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HIGHLIGHTED TOPIC | *Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block?*

NSAID therapy effects on healing of bone, tendon, and the enthesis

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Su B, O'Connor JP. NSAID therapy effects on healing of bone, tendon, and the enthesis. *J Appl Physiol* 115: 892–899, 2013. First published July 18, 2013; doi:10.1152/japplphysiol.00053.2013.—Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of skeletal injuries. The ability of NSAIDs to reduce pain and inflammation is well-established. However, the effects of NSAID therapy on healing of skeletal injuries is less defined. NSAIDs inhibit cyclooxygenase activity to reduce synthesis of prostaglandins, which are proinflammatory, lipid-signaling molecules. Inhibition of cyclooxygenase activity can impact many physiological processes. The effects of NSAID therapy on healing of bone, tendon, and the tendon-to-bone junction (enthesis) have been studied in animal and cell culture models, but human studies are few. Use of different NSAIDs with different pharmacological properties, differences in dosing regimens, and differences in study models and outcome measures have complicated comparisons between studies. In this review, we summarize the mechanisms by which bone, tendon, and enthesis healing occurs, and describe the effects of NSAID therapy on each of these processes. Determining the impact of NSAID therapy on healing of skeletal tissues will enable clinicians to appropriately manage the patient's condition and improve healing outcomes.

nonsteroidal anti-inflammatory drugs; cyclooxygenase; tissue repair; fracture healing; tendon healing

NONSTEROIDAL ANTI-INFLAMMATORY drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes in the arachidonic acid (ArA) pathway to reduce synthesis of prostaglandins. The ArA pathway and prostaglandins regulate and are potent inducers, respectively, of inflammation. Thus NSAIDs are commonly used to control pain and swelling associated with skeletal injuries and chronic skeletal diseases like osteoarthritis. However, prostaglandins and other lipid mediators produced in the ArA pathway regulate a large number of physiological processes in addition to inflammation, such as blood clotting, vascular tone, stomach lining maintenance, kidney functions, ocular pressure, and smooth muscle contraction associated with airway dilation and parturition (40). Ongoing research also indicates that the ArA pathway and COX activity have important functions in skeletal biology (73). Consequently, understanding the role of the ArA pathway and COX activity in the healing of skeletal injuries is important to evaluate the potential negative as well as positive effects that NSAID therapy may have in patients. In this review, we summarize the known effects of NSAIDs on bone, tendon, and tendon-to-bone (enthesis) healing, discuss the potential mechanism through which NSAIDs impair bone fracture healing, and provide some suggestions regarding the judicious usage of NSAIDs to treat skeletal injuries.

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THE ARACHIDONIC ACID PATHWAY AND NSAID EFFECTS

The ArA pathway is summarized in Fig. 1 (11). Synthesis begins when cytosolic phospholipase A_2 ($cPLA_2$) hydrolyzes ArA from lipid membrane stores. The now free ArA follows one of four fates: the ArA can be *1*) reinserted into the lipid membrane through the Land's cycle, *2*) converted into prostaglandin H_2 by cyclooxygenases, *3*) converted into leukotriene A_4 by 5-lipoxygenase, or *4*) undergo oxidation reactions catalyzed by cytochrome *P*-450 (not shown). Prostaglandin H_2 and leukotriene A_4 are synthetic intermediates and are rapidly converted into secreted prostaglandins, leukotrienes, lipoxins, and other lipid mediators by downstream enzymes. In turn, the secreted lipid mediators activate G protein-coupled receptors to affect intracellular cAMP or Ca^{2+} levels and thereby affect gene expression and cell function. Most of the ArA-derived lipid mediators are very labile and thus signal via autocrine and paracrine mechanisms.

The enzymes involved in the ArA pathway have different levels of cell-specific or controlled expression. Myeloid cells express many components of the ArA pathway, which is consistent with the role of many myeloid cells and the ArA

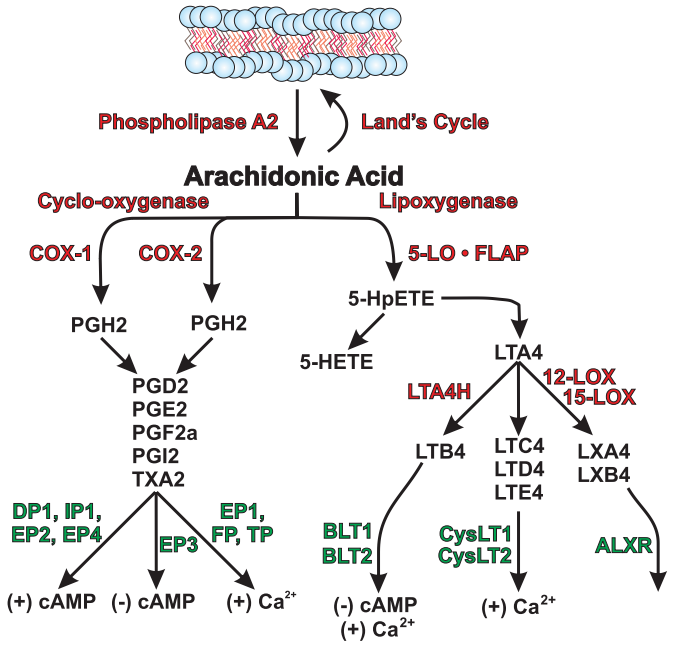

Fig. 1. Arachidonic acid metabolism and signaling. Summarized are 3 of the 4 major arachidonic acid metabolic pathways: the Land's cycle, conversion into prostaglandins which requires cyclooxygenase activity, and conversion into leukotrienes and lipoxins via 5-lipoxygenase activity. Not shown is cytochrome *P*-450 metabolism of arachidonic acid. Enzyme or enzymatic processes are shown in red text, substrates and products are shown in black text, and G protein-cell surface receptors are shown in green text. Known effects of receptor activation on downstream cyclic adenosine monophosphate (cAMP) or intracellular calcium levels are shown at the bottom. COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; 5-LO, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; PGH_2, PGD_2, PGE_2, PGF_{2a}, and PGI_2, are prostaglandins H_2, D_2, E_2, F_{2a}, and I_2, respectively; TXA_2: thromboxane A_2; 5-HpETE, 5*S*-hydroperoxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; 5-HETE, 5*S*-hydroxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4 are leukotrienes A_4, B_4, C_4, D_4, and E_4, respectively; LXA_4 and LXB_4, lipoxins A_4 and B_4; DP1, EP1-EP4, FP, and IP, prostaglandin receptors; TP, thromboxane A_2 receptor; BLT_1 and BLT_2, leukotriene B_4 receptor; CysLT1 and CysLT2: cysteinyl leukotriene receptors; ALXR: lipoxins receptor.

pathway in inflammation. However, other cells such as bone-forming osteoblasts can express ArA pathway enzymes and produce prostaglandins (39). Only portions of the pathway may be operable in any one cell or cell type under a specific physiological circumstance. For instance, neutrophils have constitutively high levels of 5-lipoxygenase while COX-2 expression can be readily induced in macrophages (13, 33). Further, cells must be stimulated to activate the ArA pathway. Stimuli that increase intracellular Ca^{2+} levels activate $cPLA_2$ and initiate ArA release from membrane stores (29). Thus lipid mediator production is dynamically controlled as to the amount and repertoire made depending upon the cells, growth factors, cytokines, or other stimuli present at the site. These variables complicate elucidation of the cells and mechanisms through which the ArA pathway operates to affect bone and tendon healing.

There are two cyclooxygenase isoforms: COX-1 and COX-2 (86). COX-1 is constitutively expressed in many cell types while COX-2 is inductively expressed. Proinflammatory stimuli including lipopolysaccharide and tumor necrosis factor-α are potent inducers of COX-2 expression. The prostaglandins produced via COX-1 or COX-2 subsequently amplify or sustain the inflammation response. More recent experiments indicate that COX-2 activity may also be important for resolving inflammation, and thus dysregulation of COX-2 function may lead to chronic inflammatory conditions (20).

At therapeutic levels, most NSAIDs inhibit COX-1 and COX-2 (99). However, COX-2-selective NSAIDs have been developed, notably the coxibs, which include celecoxib, rofecoxib, and valdecoxib (19). It was postulated that since COX-2 is inductively expressed as part of the inflammation response, preferentially inhibiting COX-2 would reduce negative side effects of NSAID therapy such as gastrointestinal bleeding because the homeostatic functions of COX-1 would be left intact. This does not appear to be wholly accurate in that the functions of COX-1 and COX-2 are both necessary for stomach lining maintenance and vascular tone (98). Still, the coxibs are effective analgesics used for a variety of acute and chronic skeletal injuries and pathologies. Thus determining and understanding the effects that inhibition of cyclooxygenase activity has on healing after an acute skeletal injury is necessary for proper patient management.

NSAID EFFECTS ON BONE HEALING

Bone fractures are common traumatic injuries, and some pathological conditions such as osteoporosis weaken bones, which makes the bone more susceptible to fracture. Bone is a highly innervated and vascular tissue. When a fracture occurs, circulation is disrupted causing localized hypoxia and hematoma formation while also being extremely painful. The tissue damage, hypoxia, blood clot, and peripheral nerves initiate an inflammatory response, which causes tissue swelling and hyperalgesia (9). NSAIDs or other analgesics are often used during this inflammatory phase of healing to reduce swelling or manage pain, further emphasizing the importance of clarifying the impact of NSAIDs on bone healing (12).

Fractures naturally heal through a tissue regenerative process in which a cartilaginous callus forms around the fracture site and is then replaced with bone (82). This natural healing process is often referred to as endochondral ossification, as it shares many features with fetal long bone development and growth (97). In contrast, surgery is often performed to align, reduce, and stabilize a fracture. When doing so, often the hematoma and periosteum near the bone fragment ends are surgically removed and the bone ends are rigidly fixed together with a plate or rod. Under these circumstances, very little or no cartilaginous callus forms and the bone heals slowly as part of the normal bone remodeling process or through a combination of bone remodeling and direct bone formation without a cartilaginous intermediate (intramembranous ossification) (82). This surgically created repair process is often called direct bone healing or primary bone healing (82). These two pathways, endochondral ossification and primary bone healing, employ distinctly different cell mechanisms and are likely differently affected by NSAID therapy.

Numerous animal studies have demonstrated a consistent negative effect of NSAID treatment on endochondral ossification during fracture healing (25). The negative impact appears to be caused by inhibition of COX-2 and not COX-1 since fracture healing appears to be normal in COX-1 knockout mice and because healing is impaired in COX-2-selective, NSAID-treated animals and in COX-2 knockout mice (84). Indeed

treatment of rats with celecoxib can cause healing failure (nonunions) in 30% or more of treated animals, and the nonunion rates increase with increasing celecoxib dose or length of treatment (85). Further, celecoxib doses that can inhibit fracture healing (1.5, 4, and 10 mg/kg) in rats are not sufficient to eliminate pain caused by the fracture. Cottrell et al. (26) measured pain in rats after fracture of the right femur as differential weight bearing between the affected right hindlimb and the control left hindlimb. Rats treated with morphine, acetaminophen, or SCIO-469 (a p38 kinase-α inhibitor) had significantly better pain relief over the first 14 days of fracture than did rats treated with 4 or 10 mg/kg of celecoxib. Further, the 4 and 10 mg/kg doses of celecoxib caused significant inhibition of fracture healing in rats whereas acetaminophen and SCIO-469 had no apparent negative effect on fracture healing (8, 27, 85). In contrast, nonselective NSAID therapy appears to delay rather than stop fracture healing. The delay effect caused by NSAIDs such as ibuprofen and indomethacin likely relates to the level of COX-2 inhibition caused by the NSAID. In rats, doses of indomethacin sufficient to inhibit most COX-2 activity cause gastrointestinal bleeding and death within days (1, 80). Since fracture healing outcomes require weeks to achieve, animals receiving doses of nonselective NSAID over this period of healing that would inhibit most COX-2 activity would also develop gastrointestinal bleeds and die. Thus it may not be possible to assess the role of COX-2 in fracture healing using nonselective NSAIDs.

In humans, retrospective studies support the conclusion that NSAID therapy can impair fracture healing. In perhaps the most compelling retrospective study, Burd et al. (14) examined data collected from a randomized, prospective trial to compare localized radiation therapy to indomethacin (a nonselective NSAID) therapy on the incidence and severity of heterotopic ossification after hip fracture surgery to determine whether NSAID therapy affects fracture healing. Heterotopic ossification is the formation of bone at sites outside of the normal skeleton and occurs through a mixture of intramembranous and endochondral ossification (6, 51, 64). Heterotopic ossification commonly occurs following hip fractures and can reduce hip mobility depending upon the extent of bone formation. To prevent heterotopic ossification after hip fracture surgery, patients are treated with localized radiation or with a 6-wk course of NSAID therapy (64, 95). Burd et al. (15) performed a randomized, prospective study to determine whether localized radiation or NSAID therapy was more effective at reducing heterotopic ossification after hip fractures (15). The study found that localized radiation or 6 wk of postoperative NSAID treatment both effectively reduced heterotopic ossification. However, many of the patients in this study also suffered additional long bone fractures coincident with their hip fractures. When the healing outcomes for those patients who suffered additional long bone fractures were compared between those who received localized radiation or no heterotopic ossification prophylaxis (74 patients) versus those that received indomethacin therapy (38 patients), 29% of the indomethacin-treated patients developed a nonunion while only 7% of patients that did not receive indomethacin developed a nonunion (14). Further, 11 of the 72 long bone fractures in the 38 indomethacin-treated patients developed nonunions while only 5 of the 118 long bone fractures in the comparator group of 74 patients developed nonunions. These data were statistically significant and clearly indicate that NSAID therapy is detrimental for fracture healing. Other retrospective studies support this conclusion (25, 44). In addition, NSAIDs inhibit heterotopic bone formation, which often develops through an endochondral ossification mechanism (71, 81). Thus it is not necessarily surprising that bone healing which requires endochondral ossification would be inhibited by NSAID treatment.

The mechanism by which inhibition of COX-2 impairs endochondral ossification during fracture healing remains unknown. There are three favored possibilities that are not mutually exclusive. First is that COX-2 function is necessary for mesenchymal cell differentiation into osteoblasts and for osteoblast function (105). Since COX-2 knockout mice form and grow skeletons, a definitive role for COX-2 in osteoblast differentiation is difficult to envision. Indeed, NSAID treatment impaired mesenchymal stem cells from differentiation into chondrocytes but had no effect on mesenchymal stem cell differentiation into osteoblasts (75). However, prostaglandins produced by COX-2 can stimulate osteoblast activity and prostaglandins or other lipid mediators made via COX-2 may be important for homing of mesenchymal cells to the fracture site. Second, prostaglandins are known to promote angiogenesis and angiogenesis is necessary for endochondral ossification (30, 53, 68). Thus inhibition of COX-2 may impair callus angiogenesis or limit fracture site circulation that impairs healing. Third, inhibition or loss of COX-2 appears to prevent terminal differentiation of chondrocytes in the fracture callus (28). In rats treated with celecoxib, cartilage forms at the fracture site but has an abnormal morphology (84). Gene expression analysis showed that fracture calluses in celecoxib-treated rats failed to express Type X collagen, which is the hallmark gene for chondrocyte terminal differentiation (hypertrophy) (28). Failure of the chondrocytes to terminally differentiate would impair endochondral ossification and prevent healing. Another possibility is that inhibition of COX-2 alters the inflammatory response such that expression of growth factor or other genes necessary for endochondral ossification is dysregulated, which impairs healing. To test this possibility without directly inhibiting COX-2, fracture healing was assessed in rats treated with SCIO-469, a p38 kinase-α inhibitor (27, 69). p38 kinase regulates several aspects of inflammation, and inhibition of p38 kinase-α can impair inflammation (83) However, fracture healing proceeded normally in rats treated with SCIO-469, suggesting that the inflammation response per se may not be essential (27).

Based upon the above findings, we hypothesize that COX-2 has a critical function in chondrocyte differentiation during fracture callus formation and endochondral ossification, and that inhibition of COX-2 with NSAIDs disturbs chondrocyte differentiation leading to delayed or failed healing. Our current model is that COX-2 expression is necessary for differentiation of the chondrocytes into hypertrophy and that inhibition of COX-2 with NSAIDs would impair hypertrophic differentiation (Fig. 2). Chondrocytes can express COX-1 and COX-2 (10, 24, 42, 70). However, mesenchymal stem cell differentiation into callus chondrocytes appears to be independent of cyclooxygenase activity since chondrocytes are evident in fracture calluses of COX-1 knockout and COX-2 knockout mice (84). Once differentiated, the callus chondrocytes elaborate an extracellular matrix that becomes calcified as the chondrocytes progress into hypertrophy. Chondrocyte hyper-

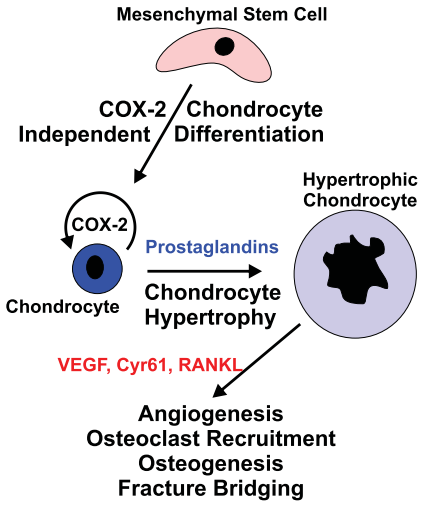

Fig. 2. Model of COX-2 function during fracture healing. During fracture healing, mesenchymal cells recruited to the fracture site can differentiate into chondrocytes in the absence of COX-2. However, COX-2 activity is required for the chondrocytes to progress into hypertrophy during which the hypertrophic chondrocytes secrete angiogenic and osteoclastogenic factors necessary for endochondral ossification. Whether COX-2 functions cell autonomously, in a cell-dependent manner via prostaglandin signaling, or using a combination of both remains to be determined. VEGF, vascular endothelia growth factor; Cyr61, also called CCN2; RANKL, receptor activator of nuclear factor kappa-B ligand.

trophy is essential for bone formation because it is during hypertrophy that chondrocytes secrete angiogenic factors necessary for osteoclast recruitment and resorption of the calcified matrix made by the hypertrophic chondrocytes and subsequent definitive bone formation by osteoblasts (43, 50, 87, 102). We have established that inhibition of COX-2 impairs chondrocyte hypertrophy in the fracture callus (28). Consistent with our observations, inhibition of COX-2 with NS398 impairs bone morphogenetic protein-2-induced differentiation of mouse chondrocytic ATDC5 cells into hypertrophic chondrocytes (100). Exogenous prostaglandin treatment can also promote chondrocyte expression of cartilage matrix proteins (45, 55, 62). However, exogenous prostaglandin effects may be limited to a specific phase as chondrocytes progress through hypertrophy since prostaglandins, particularly PGE_2, can inhibit Type X collagen expression in chicken chondrocytes (61). Thus many studies support the proposed model. Potential differential effects of prostaglandins, NSAIDs, or cyclooxygenase activity in fetal, articular, growth plate, or cultured chondrocytes could yield results specific for those chondrocyte populations but different from that observed during fracture healing. An important but still untested aspect of the model is whether COX-2 has cell-autonomous or cell-dependent effects on callus chondrocyte function.

While NSAIDs appear to impair endochondral ossification, the effects of NSAID therapy on intramembranous ossification and primary bone healing are less clear. Prostaglandins produced by COX-1 or COX-2 can promote osteoblast and osteoclast activity in vitro as well as in vivo, clearly suggesting that NSAIDs can affect intramembranous ossification and primary bone healing (48, 76, 94, 101, 104). Bone ingrowth into porous metal implants used to simulate bone healing into arthroplastic devices, such as artificial hips and knees, was impaired in rabbits treated with NSAIDs but not in dogs (23, 91). Intramembranous bone formation into bone harvest chambers implanted into rabbit tibias was inhibited by treatment with rofecoxib (a COX-2-selective NSAID) or naproxen (46). Subsequent studies showed that administration of rofecoxib for 2 wk after implantation of the chamber was not as detrimental to intramembranous bone formation into the chamber as was 6 wk of rofecoxib treatment (47). In contrast, even short-term administration of celecoxib can impair fracture healing in rats (85), suggesting a distinct difference between NSAID effects on intramembranous vs. endochondral ossification.

The intramembranous ossification models measure osteoblast activity, but primary fracture healing also relies upon osteoclast activity. NSAID effects on osteoclast activity are not clear (35, 56). Mouse studies have demonstrated that without COX-2, osteoclast differentiation in vitro is impaired, but paradoxically the mice have reduced cortical bone mass (74, 103). Retrospective clinical studies have correlated NSAID therapy with improved bone mineral density in women (but not men), suggesting that NSAIDs may reduce osteoclast activity (16, 67, 77). Which NSAID is used, the dose, and duration of treatment likely account for much of the discrepancies between in vitro, animal, and clinical studies.

NSAID EFFECTS ON TENDON AND LIGAMENT HEALING

NSAIDs are commonly used to treat pain and swelling associated with minor as well as major tendon and ligament injuries. Multiple criteria need to be met for successful tendon and ligament healing, and thus, how NSAID therapy impacts each criterion is important to understand the overall impact of NSAID treatment on healing. First, tendon and ligament mechanical strength must be reestablished. Second, tendons must be able to glide freely through the tendon sheath for full range of movement. Third, ligament healing must be sufficient to prevent joint laxity. Finally, in those cases where the tendon or ligament insertion into the bone has been disrupted, this specialized junction (enthesis) must be reestablished with functionally equivalent mechanical strength. These varied processes complicate optimizing treatments to heal ligament, tendon, and enthesis injuries. The role of inflammation and the ArA pathway in these healing events remains to be defined. Similarly, how NSAIDs affect each of these processes as well as ultimate healing outcomes are not yet clearly described.

In order to reestablish tendon and ligament strength, tendon cells must proliferate at or migrate to the injury site and secrete collagen for the repair process (60). In culture, NSAID treatment has repeatedly been shown to inhibit proliferation and migration of tendon cells, but increase collagen synthesis (63, 92, 93). Consistent with effects on proliferation and collagen synthesis, NSAID treatment was shown to decrease DNA synthesis and increase protein synthesis in human tendon fibroblasts, which suggests a negative effect on tendon cell proliferation following injury but a positive effect on collagen deposition (2). In contrast, animal studies examining the effects of NSAID therapy on healing tendon and ligament strength have been varied. Some studies reported no significant difference in the strength of healed tendons after NSAID use (3, 66, 90), while others demonstrated a lower load-to-failure and reduced tensile strength of healed tendons (31, 36). In contrast, several studies have shown that NSAIDs may enhance the biomechanical properties of healing tendons and ligaments.

Indomethacin treatment significantly improved the tensile strength of healing rabbit plantaris longus tendons that had been transected although a slight but significant decrease in the amount of soluble collagen was also seen (17). Similarly, piroxicam treatment improved medial collateral ligament (MCL) healing after transection when given 1 to 6 days postoperatively (52). Indomethacin or celecoxib treatment increased tensile stress at failure of healed rat Achilles tendons that had been previously transected, although the cross-sectional area of the tendon was decreased (38). These experiments suggest that NSAID treatment could be used to minimize thickening of healed tendons in certain clinical situations and that the potential negative effects of NSAIDs on tendon cell proliferation may be balanced by the positive effects of NSAIDs on collagen synthesis.

Inflammation, regeneration, and remodeling occur during tendon and ligament healing and the cells and molecular processes involved at each phase will respond differently to NSAID treatment and inhibition of cyclooxygenase. Thus NSAIDs impact tendon healing in different ways depending upon the initiation and duration of treatment. When rats were given parecoxib (a COX-2-selective NSAID) for the first 5 days after Achilles tendon transection, there was a decrease in force-at-failure and maximum stress. However, rats treated from *days 6–14* with parexocib showed a 16% decrease in cross-sectional area but a 29% increase in maximum stress (96).

In addition to reestablishment of mechanical strength, successful tendon healing also requires the tendon to be able to glide freely. Adhesion formation between the tendon and its surrounding sheath or other soft tissue can severely reduce range of motion. Szabo and Younger (88) have shown that NSAID treatment decreases adhesion formation and therefore increases range of motion. Four weeks of indomethacin treatment reduced adhesion formation after flexor digitorum profundus tendon transection. Injectable and oral ibuprofen significantly decreased the amount of peritendinous adhesions formed after flexor tendon repairs in primates, but also decreased the breaking strength of completely divided and repaired extensor tendons (57, 58). In contrast, in a rabbit flexor tendon repair model, ibuprofen treatment for 12 wk increased range of motion, but 6 wk of ibuprofen or rofecoxib treatment or 12 wk of rofecoxib treatment did not (89). Lack of rofecoxib efficacy in increasing range of motion and failure of 6 wk of ibuprofen therapy to increase range of motion suggest that adhesion formation or permanence may be mediated by COX-1 during the later stages of healing. However, additional research is needed to understand the role of cyclooxygenase activity in adhesion formation and its potential to affect tendon healing.

Equally important to the process of ligament healing is the ability to minimize joint laxity. Joint laxity increases the risk of ligament rerupture, so understanding how to minimize laxity is crucial to improved patient outcomes. To our knowledge, only one study has been conducted to evaluate the effect of NSAIDs on joint laxity following ligament injury. In this retrospective study, patients given ketorolac for 6 wk after bone-patellar tendon autograft anterior cruciate ligament reconstruction had a significant increase in anterior-posterior laxity at 6 wk postsurgery when compared with non-ketorolac patients (65). This finding suggests that NSAID therapy may increase joint laxity after a ligament injury or repair, but more research must be conducted to confirm this conclusion and determine whether the laxity is maintained or reduces with time.

In those cases where the tendon or ligament insertion into the bone has been disrupted, this specialized junction (enthesis) must be reestablished with functionally equivalent mechanical strength. Studies examining this final step of the healing process are discussed later.

The complex processes required for successful tendon and ligament healing make it very difficult to determine whether the effects of NSAIDs are beneficial or detrimental. To complicate matters, few clinical studies have been performed to measure effects of NSAID therapy on tendon healing. A prospective study followed 70 adult patients with severe, painful Achilles tendinopathy who were given either piroxicam or placebo (5). Results were based on residual symptoms, such as pain, tenderness, swelling, range of motion, muscle strength, and an overall assessment of efficacy. No significant differences were seen between the treated and untreated groups. In a retrospective study of 34 patients who were treated with indomethacin for 6 wk after a distal bicep tendon repair, no incidence of rerupture or significant difference in range of motion between the injured and uninjured arms was found (4). No comparator group was examined. Thus the available clinical data and the common experience of many people using over-the-counter NSAIDs to self-treat minor tendon and ligament strains does not support a detrimental effect of NSAID therapy on tendon healing.

Clarification of the relationship between cyclooxygenase activity, prostaglandins, and tendon biology will help determine the effects of NSAIDs on tendon healing. Some research has begun to delve into this complicated process. Previous studies uncovered a phenomenon of exercise-induced collagen synthesis in which collagen synthesis was dramatically upregulated in the hours following vigorous exercise (54, 59). When healthy runners were given indomethacin 72 h before running a marathon, they showed a complete blunting of the exercise-induced collagen synthesis effect in their patella tendons when compared with their placebo-dosed counterparts (21). The study concluded that use of NSAIDs reduced prostaglandin E_2 production, which significantly decreased collagen synthesis in response to weight-bearing activity. Although it is difficult to tell if there is a functional detriment to the decrease in collagen synthesis since the study only examined one episode of exercise, these findings may provide insight into the role of prostaglandins in tendon healing and demonstrate a possible negative effect of NSAIDs in this process.

NSAID EFFECTS ON TENDON-TO-BONE HEALING

The enthesis is the specialized junction between a tendon or ligament and bone (34). The enthesis progressively changes from tendon, to fibrocartilage, to calcified fibrocartilage, and finally bone (7). However, these four zones are not recreated following surgical repair but rather the tendon is joined to the bone through alternating layers of fibrovascular scar tissue (18, 41, 49, 78). This process requires chemotactic factors to guide inflammatory cells to the wound to initiate angiogenesis and scar formation, mitogenic factors to increase cell proliferation and scar matrix deposition by fibroblasts, and remodeling of collagen types I and III within the scar tissue to increase mechanical strength (41, 49). How NSAIDs affect each of

these processes individually within the context of enthesis repair is not yet known. However, animal studies have shown that overall, NSAIDs appear to inhibit proper enthesis repair. Cohen et al. (22) showed that celecoxib and indomethacin treatment of an acute supraspinatus repair in rats resulted in inconsistent regrowth of a fibrocartilage zone between the tendon and the bone, whereas control specimens showed fibrocartilage formation by 4 wk and improved collagen fiber organization by 8 wk. Parecoxib and indomethacin treatment were shown to significantly lower the maximum pull-out strength and stiffness of Achilles tendons in rats that were reattached through a bone tunnel in the distal tibia (32). Additionally, celecoxib or indomethacin therapy reduced failure loads for rotator cuff repairs in rats (22). Histological analysis showed that there were substantial differences in collagen organization and maturation, which may have contributed to the decreased failure load of the treated animal. Similar conclusions were made when several different NSAIDs produced detrimental effects on healing strength at the bone-tendon junction of rat patellar tendon (37).

NSAID therapy likely affects inflammation after surgical repair of the enthesis, but NSAID therapy could also be directly affecting scar formation and remodeling. For instance, NSAIDs can impair osteoclast activity, and inhibition of osteoclast activity can enhance healing of rabbit anterior cruciate ligament repairs (79). Of note, Rodeo and colleagues (78) demonstrated that the strength of the interface between tendon and bone increases the most during the first 4 wk after surgery, which should be a consideration when using NSAIDs during the early stages of postsurgical recovery. These findings are not entirely surprising: since tendon-to-bone healing requires bone growth, it is possible that NSAIDs affect tendon-to-bone healing through a similar mechanism as fracture healing, since both processes require extensive bone metabolism.

CONCLUSIONS

NSAIDs are readily available, over-the-counter medications that are commonly used and prescribed to manage pain and swelling associated with skeletal injuries. Despite this, the available experimental and clinical evidence indicates that NSAID therapy can impair bone fracture healing and tendon-to-bone (enthesis) healing. The effects of NSAIDs on bone and enthesis healing is likely affected by the NSAID used, the initiation, and duration of therapy. For instance, ibuprofen had an apparent less deleterious effect on bone healing than rofecoxib in rabbits, which was attributed to the shorter half-life of ibuprofen producing daily periods when cyclooxygenase was not inhibited (72). Considerably less is known of how NSAIDs affect tendon healing. In contrast to fractures, NSAID therapy may have a beneficial effect on tendon healing by decreasing adhesion formation while producing no net negative effect on tensile strength. However, these conclusions are not without exception and are subject to other aspects of patient health associated with impaired healing, such as advanced age, diabetes, and smoking. Consequently, the prescribing physician's assessment of patient health, the type of injury, and injury severity must be weighed against the benefits and potential drawbacks of using NSAIDs.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: B.S. drafted manuscript; B.S. and J.P.O. edited and revised manuscript; B.S. and J.P.O. approved final version of manuscript; J.P.O. conception and design of research; J.P.O. prepared figures.

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