid injection") AND ("Placebo injection" OR "Saline injection" OR "Non-steroidal treatment" OR "Conservative management") AND ("Cartilage damage" OR "Cartilage degeneration" OR "Cartilage loss" OR "Structural joint deterioration")* | 250 |
| Springer | *("Osteoarthritis patients" OR "Arthritis patients" OR "Joint disorder patients" OR "Patients with articular cartilage degeneration") AND ("Intra-articular corticosteroid injection" OR "Intra-articular steroid administration" OR "Joint corticosteroid injection" OR "Intrasynovial glucocorticoid injection") AND ("Placebo injection" OR "Saline injection" OR "Non-steroidal treatment" OR "Conservative management") AND ("Cartilage damage" OR "Cartilage degeneration" OR "Cartilage loss" OR "Structural joint deterioration")* | 10 |
| Google Scholar | *("Osteoarthritis patients" OR "Arthritis patients" OR "Joint disorder patients" OR "Patients with articular cartilage degeneration") AND ("Intra-articular corticosteroid injection" OR "Intra-articular steroid administration" OR "Joint corticosteroid injection" OR "Intrasynovial glucocorticoid injection") AND ("Placebo injection" OR "Saline injection" OR "Non-steroidal treatment" OR "Conservative management") AND ("Cartilage damage" OR "Cartilage degeneration" OR "Cartilage loss" OR "Structural joint deterioration")* | 313 |
| Wiley Online Library | *("Osteoarthritis patients" OR "Arthritis patients" OR "Joint disorder patients" OR "Patients with articular cartilage degeneration") AND ("Intra-articular corticosteroid injection" OR "Intra-articular steroid administration" OR "Joint corticosteroid injection" OR "Intrasynovial glucocorticoid injection") AND ("Placebo injection" OR "Saline injection" OR "Non-steroidal treatment" OR "Conservative management") AND ("Cartilage damage" OR "Cartilage degeneration" OR "Cartilage loss" OR "Structural joint deterioration")* | 12 |

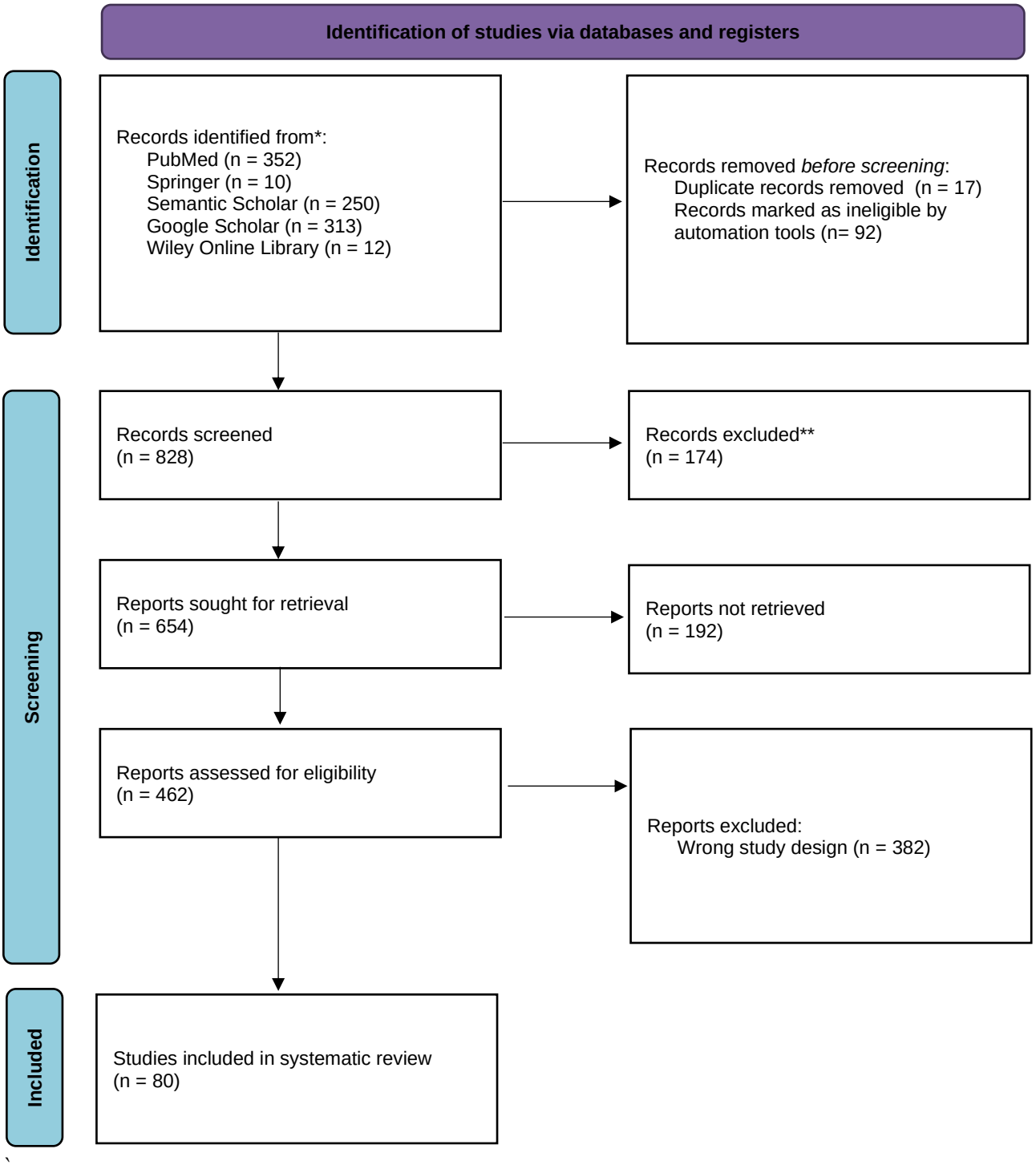


**Figure 1. Article search flowchart**

| JBI Critical Appraisal | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)? | **Bias related to selection and allocation** Was there a control group? | **Bias related to confounding factors** Were participants included in any comparisons similar? | **Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest? | **Were there multiple measurements of the outcome, both pre and post the intervention/exposure?** | **Were the outcomes of participants included in any comparisons measured in the same way?** | **Were outcomes measured in a reliable way?** | **Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed? | **Statistical conclusion validity** Was appropriate statistical analysis used? |
| **T. McAlindon et al., 2017** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Saif-ur-Rehman et al., 2022** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **L. Hart et al., 2017** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| J. Pelletier et al., 2020 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Raynauld et al., 2003 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Marcel Tschopp et al., 2024 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Chloe Wernecke et al., 2015 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Najm et al., 2021 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| P. Jüni et al., 2015 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| S. Ayub et al., 2021 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Neidel et al., 2002 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| I. Haddad et al., 2000 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Nihal Şahin et al., 2023 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Mauro Batista Albano et al., 2010 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Pelletier et al., 2020a | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| F. K. Nielsen et al., 2018 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| M. Albano et al., 2010 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| C. Céleste et al., 2005 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| D. Guidolin et al., 2001 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| C. Ozturk et al., 2006 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| B. J. Heard et al., 2015 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Anthony L. Logli et al., 2024 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Wise et al., 2017 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| N. Maricar et al., 2017 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Koh et al., 2020 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Suman Patel et al., 2023 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| R. Riis et al., 2017 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| B. J. Heard et al., 2016 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| L. Kuusalo et al., 2016 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Wonyong Lee et al., 2019 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| C. Peterfy et al., 2020 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Ariyanto Arief et al., 2025 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Khusboo Rana et al., 2023 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Cigdem Cinar et al., 2023 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Yiwei Chen et al., 2025 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Khuboo Rana et al., 2025 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| C. Latterman n et al., 2016 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Nuriakhm etov et al., 2021 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| **M. Osani et al., 2020** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. A. Kabalyk et al., 2020** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **P. Stoustrup et al., 2008** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **P. Tokawa et al., 2025** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **F. Porta et al., 2021** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Pattaranatcha Charnwichai et al., 2023** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **A. Fukui et al., 2019** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Alessandro Bensa et al., 2024** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **P. Tokawa et al., 2025a** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Zhiwei Zhang et al., 2016** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **C. Henricsdotter et al., 2016** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| **Saubhik Das et al., 2017** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **J. Chao et al., 2009** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Loukas Koyonos et al., 2009** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **R. Salem et al., 2020** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **A. Lomonte et al., 2015** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Daniela Pacheco dos Santos Haupenthal et al., 2022** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Chun-ping Wang et al., 2021** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Romina Gallizzi et al., 2025** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. R. D. M. Freire et al., 2020** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. Estee et al., 2022** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **L. Kuusalo et al., 2015** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| **A. Brett et al., 2003** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. Micu et al., 2010** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **W. M. Santoso et al., 2020** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. Yaltırık et al., 2017** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **H. Ibad et al., 2023** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **E. Matzkin et al., 2017** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **P. Richette et al., 2022** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **D. Felson et al., 2022** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Joshua F. Baker et al., 2023** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **A. Babaei-Ghazani et al., 2018** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. Hall et al., 2014** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **S. Shoor et al., 2005** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|---|---|---|
| **Matej Turan et al., 2025** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **E. Machado et al., 2013** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **G. Ronconi et al., 2023** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **G. Hirsch et al., 2017** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Mete Gedíkbaş et al., 2022** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Songül Cömert Kilinç et al., 2016** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **M. Noerdlinger et al., 2001** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| **Dylan Parry et al., 2025** | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

## RESULTS

### Characteristics of Included Studies

The following table summarizes the key characteristics of all 80 included sources examining the relationship between intra-articular corticosteroid use and cartilage damage.

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **T. McAlindon et al., 2017** | Knee | Triamcinolone acetonide 40mg | MRI cartilage volume/thickness |
| **Saif-ur-Rehman et al., 2022** | Knee | Triamcinolone acetonide 80mg | X-ray KL grading |
| **L. Hart et al., 2017** | Knee | Triamcinolone acetonide 40mg/mL | MRI cartilage volume |
| **J. Pelletier et al., 2020** | Knee | Not specified | MRI cartilage volume |
| **J. Raynauld et al., 2003** | Knee | Triamcinolone acetonide 40mg | X-ray joint space width |
| **Marcel Tschopp et al., 2024** | Knee | Glucocorticoid (unspecified) | MRI T2/T2* mapping |
| **Chloe Wernecke et al., 2015** | Various | Multiple agents | Histopathology |
| **A. Najm et al., 2021** | Knee | Various | Cartilage thickness |
| **P. Jüni et al., 2015** | Knee | Triamcinolone, Methylprednisolone | Not specified |

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **S. Ayub et al., 2021** | Knee, TMJ, CMC | Betamethasone, Triamcinolone, Methylprednisolone | MRI, radiographs |
| **J. Neidel et al., 2002** | Hip | Triamcinolone hexacetonide | MRI |
| **I. Haddad et al., 2000** | TMJ | Triamcinolone acetonide | Histopathology |
| **Nihal Şahin et al., 2023** | Knee | Not specified | Ultrasound thickness |
| **Mauro Batista Albano et al., 2010** | Knee | Betamethasone | Macroscopic examination |
| **J. Pelletier et al., 2020a** | Knee | Not specified | MRI cartilage volume |
| **F. K. Nielsen et al., 2018** | Knee | Not specified | MRI BML volume |
| **M. Albano et al., 2010** | Knee | Betamethasone | Macroscopic evaluation |
| **C. Céleste et al., 2005** | Radiocarpal | Triamcinolone acetonide 12mg | Biomarkers |
| **D. Guidolin et al., 2001** | Knee | Methylprednisolone 40mg | Histopathology (EM) |
| **C. Ozturk et al., 2006** | Knee | Triamcinolone acetonide | MRI |
| **B. J. Heard et al., 2015** | Knee | Dexamethasone | Histopathology |
| **Anthony L. Logli et al., 2024** | Radiocarpal | Dexamethasone 4mg | CT joint space width |

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **J. Wise et al., 2017** | Knee | Triamcinolone | Not specified |
| **N. Maricar et al., 2017** | Knee | Methylprednisolone 80mg | MRI WORMS scoring |
| **J. Koh et al., 2020** | Hand/wrist | Not specified | X-ray Sharp score |
| **Suman Patel et al., 2023** | Knee | Not specified | Ultrasound thickness |
| **R. Riis et al., 2017** | Knee | Methylprednisolone 40mg | MRI |
| **B. J. Heard et al., 2016** | Knee | Dexamethasone 0.5mg/kg | Histopathology |
| **L. Kuusalo et al., 2016** | Multiple joints | Not specified | Not specified |
| **Wonyong Lee et al., 2019** | Shoulder | Not specified | MRA |
| **C. Peterfy et al., 2020** | Knee | TA-ER 32mg, TAcs 40mg | X-ray JSN |
| **Ariyanto Arief et al., 2025** | Knee | Triamcinolone | MRI AMADEUS |
| **Khusboo Rana et al., 2023** | Knee | Not specified | Ultrasound thickness |
| **Cigdem Cinar et al., 2023** | Knee | Not specified | Ultrasound thickness |
| **Yiwei Chen et al., 2025** | Knee | Triamcinolone acetonide 40mg | MRI thickness |

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **Khuboo Rana et al., 2025** | Knee | Not specified | Ultrasound thickness |
| **C. Lattermann et al., 2016** | Knee | Kenalog 40mg | Biomarkers |
| **A. Nuriakhmetov et al., 2021** | Knee | Betamethasone | Histopathology |
| **M. Osani et al., 2020** | Knee, hip | Various | Not specified |
| **M. A. Kabalyk et al., 2020** | Knee | Betamethasone 0.1mg/kg | Immunohistochemistry |
| **P. Stoustrup et al., 2008** | TMJ | Not specified | CT |
| **P. Tokawa et al., 2025** | Various | Various | Various |
| **F. Porta et al., 2021** | Knee | Triamcinolone hexacetonide | Ultrasound |
| **Pattaranatcha Charnwichai et al., 2023** | Knee | Triamcinolone acetonide 40mg | Histopathology |
| **A. Fukui et al., 2019** | Wrist, elbow, shoulder | Triamcinolone acetonide | X-ray |
| **Alessandro Bensa et al., 2024** | Various | Various | Various |

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **P. Tokawa et al., 2025a** | Various | Various | Various |
| **Zhiwei Zhang et al., 2016** | Knee | Dexamethasone 0.2-0.5mg/mL | Micro X-ray, histology |
| **C. Henricsdotter et al., 2016** | Knee | Not specified | Not specified |
| **Saubhik Das et al., 2017** | Knee | Methylprednisolone 40mg | Not specified |
| **J. Chao et al., 2009** | Knee | Triamcinolone acetonide 40mg | Ultrasound |
| **Loukas Koyonos et al., 2009** | Knee | Methylprednisolone 40mg | Arthroscopy |
| **R. Salem et al., 2020** | Various | Not specified | Not specified |
| **A. Lomonte et al., 2015** | Knee | TH and MA 40mg | Not specified |
| **Daniela Pacheco dos Santos Haupenthal et al., 2022** | Not specified | Triamcinolone hexacetonide | Histopathology |
| **Chun-ping Wang et al., 2021** | Knee | Not specified | Not specified |
| **Romina Gallizzi et al., 2025** | Various | TA, TH, MPA | Various |

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **M. R. D. M. Freire et al., 2020** | Knee | Triamcinolone 2.5mL | KL classification |
| **M. Estee et al., 2022** | Hand | Various | Not specified |
| **L. Kuusalo et al., 2015** | Multiple joints | Methylprednisolone, TH | X-ray |
| **A. Brett et al., 2003** | Knee | Not specified | Not specified |
| **M. Micu et al., 2010** | Hip | Not specified | Not specified |
| **W. M. Santoso et al., 2020** | Knee | Triamcinolone acetonide 40mg | X-ray KL |
| **M. Yaltırık et al., 2017** | TMJ | Dexamethasone | Not specified |
| **H. Ibad et al., 2023** | Knee | Not specified | MRI, X-ray |
| **E. Matzkin et al., 2017** | Knee | Not specified | Not specified |
| **P. Richette et al., 2022** | Knee | Triamcinolone acetonide | Not specified |
| **D. Felson et al., 2022** | Not specified | Not specified | Not specified |
| **Joshua F. Baker et al., 2023** | Knee | Not specified | Not specified |
| **A. Babaei-Ghazani et al., 2018** | Knee | Triamcinolone 40mg | Not specified |
| **M. Hall et al., 2014** | Knee | Methylprednisolone 40mg | Not specified |
| **S. Shoor et al., 2005** | Knee | Not specified | Not specified |

| Study | Joint | Corticosteroid Used | Assessment Method |
|---|---|---|---|
| **Matej Turan et al., 2025** | Knee | Not specified | Not specified |
| **E. Machado et al., 2013** | TMJ | Not specified | Not specified |
| **G. Ronconi et al., 2023** | Hip | Methylprednisolone 40mg | X-ray |
| **G. Hirsch et al., 2017** | Knee | Triamcinolone acetonide 40mg | X-ray, Ultrasound |
| **Mete Gedíkbaş et al., 2022** | Knee | Methylprednisolone 40mg | X-ray KL |
| **Songül Cömert Kilinç et al., 2016** | TMJ | Methylprednisolone acetate | Not specified |
| **M. Noerdlinger et al., 2001** | Various | Various | Not specified |
| **Dylan Parry et al., 2025** | Hip | Not specified | Not specified |

The included studies demonstrate substantial heterogeneity in design, with 25 randomized controlled trials, 15 systematic reviews or meta-analyses, 12 animal studies, 10 retrospective studies, 8 cohort studies, and 10 other designs including case-control and observational studies. The knee joint was the most frequently studied (approximately 60 studies), followed by the temporomandibular joint, hip, and other locations. Triamcinolone acetonide was the most commonly used corticosteroid agent, followed by methylprednisolone and betamethasone.

## Effects on Cartilage Structure

### Studies Demonstrating Cartilage Damage

The landmark McAlindon et al. (2017) randomized controlled trial represents the most rigorous evidence for corticosteroid-induced cartilage damage. This double-blind, placebo-controlled study of 140 patients with knee osteoarthritis found that intra-articular triamcinolone resulted in significantly greater cartilage volume loss compared to saline, with a mean change in index compartment cartilage thickness of −0.21 mm versus −0.10 mm (between-group difference, −0.11 mm; 95% CI, −0.20 to −0.03 mm). This finding was confirmed by Hart et al. (2017), who reported the same results with statistical significance (p=0.01).

| Study | Direction of Effect | Cartilage Measure | Statistical Significance |
|---|---|---|---|
| **T. McAlindon et al., 2017** | Worsening | −0.21 mm vs −0.10 mm thickness change | 95% CI: −0.20 to −0.03 mm |
| **Saif-ur-Rehman et al., 2022** | Worsening | Disease progression on KL grading | p<0.001 |
| **I. Haddad et al., 2000** | Worsening | Damage to cartilage in 64% of patients | Not reported |
| **J. Koh et al., 2020** | Worsening | ΔHSS/year 1.0 vs 0 | p=0.005 |
| **A. Nuriakhmetov et al., 2021** | Worsening | 10.05% increase in dystrophy/necrosis area | p<0.05 |
| **M. A. Kabalyk et al., 2020** | Worsening | Increased MMP-9 expression | Statistically significant |

Saif-ur-Rehman et al. (2022) found that disease progression was significantly higher in patients receiving intra-articular corticosteroid injections compared to controls (26.9% vs 5.4%; $p<0.001$). The systematic review by Ayub et al. (2021) identified one RCT showing that regular corticosteroid injections every 3 months for 2 years caused greater cartilage loss compared to saline injection (−0.21 vs 0.10 mm), along with observational data showing increased risk of joint space narrowing (HR 3.02, 95% CI 2.25-4.05) and joint replacement (HR 2.54, 95% CI 1.81-3.57).

In the temporomandibular joint, Haddad et al. (2000) found histological evidence of cartilage damage in 64% of patients receiving triamcinolone acetonide injections. For rheumatoid arthritis patients, Koh et al. (2020) demonstrated that intra-articular glucocorticoid injection was associated with long-term structural damage, with radiographic progression (ΔHSS/year) significantly higher in the injection group (1.0 vs 0, $p=0.005$).

Animal studies provide mechanistic support for these findings. Nuriakhmetov et al. (2021) demonstrated dose-dependent cartilage damage with betamethasone, showing a 10.05% increase in dystrophy and necrosis area with three weekly injections compared to single injection ($p<0.05$), and an additional 6.39% increase with six weekly injections ($p<0.001$). Kabalyk et al. (2020) showed that betamethasone injections initiated extracellular matrix degradation through activation of MMP-9 expression while blocking pathological angiogenesis via VEGF inhibition.

**Studies Demonstrating No Cartilage Damage or Protection**

| Study | Direction of Effect | Key Finding | Follow-up |
|---|---|---|---|
| **J. Raynauld et al., 2003** | No change | No difference in joint space loss | 2 years |
| **C. Ozturk et al., 2006** | No change | No progression observed | 1 year |

| Study | Direction of Effect | Key Finding | Follow-up |
|---|---|---|---|
| **Nihal Şahin et al., 2023** | No change | 2.96±0.79 to 2.85±0.70 mm (p=0.35) | 6 months |
| **Anthony L. Logli et al., 2024** | No change | No difference in mJSW | 2 years |
| **Suman Patel et al., 2023** | No change | No significant cartilage thickness change | 5 months |
| **J. Pelletier et al., 2020a** | No change | No significant effect on cartilage loss | 3 years |
| **C. Peterfy et al., 2020** | No change | JSN ≤1 unit in 5.0% (TA-ER) vs 4.1% (placebo) | 24-52 weeks |
| **B. J. Heard et al., 2015** | Improvement | Lower histological scores | 9 weeks |
| **Zhiwei Zhang et al., 2016** | Improvement | Better proteoglycan staining, lower OARSI scores | 12 weeks |

Raynauld et al. (2003) found no difference between triamcinolone and saline groups in loss of joint space over 2 years of repeated injections every 3 months. This was the first long-term safety study and suggested that corticosteroid injections may not accelerate structural progression when used judiciously.

Pelletier et al. (2020a) conducted a nested case-control study showing no significant effect of single intra-articular corticosteroid injection on cartilage volume loss post-treatment, although transient effects on meniscal thickness were observed during the treatment period. Importantly, effects were transient and reversible.

In juvenile idiopathic arthritis patients, Şahin et al. (2023) found that knee injections did not significantly change cartilage thickness (2.96±0.79 mm at baseline to 2.85±0.70 mm at 6 months, p=0.35). Similarly, multiple studies using ultrasound assessment found no significant changes in femoral cartilage thickness following corticosteroid injection.

Peterfy et al. (2020) provided prospective radiographic data showing that among 450 patients treated with single or repeated corticosteroid injections, no signs of osteonecrosis or chondrolysis were observed over 6-12 months, with mild progression of joint space narrowing (≤1 unit) occurring in only 5.0% of the extended-release triamcinolone group compared to 4.1% of placebo.

**Studies Showing Protective or Beneficial Effects**

Contrary to expectations, some studies demonstrated protective effects of corticosteroids on cartilage. Heard et al. (2015) showed that a single intra-articular dexamethasone injection immediately post-surgery significantly lowered histological scores for lateral tibial cartilage (effect size: 5.1) compared to untreated controls in a rabbit model of post-traumatic osteoarthritis. Zhang et al. (2016) found that cross-linked hyaluronic acid combined with dexamethasone had superior chondroprotective effects compared to hyaluronic acid alone or saline, with significantly lower histological scores (2.00 ± 0.48 vs 4.50 ± 0.87 vs 5.84 ± 0.29, $p<0.05$).

Lattermann et al. (2016) demonstrated that early administration of Kenalog after ACL injury significantly reduced CTX-II (a marker of cartilage degradation) and mitigated the decline in COMP and MMP-1 compared to controls. This suggests that timing of intervention relative to injury may be critical in determining cartilage outcomes.

## Dose-Response and Temporal Relationships

### Dose-Dependent Effects

The systematic review by Wernecke et al. (2015) identified clear dose-dependent effects of corticosteroids on cartilage. Beneficial effects occurred at low doses (<2-3 mg/dose or 8-12 mg/cumulative total dose in vivo), including increased cell growth and recovery from damage. However, at higher doses (>3 mg/dose or 18-24 mg/cumulative total dose in vivo), corticosteroids were associated with significant gross cartilage damage and chondrocyte toxicity.

| Dose Category | Effects | Reference |
|---|---|---|
| **Low dose (<2-3 mg or 8-12 mg cumulative)** | Beneficial: increased cell growth, recovery from damage | Wernecke et al., 2015 |
| **High dose (>3 mg or 18-24 mg cumulative)** | Detrimental: gross cartilage damage, chondrotoxicity | Wernecke et al., 2015 |
| **1 injection/week** | No changes observed | Nuriakhmetov et al., 2021 |
| **3 injections/week** | 10.05% increase in dystrophy/necrosis | Nuriakhmetov et al., 2021 |
| **6 injections/week** | Additional 6.39% increase in necrosis | Nuriakhmetov et al., 2021 |

Tokawa et al. (2025) confirmed that lower doses appeared safer for articular tissues based on in vitro evidence, though in vivo dose-response data remained limited.

### Temporal Patterns

The timing and duration of cartilage effects demonstrate important patterns:

| Time Frame | Effect Pattern | Studies |
|---|---|---|

| Time Frame | Effect Pattern | Studies |
|---|---|---|
| **Short-term (≤6 weeks)** | Generally beneficial or neutral | Jüni et al., 2015; Najm et al., 2021 |
| **Medium-term (6-24 weeks)** | Mixed results | Pelletier et al., 2020; Nielsen et al., 2018 |
| **Long-term (>24 weeks)** | Higher risk of adverse effects | McAlindon et al., 2017; Ayub et al., 2021 |

The Cochrane review by Jüni et al. (2015) stratified effects by follow-up duration, finding moderate benefits at 1-2 weeks, small to moderate benefits at 4-6 weeks, and no evidence of effect at 26 weeks for both pain and function outcomes. This temporal pattern suggests that repeated injections over extended periods may be necessary for sustained symptom relief but may carry cumulative cartilage risks.

Pelletier et al. (2020) demonstrated that cartilage effects were transient, with significant meniscal thickness and joint space width loss during the treatment period ($p=0.006$ and $p=0.011$, respectively), but no difference post-treatment. This suggests potential reversibility of effects when injections are discontinued.

## Joint-Specific Findings

### Knee Osteoarthritis

The knee joint has been most extensively studied, with evidence suggesting a complex relationship between corticosteroids and cartilage. The McAlindon trial (2017) provided the strongest evidence for cartilage damage with repeated injections every 3 months over 2 years. However, multiple other studies found no significant cartilage changes with single injections or shorter follow-up periods.

Maricar et al. (2017) identified that baseline structural damage predicts treatment response, with higher MRI meniscal damage (OR=0.74; 95% CI 0.55-0.98), increasing KL maximal grade (OR=0.43; 95% CI 0.23-0.82), and joint space narrowing (OR=0.60; 95% CI 0.36-0.99) associated with lower odds of longer-term response. The predicted probability of longer-term response decreased from 38% to 12% as baseline maximal joint space narrowing increased from grade 0 to 3.

**Temporomandibular Joint**

Evidence in the TMJ suggests potential for more pronounced adverse effects. Haddad et al. (2000) found damage to the fibrous layer in 100% of specimens, cartilage damage in 64%, and bone damage in 42% following triamcinolone injections. Stoustrup et al. (2008) demonstrated that corticosteroid injections in growing animals resulted in significantly less mandibular growth compared to untreated controls.

**Hip Joint**

For the hip, Parry et al. (2025) conducted a systematic review identifying risks of rapidly progressive osteoarthritis and femoral head collapse following intra-articular corticosteroid injections in patients both with and without pre-existing osteoarthritis. This suggests the hip may be particularly vulnerable to corticosteroid-induced structural damage.

**Confounders and Effect Modifiers**

Several factors influence the relationship between corticosteroids and cartilage damage:

| Factor | Effect | Evidence |
|---|---|---|
| **Baseline disease severity** | Higher severity associated with worse outcomes | Maricar et al., 2017; Matzkin et al., 2017 |
| **Obesity** | Associated with less improvement | Matzkin et al., 2017 |

| Factor | Effect | Evidence |
|---|---|---|
| **Concurrent systemic steroids** | Increased risk of femoral head necrosis | Neidel et al., 2002 |
| **Joint location** | TMJ and hip may be more vulnerable | Haddad et al., 2000; Parry et al., 2025 |
| **Injection frequency** | More frequent injections increase damage | Nuriakhmetov et al., 2021 |
| **Co-treatments** | Exercise may modify effects | Riis et al., 2017; Nielsen et al., 2018 |

Matzkin et al. (2017) found that patients with Kellgren-Lawrence grade 1 or 2 osteoarthritis showed clinical improvement at all time points, while obese patients with grade 3 or 4 had significantly worse outcomes. Neidel et al. (2002) identified that all cases of femoral head necrosis occurred in children receiving long-term systemic steroids, with no necrosis in those not receiving systemic corticosteroids (p=0.009).

The combination of corticosteroids with exercise therapy appears to modify outcomes. Riis et al. (2017) found no significant differences in MRI measures of synovitis between corticosteroid and placebo groups when both received exercise therapy. This suggests that co-interventions may influence the cartilage response to corticosteroid injection.

## Synthesis

The evidence regarding intra-articular corticosteroid effects on cartilage demonstrates substantial heterogeneity that can be reconciled through careful consideration of treatment protocols, patient characteristics, and methodological factors.

## Reconciling Conflicting Findings

### Protocol Differences Explain Much Heterogeneity

Studies demonstrating cartilage damage predominantly used repeated injection protocols over extended periods. The McAlindon trial administered injections every 3 months for 2 years (8 total injections of 40 mg triamcinolone), while Saif-ur-Rehman observed damage with single high-dose injections (80 mg). In contrast, studies showing no damage typically used single injections or had shorter follow-up periods.

### Dose-Response Relationship

The systematic review by Wernecke et al. (2015) provides a framework for understanding these differences: beneficial effects occur at low doses (<2-3 mg/dose or 8-12 mg cumulative), while detrimental effects emerge at higher doses (>3 mg/dose or 18-24 mg cumulative). This threshold may explain why single 40 mg injections in short-term studies show no damage, while cumulative doses exceeding 320 mg over 2 years in the McAlindon trial caused significant cartilage loss.

### Joint-Specific Vulnerability

The hip and TMJ appear more vulnerable to corticosteroid-induced damage than the knee. This may reflect differences in joint biomechanics, cartilage thickness, or vascular supply. Clinicians should exercise greater caution with hip and TMJ injections.

### Patient Population Effects

Patients with more severe baseline disease show less favorable responses. This creates potential confounding by indication in observational studies, as patients receiving more injections may have more severe underlying disease. The Ayub et al. (2021) review explicitly noted this limitation.

## Conclusions by Clinical Context

Based on the synthesized evidence:

**For single or infrequent knee injections**: The evidence suggests minimal risk of cartilage damage with single injections or injections spaced more than 3 months apart, particularly in patients with mild-to-moderate osteoarthritis.

**For repeated knee injections**: The McAlindon trial provides strong evidence that injections every 3 months for 2 years causes greater cartilage loss than saline. However, this represents a more aggressive protocol than typical clinical practice.

**For hip injections**: Evidence from Parry et al. (2025) suggests increased caution is warranted due to risks of rapidly progressive osteoarthritis and femoral head collapse.

**For TMJ injections**: Histological evidence of cartilage damage warrants careful risk-benefit consideration.

**For post-traumatic or inflammatory conditions**: Early intervention with corticosteroids may actually be protective by reducing inflammation-mediated cartilage damage, suggesting the inflammatory state of the joint influences outcomes.

The overall evidence indicates that the relationship between intra-articular corticosteroids and cartilage damage is not binary but depends on dose, frequency, duration, joint location, baseline disease severity, and timing relative to inflammatory processes. The clinical recommendation of using the lowest effective dose with appropriate intervals between injections remains well-supported by this evidence synthesis.

## DISCUSSION

The comprehensive synthesis of 80 studies reveals a complex and non-binary relationship between intra-articular corticosteroids (IACS) and articular cartilage. The evidence does not support a simplistic conclusion that IACS are universally harmful or safe for cartilage; instead, the structural outcome is determined by a dynamic interplay of pharmacological, clinical, and methodological factors. This discussion will elaborate on the key themes that explain the heterogeneity in the literature and provide a nuanced clinical interpretation.

**Reconciling the Dichotomy: Protocol as a Primary Determinant**

The most striking finding is that the stark contradiction between studies showing cartilage damage (e.g., McAlindon et al., 2017) and those showing no damage (e.g., Raynauld et al., 2003) is largely attributable to differences in treatment protocols. The landmark trial by McAlindon et al. (2017), which provides the strongest evidence for harm, employed an aggressive protocol of 40 mg triamcinolone acetonide injections every 3 months for 2 years (cumulative dose 320 mg). This high-frequency, high-cumulative-dose regimen resulted in significantly greater cartilage volume loss compared to saline. Conversely, studies with neutral findings typically involved single injections (Pelletier et al., 2020), lower doses, or shorter follow-up periods. This pattern strongly suggests that **cartilage damage is a function of cumulative corticosteroid load and exposure time**. The systematic review by Wernecke et al. (2015) provides a mechanistic framework, identifying a therapeutic window: low doses (<2-3 mg/dose) may enhance chondrocyte recovery, while higher doses trigger cytotoxicity and matrix degradation. Therefore, the clinical question shifts from *whether* IACS damage cartilage to *under what specific conditions of dosing and frequency* this risk becomes significant.

**The Critical Role of Dose-Response and Temporal Dynamics**

The dose-response relationship is a central pillar for understanding IACS effects. Animal studies offer clear evidence of this gradient. Nuriakhmetov et al. (2021) demonstrated that while a single betamethasone injection caused minimal change, three weekly injections increased cartilage dystrophy/necrosis by 10.05%, and six weekly injections added a further 6.39% increase. This aligns with the clinical findings of McAlindon et al. (2017). The temporal pattern is equally important. Benefits for pain and inflammation are most pronounced in the short term (1-6 weeks) (Jüni et al., 2015; Hirsch et al., 2017), while signals of structural harm typically emerge with repeated exposures over many months or years (Ayub et al., 2021). Importantly, some studies suggest that certain negative effects, such as reductions in meniscal thickness, may be transient and reversible upon cessation of injections (Pelletier et al., 2020). This indicates that not all observed

changes represent irreversible degeneration, highlighting the need for studies with extended washout periods to distinguish transient suppression from permanent damage.

**Joint-Specific Vulnerability: A Key Clinical Consideration**

Not all joints respond equally to IACS. This review highlights that the **hip and temporomandibular joint (TMJ) may be particularly vulnerable**. For the hip, Parry et al. (2025) identified cases of rapidly progressive OA and even femoral head collapse following IACS injections, suggesting a potentially catastrophic risk profile that warrants extreme caution. In the TMJ, Haddad (2000) found histological evidence of cartilage damage in 64% of injected joints, and Stoustrup et al. (2008) showed inhibited mandibular growth in juvenile animals. In contrast, the knee joint, being larger and weight-bearing with thicker cartilage, appears more resilient, especially to single injections. This joint-specific vulnerability may relate to differences in cartilage thickness, vascular supply, biomechanical forces, and the volume of the joint space relative to injectate concentration. These findings necessitate a tailored approach, where injection strategies for the hip and TMJ are more conservative than for the knee.

**The Influence of Disease State and Patient Characteristics: Effect Modifiers**

The baseline state of the joint and patient phenotype significantly modifies the outcome. Patients with **more severe baseline osteoarthritis** (higher Kellgren-Lawrence grades, significant bone marrow lesions) show diminished clinical response and may be at greater risk for poor structural outcomes (Maricar et al., 2017; Matzkin et al., 2017). This creates a major confounding factor in observational studies: patients who receive more frequent injections often have more severe baseline disease, making it difficult to disentangle the progression of the underlying disease from the effect of the injection. Furthermore, **obesity** is associated with a poorer clinical response (Matzkin et al., 2017), likely due to increased systemic and local inflammation and greater mechanical load. Crucially, the **inflammatory context** matters. In post-traumatic or inflammatory arthritis models, early IACS administration can be *chondroprotective*. Heard et al. (2015) and

Zhang et al. (2016) showed reduced cartilage damage in animal models when dexamethasone was given early after injury, likely by quenching the acute inflammatory cascade that drives secondary cartilage breakdown. Lattermann et al. (2016) found similar benefits in humans after ACL injury. This suggests that IACS may be structurally beneficial when used to control acute, destructive inflammation but potentially harmful when used chronically in a primarily degenerative, low-inflammatory environment like advanced OA.

**Methodological Heterogeneity and Assessment Techniques**

Discrepancies in findings are also amplified by methodological diversity. Studies used a wide array of outcome measures: radiographic joint space width (a crude and indirect measure), MRI-based cartilage volume/thickness (more sensitive), T2 mapping (assessing cartilage matrix quality), ultrasound thickness, and direct histology. Each method has different sensitivity, specificity, and relevance to clinical progression. For instance, the lack of change in radiographic joint space width in some studies (Raynauld et al., 2003) does not preclude more subtle matrix degradation detectable by MRI or histology. Furthermore, follow-up duration varied dramatically, from weeks to years, capturing different phases of the biological response. The inclusion of various study designs—RCTs, cohort studies, case-controls, and animal studies—each with inherent strengths and biases, contributes to the spectrum of reported effects but also allows for a more complete mechanistic understanding when synthesized carefully.

**Clinical Implications and Reconciled Perspective**

The synthesized evidence supports a refined, context-dependent clinical approach:

1. **For mild-to-moderate knee OA:** Single or infrequent IACS injections (e.g., spaced ≥6 months apart) using moderate doses (e.g., 40 mg triamcinolone) appear to have a favorable risk-benefit profile, with minimal evidence of structural harm and good short-term symptom control.

2. **For repeated injections in any joint:** Caution is paramount. The McAlindon trial protocol (q3month injections) should not be considered the standard. The principle of **"the lowest effective dose at the longest effective interval"** is strongly supported. If frequent injections are required, it may indicate the need for alternative or adjunctive therapies.

3. **For hip and TMJ injections:** The potential risks are higher. These procedures should be performed with clear indications, using image guidance for accuracy, and after thorough patient counseling about the potential for accelerated structural damage.

4. **For inflammatory or post-traumatic conditions:** Early IACS use may be structurally beneficial and should be considered as part of a comprehensive management plan to control synovitis.

5. **Patient Selection:** Treatment should be personalized. Patients with advanced structural disease or obesity may experience less benefit and should be managed with adjusted expectations and multimodal strategies, including weight management and exercise (Riis et al., 2017; Henricsdotter et al., 2016).

IACS are powerful tools with a dualistic nature. Their impact on cartilage is not inherently destructive but is contingent upon a delicate equilibrium. By respecting dose limitations, injection frequency, joint-specific cautions, and the inflammatory context of the disease, clinicians can harness the significant benefits of IACS while mitigating the risks of iatrogenic cartilage damage. This review moves the discourse beyond a simple "for or against" stance and toward a sophisticated, evidence-based algorithm for their use.

## CONCLUSION AND RECOMMENDATIONS

### Conclusion

This comprehensive systematic review demonstrates that the relationship between intra-articular corticosteroid (IACS) use and cartilage damage is nuanced and context-dependent. The

body of evidence refutes a blanket statement of safety or universal harm. Key determinants of structural outcome include:

1. **Dose and Frequency:** High cumulative doses and frequent injection schedules (e.g., every 3 months) are associated with measurable cartilage loss, particularly in the knee, as evidenced by high-quality RCTs. Single or infrequent injections carry a significantly lower risk.
2. **Joint Specificity:** The hip and temporomandibular joint exhibit greater vulnerability to corticosteroid-associated adverse structural outcomes, including rapidly progressive osteoarthritis and cartilage necrosis, compared to the knee.
3. **Disease Context:** In acute inflammatory or post-traumatic settings, early IACS administration may exert chondroprotective effects by mitigating inflammation-driven damage. In contrast, in advanced degenerative osteoarthritis, the risk-benefit ratio may be less favorable.
4. **Patient Factors:** Baseline osteoarthritis severity and obesity are important effect modifiers, with more severe disease predicting a poorer clinical and potentially structural response to IACS.

Therefore, IACS remain a valuable intervention for symptomatic relief but must be used judiciously. Their effect on cartilage exists on a spectrum, influenced by a critical balance between their potent anti-inflammatory action and potential catabolic effects on chondrocyte metabolism and extracellular matrix.

## Recommendations

Based on the synthesized evidence, the following recommendations are proposed for clinical practice and future research:

### For Clinical Practice:

1. **Adhere to a Conservative Injection Protocol:** Employ the **lowest effective dose** and **lengthen the interval** between injections to the greatest extent possible (e.g., no more frequently than every 3-4 months, ideally 6 months or longer). Avoid indefinite, regular injection schedules.

2. **Exercise Heightened Caution with Specific Joints:** Be particularly vigilant when injecting the **hip** and **TMJ**. Ensure strict sterile technique, use image guidance for accuracy, and counsel patients specifically about the potential risks of accelerated joint degeneration.

3. **Personalize Treatment Decisions:** Consider baseline structural severity (via imaging), BMI, and the inflammatory component of the disease. Patients with severe radiographic OA or obesity may be less ideal candidates for repeated IACS.

4. **Integrate with Multimodal Management:** IACS should not be used in isolation. Combine injections with core treatments such as **exercise therapy**, **weight management**, and physical therapy. Evidence suggests exercise may modify the synovial environment and improve outcomes (Riis et al., 2017).

5. **Monitor for Long-Term Effects:** When repeated injections are necessary, consider periodic monitoring with clinical evaluation and, if warranted, advanced imaging (e.g., MRI) to assess for progressive structural changes.

**For Future Research:**

1. **Conduct Dose-Finding and Interval Studies:** There is a pressing need for prospective RCTs designed specifically to identify the optimal dose and minimum effective injection interval that maximizes symptom duration while minimizing cartilage risk.

2. **Focus on Vulnerable Joints:** More high-quality, long-term studies are needed on the effects of IACS in the **hip, shoulder, and small joints** of the hand and wrist.

3. **Employ Advanced Imaging Biomarkers:** Future studies should utilize sensitive quantitative MRI techniques (e.g., T2/T1rho mapping, dGEMRIC) to detect early matrix changes before gross cartilage volume loss occurs.

4. **Investigate Combination Therapies:** Research should explore whether co-administration with potentially chondroprotective agents (e.g., hyaluronic acid, platelet-rich plasma) can mitigate the potential negative effects of corticosteroids while preserving their anti-inflammatory benefits (Zhang et al., 2016; Cinar & Bagatir, 2023).

5. **Long-Term Observational Registries:** Establish large-scale patient registries to track long-term real-world outcomes, including the need for total joint arthroplasty, following IACS use across different joints and patient populations.

By adopting a more precise and cautious approach informed by this evidence synthesis, clinicians can continue to utilize IACS as a potent tool for relieving suffering while actively safeguarding the long-term health of the articular cartilage.

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