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Authors' Affiliation:
[1]Central Clinical Hospital of Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland
[2]Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
[3]Medical University of Lodz, Kościuszki 4, 90-419 Lodz, Poland
[4]University Clinical Hospital No.2 of the Medical University of Lodz, Żeromskiego 113, 90-549 Łódź, Poland
[5]Pope John Paul II Independent Public Regional Hospital in Zamość, ul. Aleje Jana Pawła II 10, 22-400 Zamosc, Poland

***Corresponding author:**
Brzyska Agata
Central Clinical Hospital of Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland, E-mail a.brzyska@o2.pl; +48 507050754

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Non-steroidal anti-inflammatory drugs and their role in soft tissue and bone healing after sports injuries: a literature review

Brzyska Agata[1]*, Kucharski Tomasz[2], Steć Greta[1], Pawlak Magdalena[1], Prolejko Sandra[3], Gajęcki Błażej[1], Kopala Justyna[4], Wiśniewski Mikołaj[5], Siemianowski Jan[1], Kotnis Weronika[3]

ABSTRACT

Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used drugs in healing musculoskeletal injuries in sports medicine. However, this approach is controversial because NSAIDs inhibit the inflammatory response, which is necessary for proper tissue healing. The purpose of this article was to present the current state of knowledge on the effects of NSAIDs on soft tissue and bone healing and to assess whether there are grounds for changing clinical management in sports medicine. Methods: A systematic search of MEDLINE (PubMed and Ovid) identified 35 relevant publications, including clinical trials, preclinical studies, systematic reviews, and meta-analyses. We analyzed the studies assessing the impact of NSAIDs on soft tissue and bone healing qualitatively with attention to clinical significance. Results: Animal studies indicate the adverse effects of some NSAIDs on bone healing, especially indomethacin and celecoxib. Deteriorated healing results were observed in soft tissues, especially after rotator cuff reconstruction, following the use of celecoxib. Non-selective NSAIDs, such as ibuprofen, showed a neutral or beneficial effect in most studies. However, clinical data remain limited and inconsistent, with some meta-analyses showing a relationship with patient age while others show no significant differences. Conclusions: Some NSAIDs, especially selective COX-2 inhibitors, may slow down the healing of soft tissue, and indomethacin may also slow down the healing of bones. Because there are no clear, high-quality clinical trials, medical professionals should be careful when giving NSAIDs and only give the lowest dose for the shortest amount of time that works.

Keywords: non-steroidal anti-inflammatory drugs (NSAID); cyclooxygenase (COX); bone healing; soft tissue healing; sports medicine

1. INTRODUCTION

Sports injuries are among the most common and serious health problems affecting athletes. The most common injuries are to muscles, especially hamstring muscles (Giraldo-Vallejo et al., 2023; Tipton, 2013), ligaments, and joints. The analysis of sports success showed that the lower the number of sports injuries, the higher the sports performance (Giraldo-Vallejo et al., 2023; Phillips, 2014). With resulting injuries, NSAIDs are commonly used, often as a first-line treatment to relieve post-traumatic pain. However, the use of this group of drugs is controversial, as the combination creates a potential conflict with the scope of NSAIDs as inflammation inhibitors and the need for controlled inflammation in tissue healing.

The purpose of this article is to present current knowledge on the effects of NSAIDs on soft tissue and bone healing and to determine whether there is enough evidence to change clinical management after sports injuries and to stop prescribing NSAIDs so that they do not adversely affect the healing process of these injuries.

2. REVIEW METHODS

We conducted an extensive literature review using the Medline database (accessed using the PubMed and Ovid platforms). We analyzed only articles published in English, including original research in clinical and preclinical studies, systematic reviews, and meta-analyses. The articles evaluated the effects of NSAIDs on soft tissue and bone healing (Figure 1).

We excluded articles that did not address the healing process, did not address trauma, or did not consider the use of NSAIDs and their effects on the healing process. We analyzed all papers in detail and extracted data on the type of injury (bone or soft tissue), the type of NSAID, and the healing process results.

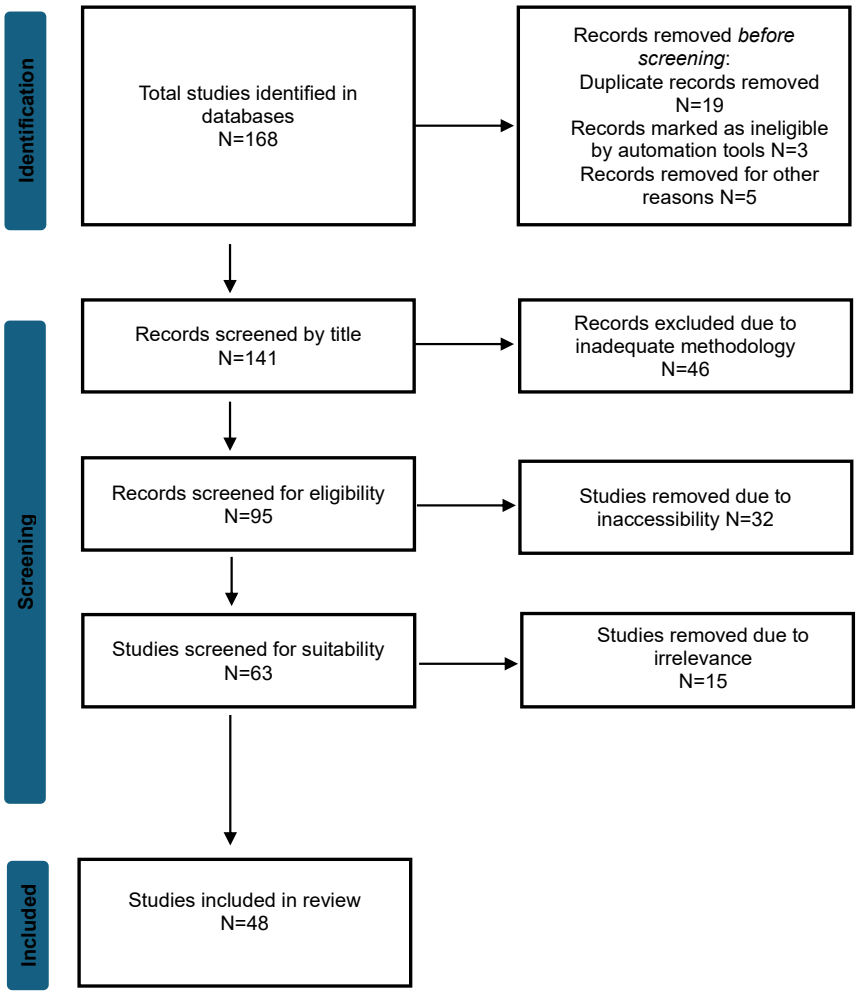

Figure 1. PRISMA flow chart diagram of the study selection process

3. RESULTS & DISCUSSION

NSAIDs are a frequently used group of drugs characterized by analgesic, anti-inflammatory, and antipyretic effects. Their mechanism of action involves the inhibition of cyclooxygenase (COX), which causes the inhibition of prostaglandin synthesis (Abdul-Hadi et al., 2009; Chen & Dragoo, 2013).

The cyclooxygenase enzyme can be divided into two main isoforms: COX-1 and COX-2. COX-1 is a constitutive enzyme that is constantly present in almost all tissues. Its primary role is to maintain homeostasis in the body and regulate important cellular processes, including gastrointestinal mucosal protection, platelet aggregation, vascular hemostasis, and renal blood flow. COX-1 inhibition leads to adverse effects in these organs, such as gastrointestinal disorders, blood clotting disorders, and nephrotoxicity. Growth factors, cytokines, and inflammatory stimuli contribute to the induction of COX-2, which is essential for controlling the inflammatory response. COX-2 inhibition is responsible for the anti-inflammatory effects of NSAIDs.

NSAIDs are divided into non-selective and selective inhibitors (Table 1). Non-selective NSAIDs inhibit both COX-1 and COX-2, leading to an increased risk of adverse effects from COX-1 inhibition. Selective COX-2 inhibitors inhibit COX-2, resulting in anti-inflammatory effects and a lower incidence of side effects because they do not affect COX-1.

Table 1. Non-selective and selective NSAIDs currently in clinical use

Non-selective NSAIDs	Selective COX-2 inhibitors
Ibuprofen	Celecoxib
Naproxen	Etoricoxib
Diclofenac	Parecoxib
Ketoprofen	
Indomethacin	
Piroxicam	
Aspirin	

The mineralization, creation, and resorption processes cause bone tissue to remodel continuously. In contrast to other tissues, bone recovers from fractures by appropriate regeneration instead of scarring. Prostaglandin E2 (PGE2) is a primary mediator of this process. They are essential for maintaining the physiological balance between osteoblast and osteoclast activity (Lisowska et al., 2018; Schug, 2006).

Similar to developing bone growth, bone healing is characterized by a critical inflammatory phase that triggers the repair process. This phase begins immediately after fracture with the formation of a hematoma and the release of inflammatory mediators and cytokines, which stimulate prostaglandin synthesis. PGE2 is the most prevalent isoform of prostaglandins, which are produced mainly by osteoblasts and build up inside the fracture callus. PGE2 increases osteoblast function to enhance mechanical strength, increase bone mass, and accelerate bone formation. In addition, it acts as a potent agonist for osteoclasts, which promotes bone resorption. Other prostaglandins also lead to increased osteoclast activity and quantity.

Cyclooxygenase-2 (COX-2) regulates the production of PGE_2 and other prostaglandins. This inducible enzyme facilitates prostaglandin synthesis and is key in differentiating mesenchymal stem cells into osteoblasts. Given this pathway, non-steroidal anti-inflammatory drugs and selective COX-2 inhibitors directly influence bone repair. By inhibiting COX-2 activity, they suppress prostaglandin synthesis and reduce the differentiation and activation of both osteoblasts and osteoclasts, particularly in the early stages of fracture healing.

Animal studies have shown that local administration of exogenous prostaglandins can stimulate bone formation (Ke et al., 1992; Keller et al., 1993). Moreover, preclinical models demonstrate that complete inhibition of COX-2 activity entirely disrupts the fracture healing process—mice with a homozygous deletion of the COX-2 gene failed to regenerate bone, whereas COX-1-deficient mice exhibited routine healing (Reikeraas & Engebretsen, 1998; Zhang et al., 2002). These findings further suggest a potentially significant role of NSAIDs in modulating bone repair processes.

Among animal studies investigating the effects of NSAIDs on bone healing, findings are often conflicting, even when evaluating the same active compound. NSAIDs have been shown to have a detrimental effect on fracture repair in some studies (Krischak et al., 2007; Leonelli et al., 2006; O'Connor et al., 2009), but little or no impact in others (Akritopoulos et al., 2009; Utvag et al., 2010).

In several animal model studies, indomethacin's adverse effects have been repeatedly verified, making it the NSAID most strongly linked to decreased bone repair (Brown et al., 2004; Dimmen et al., 2009; Karachalios et al., 2007). Preclinical studies have also noted the adverse effects of selective COX-2 inhibitors on fracture healing in rats (Li et al., 2013; Simon & O'Connor, 2007) through inhibition of ossification and impaired callus strength. Clinical studies have not confirmed these data. Meta-analyses of clinical cases also show discrepancies. According to one meta-analysis of human research, there was no discernible effect of NSAID use on fracture healing (Chuang et al., 2024). On the other hand, NSAIDs may have an age-dependent influence on delayed union or bone healing, according to another meta-analysis (Wheatley et al., 2018).

In this study, the researchers did not present any significant evidence of an adverse effect of NSAIDs on bone healing in children; an adverse effect was only observed in the adult population. What is worth mentioning is the fact that the researchers did not divide the adult population into age groups, which not only reduced the reliability of the data but also limited the scope of its use. Soft tissue heals through an inflammatory and non-inflammatory pathway (Chen & Dragoo, 2013). The first one, also known as "classical", activates after the initiation of the inflammatory cascade. Partially, through prostaglandins' chemotactic action (Ricciotti & FitzGerald, 2011)

The first immune cells that arrive at the location of injury are neutrophils. They increase the inflammatory response by secreting pro-inflammatory cytokines and phagocytosing pathogens and cellular debris. Following them, macrophages take over as the predominant cell type. Macrophages generate growth factors that promote tissue regeneration and eliminate apoptotic cells and tissue remains (Eming et al., 2007; Nikoloudaki et al., 2020).

In order to aid in tissue regeneration and progressively strengthen the wounded area, active fibroblasts start to produce extracellular matrix components, mainly collagen, as the healing process proceeds (Gurtner et al., 2008). Fibroblasts are the first to deposit type III collagen, which serves as a temporary scaffold for the wound healing process. It is then replaced by type I collagen, which gives the tissue a better structure and mechanical integrity (Ferrando et al., 1996; Rodrigues et al., 2019).

Growth factors directly start regeneration in the non-inflammatory soft tissue repair pathway, negating the necessity for a full-blown inflammatory reaction. A key initiator of this route is the rapid release of platelet-derived growth factor (PDGF) by platelets following tissue damage. This process is critical for minor injuries, such as exercise-induced muscle microtrauma, where inflammation is minimal or transient (Barton-Davis et al., 1999; Philippou et al., 2007). PDGF exhibits chemotactic and mitogenic effects on a wide range of cell types, including neutrophils, monocytes, smooth muscle cells, and fibroblasts. Significantly, it can stimulate fibroblasts without the need for inflammatory cytokines (Deuel et al., 1982; Takamura et al., 2021). After activation, fibroblasts begin producing extracellular matrix proteins, primarily collagen, that support tissue repair and structural reinforcement.

Other growth factors, such as fibroblast growth factor (FGF) and insulin-like growth factor 1 (IGF-1), are particularly important in muscle micro-injuries. They activate satellite cells, that is, muscle stem cells, and promote tissue repair without triggering an inflammatory process. These growth factors alter or circumvent the traditional immune response while promoting protein synthesis, cell division, and matrix remodeling (Philippou et al., 2007; Yoshida & Delafontaine, 2020).

The non-inflammatory tissue healing pathway can only dominate under certain physiological conditions, especially if the damage is minor. It enables regeneration via local growth factor signaling rather than extensive leukocyte infiltration (Philippou et al., 2007). Soft tissue recovery involves several pathways; therefore, using NSAIDs to reduce inflammation might not always impair healing. NSAID activity does not affect the growth factor–mediated pathway initiated by PDGF, which may continue to support tissue regeneration independently (Chen & Dragoo, 2013).

Studies on the effects of NSAIDs on soft tissue healing are more limited than the effects on bone healing. Few clinical studies exist, with most data coming from animal and in vitro studies. Investigations have focused mainly on celecoxib, ibuprofen, and indomethacin (Chen & Dragoo, 2013; Ghosh et al., 2020; Li et al., 2013), with conflicting results reported (Constantinescu et al., 2019; Gurtner et al., 2008). Available animal studies show highly contradictory results.

In available studies evaluating the effects of this group of drugs on rotator cuff repair in rabbits (Li et al., 2013; Lu et al., 2015), non-selective NSAIDs, including ibuprofen, did not adversely affect healing, and flurbiprofen showed only minimal effects at an early stage. In contrast, selective COX-2 inhibitors, especially celecoxib, resulted in lower mechanical strength of the adhesion. A literature review by Ghosh et al. (2020) reported poorer soft tissue healing outcomes with coxib use, but no adverse effects in animals treated with either coxibs or non-selective NSAIDs.

The number of studies of selective NSAIDs is limited; the data allowed for evaluation only of celecoxib and parecoxib. Of these, most studies indicated an adverse effect of both drugs (5/7 and 4/5 studies, respectively). Among non-selective NSAIDs, studies most

often examined indomethacin and ibuprofen, obtaining a preponderance of results with positive or neutral effects (7/10 and 4/6, respectively). The study used various animal models and different surgical procedures, including the repair of the Achilles tendon, soleus tendon, rotator cuff, palmar flexor tendons, patella tendon, anterior cruciate ligament, and medial collateral ligament (MCL).

The researchers assessed biomechanical parameters by measuring tensile strength, stiffness, and fracture toughness; biochemical parameters by measuring collagen synthesis rate; and biological parameters by measuring the total number of tenocytes. A review study on the effect of NSAIDs on soft tissue healing, mainly after medial collateral ligament transection, supports these observations (Solaiman et al., 2024). The often-observed adverse effect of selective COX-2 inhibitors on soft-tissue healing and tendon-bone healing, with no adverse effect when using non-selective NSAIDs.

A systematic review of animal studies on tendon-bone junction healing was limited by the heterogeneity of reported results (Karachalios et al., 2007). However, subgroup analysis of homogeneous studies found no significant effect of NSAIDs (Li et al., 2013). Despite the limited results, based on a small number of studies, it can be suspected that both indomethacin and celecoxib at high doses may adversely affect tendon-bone healing (Chen & Dragoo, 2013). A randomized human clinical trial (Oh et al., 2018) evaluating the effect of analgesics after rotator cuff repair found a higher rate of tendon re-tears in the celecoxib group compared to those using ibuprofen and tramadol (Li et al., 2013; Oh et al., 2018). At the same time, there were no statistically significant differences in pain intensity or functional outcomes between groups.

Similar observations were presented in a systematic review of the literature (Constantinescu et al., 2019), which also showed that patients who received celecoxib instead of ibuprofen during rotator cuff reconstruction had a statistically significant increased risk of rotator cuff re-tear. The same study found that, independent of NSAID use, patients who underwent meniscal repair, ACL reconstruction, and Bankart repair did not require reoperation in a statistically significant way (Ferrando et al., 1996).

A systematic review (Solaiman et al., 2024) assessed the effect of NSAIDs in patients undergoing isolated ACL reconstruction, isolated meniscus suturing, or combined procedures. We evaluated studies using a selective COX-2 inhibitor and a non-selective NSAID, and comparisons between these groups. In contrast to placebo/no NSAID, none of the trials demonstrated a statistically significant difference in NSAID use-related surgical failures (preoperative, intraoperative, or postoperative). Following ACL surgery, knee stability and subjective results were unaffected by NSAIDs or opioids (Schug, 2006).

Animal research provides the majority of the information currently available on how NSAIDs affect bone repair. In preclinical studies, prostaglandin administration stimulated bone formation (Ke et al., 1992; Keller et al., 1993), while complete COX-2 inactivation impaired animal fracture healing. Indomethacin, in particular, has shown especially adverse effects. Many studies have confirmed its adverse impact on bone regeneration. Researchers have also reported negative effects of selective COX-2 inhibitors on ossification.

Results in clinical trials remain inconsistent. Some clinical meta-analyses have shown no significant effect of NSAIDs on bone healing. In contrast, others have shown an adverse or age-dependent effect, with a greater impact in adults compared to the pediatric population.

The effect of NSAIDs on soft tissue healing, due to the existence of an alternative repair pathway, should be less controversial. NSAIDS can interfere with the classic pathway of soft tissue healing, while leaving the alternative pathway. Unfortunately, studies on soft tissue are not only limited, but also mainly preclinical. Preclinical studies compared non-selective and selective NSAIDS. The results revealed impaired healing with selective NSAIDS (coxibs) as well as neutral to little effect with non-selective NSAIDs. Li et al. and Solaiman et al. have concluded from studies on the healing of the rotator cuff and the medial collateral ligament.

Literature presents a higher risk of rotator cuff re-tears for patients being treated with selective COX-2 inhibitors than in groups with ibuprofen and tramadol treatment. Researchers did not register any difference in pain control (Constantinescu et al., 2019; Li et al., 2013; Oh et al., 2018). On the other hand, the above-mentioned correlation did not occur after meniscus suture, ACL reconstruction, or Bankart surgery (Ferrando et al.,1996; Schug, 2006; Solaiman et al., 2024). For this reason, there is a possibility that the negative impact of COX-2 inhibitors may differ in distinct types of tissue, and/or may partially depend on the type of surgery.

This literature review reveals that among researchers, there is an ambivalent opinion on the effects of non-selective NSAIDs. Some articles postulate their negative impact on tissue healing. On the contrary, most studies show that the effect is neutral. Conclusions appear to be contradictory, but the results probably result from the differences in the studied dose of the drug, other risk factors, or limitations of the study's methodology.

4. CONCLUSION

In conclusion, studies have shown that NSAIDs negatively affect healing after both soft tissue and bone injuries. While indomethacin adversely affects bone regeneration, specific COX-2 inhibitors may hinder soft tissue recovery. However, there is a lack of conclusive and high-quality clinical data to make clear recommendations on the use or avoidance of NSAIDs in clinical practice. Further research is needed, primarily randomized clinical trials in humans.

With the current state of knowledge, extreme caution should be exercised in the use of these drugs, limiting their use to the lowest effective dose and the shortest possible time. These findings may be particularly relevant to sports medicine physicians, physiotherapists, and coaches responsible for therapy decisions immediately following injury.

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Author's Contribution

Conceptualization: Greta Steć, Sandra Prolejko, Magdalena Pawlak
Methodology: Magdalena Pawlak, Błażej Gajęcki, Justyna Kopala
Formal analysis: Agata Brzyska, Tomasz Kucharski, Greta Steć
Resources: Jan Siemianowski, Weronika Kotnis, Justyna Kopala
Investigation: Agata Brzyska, Tomasz Kucharski, Mikołaj Wiśniewski
Writing rough preparation: Mikołaj Wiśniewski, Tomasz Kucharski, Błażej Gajęcki
Writing review and editing: Sandra Prolejko, Jan Siemianowski, Weronika Kotnis
Supervision: Brzyska Agata
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Not applicable.

Ethical approval

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this work are present in the paper.

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