REVIEW

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Is there any role for the selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in the postoperative flexor tendon adhesion formation? A literature review

Dimitrios Skouteris MD, PhD[1], Aristides B. Zoubos MD, DSc[2]

[1]*5th Orthopaedic Department, "Asklepeion Voulas" General Hospital, Athens, Greece*

[2]*Orthopaedic Research and Education Center (OREC) "Panayotis N. Soucacos", 1st Department of Orthopaedic Surgery, National and Kapodistrian University of Athens, "Attikon" University Hospital, Haidari, Athens, Greece*

ABSTRACT

Tendon injuries are considered the second most frequent lesions of the hand (29%), whereas fractures are first (42%). Despite the progress in the surgical techniques and postoperative rehabilitation protocols for preventing adhesions, still several pharmacological agents are being studied in order to inhibit the excessive inflammatory response and the production of growth factors that follow tendon injuries and repair.

A large number of studies has targeted the inflammatory cascade, and in particular COX enzyme isoforms in an effort to inhibit adhesion formation and promote tendon healing and although results have been promising regarding adhesion formation, non-steroidal anti-inflammatory drugs (NSAIDs) have repeatedly shown concomitant losses in the strength of repair, a concerning outcome for tissues that experience high loads such as the flexor tendons.

In conclusion, selective and non-selective NSAIDs seem to have a significant effect in limiting adhesion formation. Nonetheless, the questions that arise about their role on tendon healing, and their potential detrimental effect, are primarily to be addressed by larger animal studies that will provide a better viewpoint for statistical implementation and will check the safety of these drugs for side effects and the danger of tendon re-rupture.

KEY WORDS: Flexor tendons, adhesion, NSAID, COX-2

CORRESPONDING AUTHOR, GUARANTOR

Dimitrios Skouteris MD, PhD
Avras 4 Str, 16673, Voula, Athens
Tel. 6945181400
E-mail: dskouterismd@gmail.com

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Introduction

Tendon injuries are considered the second most frequent lesions of the hand (29%), whereas fractures are first (42%) [1]. According to the study by de Jong et al. the incidence of traumatic injuries of tendons reached 33.2 patients per 100,000 people with an average age at injury of 35.9 years [2,3]. More specifically, regarding flexor tendons in the hand, the most frequently involved anatomical location was the flexor zone II (19.1%) [2]. Up to 30-40% of these injuries result in postsurgical adhesion formation between the tendon and the surrounding tissues leading to poor functional results [4] and a significant burden for both the individual and society because they usually involve young blue and white collar workforce [5].

Despite the progress in the surgical techniques and postoperative rehabilitation protocols for preventing adhesions, still several pharmacological agents are being studied in order to inhibit the excessive inflammatory response and the production of growth factors that follow tendon injuries, including corticosteroids, NSAIDs, antimetabolites, hyaluronic acid, antibodies for TGF-b1, nanoparticles and novel gene therapy models [5-17]

In particular, the NSAIDs, as a specific and distinct group of drugs prescribed on a daily basis for a large number of orthopaedic pathologies, have been studied extensively since the early 1980s in vitro and in vivo experimental studies with inconclusive results on flexor tendon adhesion formation after repair.

General considerations on NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide. They are mainly prescribed for chronic orthopaedic conditions such as osteoarthritis or other soft tissue injuries.

NSAIDs competitively inhibit cyclooxygenase (COX), an enzyme essential for the metabolism of arachidonic acid to prostaglandins [8]. COX, as an enzyme, metabolizes arachidonic acid by acting sequentially as a dioxygenase and peroxidase leading to the formation of prostaglandin G (PGG2) initially and prostaglandin H (PGH2) thereafter [18].

Historically, NSAIDs came from the discovery of some plants and their extracts that were occasionally used to relieve pain or as antipyretics. In the mid 19th century salicylates were discovered as new active ingredients, which allowed the synthesis of salicylic acid, known as aspirin (Aspirin). Subsequently, progress during the 19th and 20th century led to the development of the first NSAIDs, most of which were organic acids, and compounds of completely different composition [19]. After World War II, there was a period until 1970, when the role of prostaglandins had not yet been fully understood. During this period the development of new NSAIDs was mainly based on the empirical study of the analgesic, antipyretic and anti-inflammatory properties of these molecules in laboratory animal models. In the early 1980s, studies started focusing on the ability of drugs to inhibit prostaglandin synthesis and production, while after the discovery of the Cycloxygenase (COX) isoforms in the 1990s, studies focused on a purely molecular level [20].

The development of the first compound of this large class of NSAIDs was phenylbutazone in 1946 by JR Geigy in Basel, Switzerland, while indomethacin was discovered by Merck & Co, USA, in the 1960s. At the same time, ibuprofen was discovered by Boots in the UK and because of its safe side effects profile, it became the first non-prescribed NSAID after aspirin. The discovery of ibuprofen was followed by the development of a large number of medicinal products with different biological and chemical properties [21].

Since the late 1980s, the isoform of the COX-2 enzyme has been recognized, launching the search for new safer NSAIDs [22]. This way, COX-2 selective NSAIDs could inhibit the isoform involved in the inflammatory response without inhibiting COX-1 enzyme, which is essential for the production of the "protective" or "house-keeping" prostaglandins in various organs. The main goal was to produce pharmacological compounds that would maintain their analgesic and anti-inflammatory action while reducing at the same time the side effects of the older non-selective NSAIDs. Today NSAIDs can be categorized by their selectivity in

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inhibiting the two isoforms of COX enzyme. By determining the drug concentration needed to inhibit COX-1 and COX-2 by 50% (IC50) and calculating the COX-1/COX-2 IC50 ratio, selectivity of each drug can be compared. (table) [23, 24]

The first COX-2 selective inhibitors were approved by the United States FDA in 1999 for clinical use and released in more than 80 countries worldwide. In the mid 2000s, second generation COX-2 inhibitors such as valdecoxib, parecoxib and etoricoxib were approved for clinical use, presenting fewer side effects regarding the cardiovascular system [23].

NSAIDs in Orthopaedic Surgery and Trauma

NSAIDs are largely prescribed for the symptomatic treatment of musculoskeletal injuries and postoperative pain, and despite their indisputable contribution to the management of symptoms of bone and ligament injuries, clinical experience has raised questions and concerns regarding the adverse effects of these drugs particularly on fracture healing and the restoration of bone biomechanical properties [24].

NSAIDs side effects on fracture healing have been extensively studied over the last four decades [25, 26]. These studies have shown that all selective and non-selective NSAIDs can influence and impair the process of fracture healing, reducing the mechanical stability of the fracture callus as well [27].

A number of studies have shown that traditional non selective NSAIDs such as aspirin, indomethacin and ibuprofen inhibit fracture healing in various animal experimental models [25,33, 35, 29, 30, 28, 26, 31, 32, 27, 34].

With the advent of selective COX-2 NSAIDs, with their aforementioned advantages over traditional NSAIDs, research focused on the effect of COX-2 inhibitors on fracture healing. The first studies comparing non selective and selective NSAIDs argued that COX-2 inhibitors did not have the same deleterious effect on fracture healing as traditional NSAIDs such as indomethacin [36, 37, 38, 39].

Most of the animal studies to date show the inhibitory effect of these drugs on fracture healing [40, 41, 42]. According to Singh et al. administration of etoricoxib on rabbits has led to a smaller callus formation with various histological differences [43]. In addition, studies on femoral fractures in rats have shown that celecoxib and rofecoxib have the same inhibitory effect as the rest of the COX-2 inhibitors [44]. Several other studies have led to the same conclusions regarding the inhibitory effect of NSAIDs on fracture healing. On the other hand, a much smaller number of studies have led to different results. Karachalios et al., Gerstenfeld et al and Brown et al. have shown that selective NSAIDs did not affect fracture healing in terms of radiological imaging and biomechanical stability [38, 37, 28, 43].

Studies on humans are fewer in number and more controversial. They mainly investigate long bone fracture healing and spinal fusions [46, 47, 48, 49, 50].

All these results have raised concerns about the clinical consequences of NSAIDs on fracture callus formation and healing and although the conclusions are mainly based on experimental models with specific limitations, the current data document the following points [39]:

- Most NSAIDs studied have the potential to inhibit bone formation
- NSAIDs tend to have their greatest effect during the early phase of bone healing.
- NSAIDs have a dose-dependent effect on bone healing
- NSADs have duration-dependent and reversible effects on bone healing
- NSAID use before bone injury or fracture does not affect bone healing

NSAIDs on flexor tendon adhesion formation. What's the supporting evidence?

The proper function of the hand after tendon injury requires on one part the immediate tendon surgical repair [51 52, 53, 54] and, on the other part, to maintain the ability to slide freely within their sheath [55]. The inflammatory response and scarring, following injury and suture of the flexor tendons, promote healing, but at the same time prevent them from sliding into their sheath [56, 57].

Tendon healing occurs in three overlapping phas-

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es. In the initial, inflammatory phase, erythrocytes and inflammatory cells, particularly neutrophils, enter the site of injury. In the first twenty-four hours, monocytes and macrophages predominate and phagocytosis of necrotic materials occurs. Vasoactive and chemotactic factors are released with increased vascular permeability, initiation of angiogenesis, stimulation of tenocyte proliferation, and recruitment of more inflammatory cells [58]. Tenocytes gradually migrate to the wound, and type-III collagen synthesis is initiated [59]

After a few days, the proliferative phase begins. Synthesis of type-III collagen peaks during this stage and lasts for a few weeks. Water content and glycosaminoglycan concentrations remain high during this stage [59, 60].

The remodeling phase begins after approximately four to six weeks characterized by decreased cellularity and collagen formation and glycosaminoglycan synthesis. Repair tissue changes from cellular to fibrous. Tenocyte metabolism remains high and tenocytes and collagen fibers (higher proportion of type I collagen) become aligned in the direction of stress [61].

Tendon healing can occur intrinsically, by proliferation of epitenon and endotenon tenocytes, or extrinsically by invasion of cells from the surrounding tissues, particularly sheath and synovium according to the studies by Gelberman et al [62]. As already shown, intrinsic healing results in better biomechanics and fewer complications. In particular, a normal gliding mechanism within the tendon sheath is preserved. In extrinsic healing, scar tissue results in adhesion formation, which disrupts tendon gliding [60]. Therefore, while the formation of scar tissue provides the necessary physical continuity between the sutured ends of the tendon, it restricts, at the same time, the range of motion of the fingers [63]. The problem is particularly evident when the injury involves the anatomical flexor tendon zone II, which not by chance, was considered by surgeons as "no man's land" because of the poor postoperative results.

As aforementioned, despite the progress in the surgical techniques and postoperative rehabilitation protocols for preventing adhesions, still several pharmacological agents are being studied in order to inhibit the excessive inflammatory response and the production of growth factors that follow tendon injuries.

In particular, the NSAIDs, as a specific and distinct group of drugs prescribed on a daily basis for a large number of orthopaedic pathologies, have been studied in vitro, in vivo on animal tendon models and occasionally in human clinical trials (Table 1). According to the main hypothesis of these studies, the net effect of treatment with NSAIDs is to decrease the metabolites and by-products of arachidonic acid metabolism and, consequently, their effect on local tissues. By reducing these pro-inflammatory agents, endogenous local damage may be decreased after trauma. The consequence could be a decrease in peritendinous adhesions [64].

Most of these studies, apart from the anti-adhesion effect of the NSAIDs, also take under consideration the decrease of the breaking strength or load to failure of the tendons under investigation, as a possible adverse side effect of these drugs.

Since the early 1980s, experimental studies on animal models demonstrated the anti-adhesion effect of indomethacin and ibuprofen. Kulick et al. demonstrated the anti-adhesion effect of ibuprofen after oral administration in 21 primates with concomitant reduction of the breaking strength of the repaired tendons after 4 and 6 weeks [9]. Szabo et al. investigated on the indomethacin effect on adhesion formation after zone II flexor tendon repair in rabbits. They concluded that the animals treated with indomethacin had a greater tendon excursion and angular rotation of the joint than the control animals, implying a suppression of peritendinous adhesions. Results were controversial regarding the tensile strength of the repaired tendons, concluding that the action of indomethacin in suppressing adhesions is not a general suppression of collagen synthesis [65].

On the other hand, Vogel et al. found that systemic indomethacin increased tensile strength and collagen cross-linking in rat tail tendons [66], while Carlstedt et al. demonstrated that indomethacin accelerates recovery of tensile strength after repair of transected rabbit plantaris longus tendons through

increased cross-linking of collagen [66, 67].

During the same period of time in vitro studies with non-selective NSAIDs on human tendon fibroblasts showed that NSAID medication may have potentially negative effects during the proliferative phase since it is associated with decreased DNA synthesis, but beneficial effect in the maturation and remodeling phase since it stimulates protein synthesis [68].

Furthermore, in another in vitro study, Tsai et al. showed that non-selective NSAIDs can inhibit cell migration, such as neutrophils during the early inflammatory phase of tendon healing. The authors postulated that ibuprofen inhibited tendon cell migration associated with downregulation of paxillin expression, not related to the expression of focal adhesion kinase [69].

In the first study of its kind to be performed in humans, Rouhani et al. investigated on the effect of ibuprofen in a double-blind clinical trial on 35 patients after complete flexor tendon laceration and tenorraphy in zone II. The intervention group received a high dosage of ibuprofen (2400mg/day) and according to their findings, the administration of high-dose ibuprofen with anti-inflammatory effects had a statistically significant effect on range of motion improvement after operation and flexor tendon repair. No adverse reactions to the medication and no re-ruptures were observed [70].

All these results on the traditional non-selective NSAIDs have been insufficient to warrant recommendation of NSAIDs for the adhesion formation inhibition on flexor tendons after repair.

With the advent of the selective COX-2 NSAIDs during the late 1990s and early 2000s there have been several comparative in vivo animal studies between non-selective and COX-2 selective NSAIDs with inconsistent results. According to Dimmen et al. parexocib, when administered short-term, caused a significant reduction in functional stiffness and thus better biomechanical behavior compared to indomethacin and placebo groups, but tensile strength was also reduced marking the negative effects of both NSAIDs in the tendon healing process. Thus, the authors suggested that short-term COX inhibition can delay tendon healing but administered in the later phase of healing might be beneficial [71].

Forslund et al. in their in vivo study in rats showed that both indomethacin and celecoxib treated groups presented reduced cross-sectional areas compared to the control group, without affecting the failure loads. In fact, tensile strength seemed to increase for both treated groups in different time-points. This data would suggest that COX inhibitors could be beneficial in clinical situations where swelling of the healing tendon would represent a problem, like in zone II flexor tendons after repair [72].

In another comparative in vivo study between selective and non-selective NSAIDs, Tan et al. comparing the anti-adhesion effects of rofecoxib and ibuprofen on a rabbit model found no differences between them at 6 weeks, based on histology, but significantly better results were found for ibuprofen treated rabbits at 12 weeks, based on ROM results. No load to failure was measured by the authors [73].

Furthermore, Virchenko et al. showed that parecoxib impairs early tendon repair but improves later remodeling of the tendon. In particular administration of parecoxib in the first five days did not affect the size of the early callus, but the force at failure was decreased, indicating normal proliferation and a disturbance of differentiation and matrix production, similar to bone repair. On the other hand, avoiding administration of the COX-2 inhibitor for the first five days resulted in decreased cross-sectional area and higher maximum strength, maybe because parecoxib inhibited the negative effects of inflammation during the remodeling phase of tendon [74].

One of the latest studies on COX-2 inhibitors and tendon healing was conducted by Blomgran et al. in 44 rats after Achilles tendon transection. Cross-sectional area, peak force and stiffness were reduced by parecoxib. Looking at all cell subpopulations at two time points separately, no significant effect of parecoxib could be seen, and the pattern of cell composition appeared quite similar between the parecoxib and control groups at each time point, but different between day 3 and day 10 [75].

These in vivo studies on animals are in accordance with the concept that NSAID treatment has an inhibitory effect on migration and proliferation of tenocytes during the tendon healing process. Tsai et al. investigated the effects of a COX-2 inhibitor like celecoxib, on cell migration, proliferation and collagen expression in isolated tendon cells in vitro. It turned out that celecoxib inhibited tendon cell migration, and furthermore, this effect was dose-dependent. On the other hand, celecoxib did not interfere with the expression of type I and III collagen. The results of this study suggest that decreased tendon cell migration and proliferation might compromise and impair the early inflammatory phase of tendon healing after repair [76].

Celecoxib, in particular, as a COX-2 inhibitor can reduce inflammation as well as neovascularization and thus provide inhibition of intra-abdominal adhesions. [77]. In that direction, Li et al. conducted an in vitro and in vivo study on a chicken experimental model. They tested the release of celecoxib from a bi-layer biomimetic tendon sheath in order to prevent flexor tendon adhesion. The data confirmed that the celecoxib-loaded outer PELA layer can prevent adhesion and associated inflammation. Thus, a celecoxib-loaded anti-adhesive tendon sheath can continuously act as a bi-layer biomimetic tendon sheath releasing celecoxib from the outer layer to prevent tendon adhesion [78].

During the last decade, some new gene therapy models have been used. More specifically, Zhou et al. developed a local sustained gene delivery system to regulate the expression of COX enzymes as an effective therapeutic strategy for tendon adhesions and tested it on chickens. The engineered miRNA plasmid/nanoparticles embedded in hyaluronic acid hydrogel were synthesized to downregulate the expression of cyclooxygenases in the tendon tissue during the early stage of tendon healing with inflammatory response. After six weeks, the treated group presented smaller scores in the adhesion grading and increase of the tensile strength of the repaired tendons [79].

Finally, instead of focusing exclusively on the inhibition of the COX enzyme that catalyzes the conversion of Arachidonic acid to Prostaglandins, there has been an effort to directly inhibit the deleterious effects of the inflammatory response on tendons and specifically the Prostaglandin E2 (PGE2) effects via the deletion and/or the antagonism of the prostanoid receptors (EP1-4). Prostaglandin E2 has been implicated as an inflammatory mediator in tendon injuries and tendinopathy and through one of the downstream receptors EP1 - EP4, all of which belong to the superfamily of G-protein coupled receptors [80]. Various authors have suggested a potential therapeutic role for selective EP4 receptor antagonists with controversial results [81].

Studies conducted by Geary et al. on a murine model showed that flexor tendon repairs treated with a systemic EP4 antagonist exhibited impaired early ROM and increased gliding resistance while the biomechanical properties of the repair were no different between antagonist treated mice and control group [80].

On the other hand, Ackerman et al. suggested that deletion of EP4 receptor in mice reduces scar tissue formation and adhesions during the early stages of tendon healing (14 days post-surgery) while tendon gliding is impaired during the later stages of healing (28 days post-surgery) due to an up-regulation of EP4 by an alternative cell population, possibly myofibroblasts, reactivating inflammation and promoting scar mediated tendon healing [82].

Discussion

A large number of studies have targeted the inflammatory cascade in an effort to improve flexor tendon healing after repair over the last forty years. Common among these studies has been the use of selective and non-selective NSAIDs while more recently, new studies have focused on COX isoforms, Prostaglandins and Prostanoid receptors (EP1-4).

All data up to date suggests that while inflammation is required for repair, including recruitment of new cells that synthetize granulation tissue and collagen, an excessive inflammatory response contributes to adhesion formation between the tendon and surrounding structures [80]. Main hypothesis of most of these studies, is that attenuation of the

inflammatory response through the use of NSAIDs and COX inhibition, can decrease adhesion formation after tendon repair, but compromising the strength of the repair at the same time.

In vivo experimental studies

In vivo studies on animal experimental models try to elucidate these two main issues by measuring a) adhesion formation on one hand and b) tensile strength of the repair on the other.

In regard to adhesion formation most of these experimental models focus mainly on the biomechanical testing and the histological analysis of the specimens' tendons with the help of various grading systems. In addition, a smaller number of studies use the macroscopic evaluation of adhesion formation. Tensile strength of the repair, on the other hand, is usually evaluated by measuring the load to failure under traction in various post-operative time points.

In vitro experimental studies

In vitro experimental studies mainly focus on DNA and protein synthesis (collagen types I and III in particular). More specifically, these studies investigate on tenocyte, macrophage, and neutrophil proliferation and migration during the different phases of tendon healing.

In accordance with the data from most of the studies aforementioned:

- Selective and non-selective NSAIDs seem to have a significant effect in limiting adhesion formation after tendon repair.

Early experimental studies on traditional non-selective NSAIDs showed the anti-adhesion effect of indomethacin and ibuprofen [9, 65], while some showed no differences between indomethacin and control groups [67]. Later studies on COX-2 selective NSAIDs like parecoxib, celecoxib and rofecoxib suggested the effect of these drugs in limiting tendon adhesion formation under certain conditions and different post-operative time points [32, 74, 72, 73]. Finally, the study of NSAIDs on human flexor tendons showed that ibuprofen was effective in improving the range of motion of the involved fingers after injury and repair [70].

In vitro investigations on cell populations such as tenocytes, macrophages, fibroblasts and myofibroblasts etc, could not directly provide answers on adhesion formation, but most likely on the biomechanics and the possible side effects of NSAIDs on tendon healing. Finally, studies on deletion of EP4 prostanoid receptor resulted in contradictory time-dependent results regarding the biomechanical behavior of tendons [82], while flexor tendon repairs treated with a systemic EP4 antagonist exhibited impaired early ROM and increased gliding resistance while the biomechanical properties of the repair were no different between antagonist treated mice and control group [80].

- Selective and non-selective NSAIDs impair tendon healing after repair.

One of the major concerns regarding the use of NSAIDs after tendon injuries is the possible negative effect on the tensile strength of the repair. The proven inhibitory effect of these drugs on fracture healing has led to serious debates about the safety of NSAIDs after flexor tendon repairs. Most of the in vivo experimental studies aforementioned take under consideration the breaking strength of the tendons by measuring the load to failure under traction in various post-operative time points. Although results have been controversial until now, the majority of studies suggest that selective and non-selective NSAIDs can impair tendon healing. Traditional NSAIDs such as ibuprofen and COX-2 inhibitors, such as parecoxib and rofecoxib can have negative or even detrimental effects on the tensile strength of the tendon [9, 32, 73, 74]. In contrast, some studies showed that COX-inhibitors do not affect tendon healing adversely, or that can even have a beneficial effect, suggesting that NSAIDs would not have the same drawbacks for tendon repair as they might have for bone healing [67, 72]. Furthermore, NSAID treatment with ibuprofen after flexor tendon injury and repair in humans did not increase the re-rupture rate suggesting that COX-inhibitors do not affect the tendon's biomechanics and tensile strength [70].

In culture, NSAID treatment was shown to decrease DNA synthesis and, increase, at the same time, protein synthesis in human tendon fibro-

blasts which suggests a negative effect on tendon cell proliferation in the early phase of tendon healing but a positive effect on collagen deposition [68]. Similarly, various in vitro studies showed that NSAIDs can inhibit proliferation and migration of tendon cells, but increase collagen synthesis [69, 76, 83].

- Selective and non-selective NSAIDs have a dose-dependent and time-dependent effect of tendon healing after repair.

Inflammation, regeneration and remodeling occur during tendon healing and the cells and molecular processes involved at each distinct phase will respond differently to NSAID treatment and inhibition of COX enzyme isoforms. Thus, NSAIDs impact tendon healing in different ways depending upon the dosage, the initiation and duration of treatment [84]. Virchenko et al. showed that early administration of parecoxib for the first five days after injury led to decreased maximum strength of the tendon. When parecoxib was given after the first five days post-injury there was a decrease in cross-sectional area but a substantial increase in maximum strength [74]. Further studies showed that NSAID treatment has an inhibitory effect on migration and proliferation of tendon cells in culture, coinciding with the early inflammatory phase, but does not affect the collagen expression of the regeneration and remodeling phase of tendon healing [69, 75, 76]

Finally, most of the studies where different dosages of NSAIDs were used, present controversial and inconsistent results. Some of them suggest that NSAIDs have a dose-dependent effect on tendons and adhesion formation in particular [72, 76] while others present no differences or inversely proportional results when compared.

- COX-2 Selective NSAIDs have a more significant effect compared to non-selective NSAIDs in inhibiting adhesion formation after tendon repair.

With the advent of COX-2 selective NSAIDs there has been a number of studies comparing the effect of COX-2 inhibitors with the traditional NSAIDs such as ibuprofen and indomethacin. Some of them suggested that COX-2 selective NSAIDs like parecoxib had a more significant effect compared to non-selective NSAIDs in inhibiting adhesion formation through the measurement of functional stiffness [32], while others found no difference between selective and non-selective NSAIDs [72]. In another comparative in vivo study between selective and non-selective NSAIDs, Tan et al. comparing the anti-adhesion effects of rofecoxib and ibuprofen on a rabbit model found no differences between them at 6 weeks, based on histology, but significantly better results were found for ibuprofen treated rabbits at 12 weeks, based on ROM results [73]. In all cases, COX-2 inhibitors seemed to impair tendon healing and mechanical strength the same way traditional NSAIDs did. In conclusion, comparative studies on the effect of selective and non-selective NSAIDs to date seem inconclusive.

Experimental studies have certain limitations that must be taken under consideration. First of all, the differences between the species in terms of anatomy, structure and physiological functions as well as metabolism of drugs should be taken into account. In particular, small mammals and rodents exhibit higher metabolic rates leading to different concentrations of nutrients and drugs and different rates of excretion [85]. Therefore, results of experimental in vivo and in vitro studies cannot be directly extrapolated and applied to the human clinical setting.

Furthermore, all of the aforementioned studies use different ways of administration, dosages and post-operative time-points on different animals. This large number of variables makes result interpretation difficult.

Literature on the effects of NSAIDs on tendon healing and adhesion formation seems inconsistent. A large number of studies has targeted the inflammatory cascade, and in particular COX enzyme in an effort to inhibit adhesion formation and promote tendon healing. NSAIDs have been tested for the last forty years and although results have been promising regarding adhesion formation, COX-inhibitors have repeatedly shown concomitant losses in the strength of repair, a concerning outcome for tissues that experience high loads such as the flexor tendons. While inflammatory

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response is essential for repair, excessive inflammation contributes to adhesion formation between tendon and surrounding tissue. These discrepancies are probably due to timing issues, as it has been shown that NSAIDs have a detrimental effect in the early inflammatory phase, but a slight positive effect during remodeling [74, 75]

In conclusion, selective and non-selective NSAIDs seem to have a significant effect in limiting adhesion formation. Nonetheless, the questions that arise about the role of NSAIDs on tendon healing, and their potential detrimental effect, are primarily to be addressed by larger animal studies that will provide a better viewpoint for statistical implementation and will check the safety of these drugs for side effects and the danger of tendon re-rupture.

Conflict of Interest Disclosure:

The authors declare that there is no conflict of interest

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