Minireview

Emerging evidence that adaptive bone formation inhibition by non-steroidal anti-inflammatory drugs increases stress fracture risk

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Impact statement

In this article, we review evidence for non-steroidal anti-inflammatory drugs (NSAIDs) as an emerging risk factor for stress fractures. These injuries are common in military and athletic populations and are responsible for time away from duty or athletic activity. Use of NSAIDs is widespread in both military and athletic populations, and therefore conservative use of these drugs could have important preventative implications for stress fracture development in at-risk populations. Gaps in experimental evidence must be addressed before recommendations can be made. This article addresses these gaps and offers a path forward toward informed guidelines for NSAID use in at-risk populations.

Abstract

There is mounting evidence suggesting that the commonly used analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), may inhibit new bone formation with physical training and increase risk of stress fractures in physically active populations. Stress fractures are thought to occur when bones are subjected to repetitive mechanical loading, which can lead to a cycle of tissue microdamage, repair, and continued mechanical loading until fracture. Adaptive bone formation, particularly on the periosteal surface of long bones, is a concurrent adaptive response of bone to heightened mechanical loading that can improve the fatigue resistance of the skeletal structure, and therefore may play a critical role in offsetting the risk of stress fracture. Reports from animal studies suggest that NSAID administration may suppress this important adaptive response to mechanical loading. These observations have implications for populations such as endurance athletes and military recruits who are at risk of stress fracture and whose use of NSAIDs is widespread. However, results from human trials evaluating exercise and bone adaptation with NSAID consumption have been less conclusive. In this review, we identify knowledge gaps that must be addressed to further support NSAID-related guidelines intended for at-risk populations and individuals.

Keywords: Non-steroidal anti-inflammatory drugs, prostaglandins, mechanical loading, cyclooxygenase, bone, stress fracture

Experimental Biology and Medicine **2021; 246: 1104–1111. DOI: 10.1177/1535370221993098**

Introduction

Stress fractures are common overuse injuries known to affect military personnel and athletes such as distance runners, basketball players, and gymnasts.[1,2] In US Army personnel, stress fractures are most common during initial military training, when up to 21% of women and 5% of men experience a stress fracture.[3,4] These injuries are responsible for lost training days and negatively impact military readiness.[5] In military personnel, stress fractures are most common in the lower extremities, with 54% of all stress fractures occurring in the long bones of the leg and 20% in the feet.[6] Unlike traumatic fractures which often occur from a single incident of elevated loading, stress fractures develop with repetitive loading from stresses below the magnitude needed to cause traumatic fracture. Recurrent repetitive loading leads to a cycle of generation of tissue microdamage, repair, resultant temporary porosity, and continued mechanical loading until fracture.[7]

There are a number of factors reported to increase one's susceptibility to stress fracture. For example, women have been shown to have a 2- to 4-fold higher risk of stress fracture compared to men in both athletic and military populations.[8,9] Race and ethnicity also contribute to stress fracture risk in the military, with White soldiers at greatest risk, Black soldiers at lowest risk, and Hispanic soldiers at an intermediate risk.[10] Low aerobic fitness has also been

identified as a risk factor for stress fractures, particularly for those entering highly physically demanding training programs.[11,12] Other factors thought to predispose individuals to stress fracture include rapid increases in training volume, inherent bone and muscle properties, gait biomechanics, previous exercise history, sustained negative energy intake, and sex hormone and menstrual disturbances.[4,7,13–15] Historical [16–19] and recent studies [6,20,21] reveal another emerging risk factor for stress fractures—non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are some of the most commonly used analgesic drugs in the world. Widespread use of these drugs by military personnel [22] and athletes [23] provides an opportunity to significantly influence stress fracture risk in these groups. However, before clinical recommendations can be made regarding NSAID use in at-risk populations, more research is needed to provide the necessary evidence to support such recommendations. In this review, we will discuss experimental and population-level studies suggesting that NSAIDs may increase the risk of stress fractures. There is abundant literature suggesting NSAIDs may interfere with fracture healing and bone repair, [24–30] but in this review, we focus specifically on the literature regarding the influence of NSAIDs on mechanical loading and stress fracture development. We will also discuss potential mechanisms underlying this relationship, citing evidence from cell, animal, and human studies. We conclude with a discussion of the experimental evidence necessary to further inform clinical recommendations for NSAID use in populations at risk for stress fractures.

NSAID overview

NSAIDs are one of the most commonly used over-the-counter and prescription medications for their analgesic, antipyretic, and anti-inflammatory properties. In military populations, 80% of active duty soldiers fill at least one NSAID prescription annually,[22] and use is widespread in the general public as well, with an estimated 12% of the U.S. population reportedly taking NSAIDs on a regular basis.[31]

NSAIDs function by blocking cyclooxygenase's (COX) conversion of inflammation-induced arachidonic acid to prostaglandins, resulting in analgesia and reduction of inflammation through minimizing prostaglandin production. However, prostaglandins play an important role in bone adaptation to mechanical loading [32] and ultimate improvement in fatigue resistance properties of bone.[33] COX enzymes exist in two major isoforms: COX-1 and COX-2, and NSAIDs may inhibit one or both enzymes. COX-1 is constitutively expressed and is inhibited by NSAIDs such as aspirin and indomethacin. Long-term consumption of COX-1 specific NSAIDs may interfere with the functioning of gastric mucosa and platelet aggregation.[34] COX-2 selective NSAIDs, such as the coxibs, preferentially inhibit the inducible COX-2 isoform, which functions in the local inflammation response.[34] Some of the most commonly prescribed and over-the-counter (OTC) NSAIDs, such as ibuprofen and naproxen, block both COX-1 and COX-2 in a non-selective manner, with varying affinities for either isoform. Commonly used OTC NSAID formulations are rapidly absorbed, reaching maximum circulating concentration within approximately 30 min to 2 h and have a circulating half-life of approximately 1–2 h (naproxen being an exception with a significantly longer half-life).[34] Varying durations of action could have important implications for timing of use regarding the response of bone to mechanical loading, as we discuss below.

NSAIDs and stress fracture risk

Recent epidemiologic investigations have revealed an increased incidence of stress fracture that is associated with NSAID prescriptions in military populations. In a case-control study of the entire US Army population between 2002 and 2011, prescribed NSAIDs were associated with a nearly 3-fold increased risk of stress fracture.[21] In this study, soldiers prescribed NSAIDs during rigorous initial military training had a 5.3-fold greater risk for stress fracture compared to soldiers in initial military training who were not prescribed NSAIDs.[21] The increased risk of stress fracture with NSAID prescription during initial military training, a period of heightened physical activity, indicated a significant negative impact of NSAID use on stress fracture risk. This has important implications for other populations who may increase physical training for athletic and fitness goals. A similar but more muted relationship was recently reported across all U.S. Service branches, with a 1.7-fold increased risk of stress fracture among Service Members prescribed NSAIDs compared to matched controls.[6] While these studies provide evidence for a relationship between NSAID use and stress fracture risk, they do not signify causation, nor do they reveal the potential mechanistic underpinnings for the relationship. To best understand the relationship between NSAIDs and stress fracture risk, it is important to consider stress fracture pathophysiology.

Effect of NSAIDs on stress fracture pathophysiology

Unlike traumatic fractures, stress fractures occur with repetitive loading. Repetitive loading can result in accrual of microdamage, often in the form of linear microcracks, within the bone tissue.[35] This microdamage is detected by the resident cells of bone, osteocytes.[36] Osteocytes, in-turn, can signal for bone resorption by osteoclasts and subsequent formation by osteoblasts, which effectively remove and replace the fatigue damage in a process called targeted remodeling.[37] In normal bone, the remodeling cycle is approximately 120–150 days long.[38] When remodeling repairs damaged bone tissue, it extends the fatigue life of the structure.[39] However, remodeling also results in temporary porosity, while the formation process is completed within each bone multicellular remodeling unit. Areas with temporary porosity are thought to act as stress concentrators, and during periods of continued repetitive loading, result in further generation and accumulation of microdamage, increased porosity, and ultimately, structural failure.[35] Therefore, targeted remodeling to repair

microdamage in bone is thought to paradoxically contribute to, and protect from, stress fractures.[35,40] The influence of NSAIDs on the process of targeted remodeling has not been extensively studied, but there is some evidence that NSAIDs inhibit remodeling within cortical bone which in turn could lead to increased bone density with extended use in a similar fashion as anti-resorptive medications.[18,32,41–43] Nevertheless, because bone remodeling appears to play both a protective and contributory role in stress fracture generation, it is unclear how the effect of NSAIDs on targeted remodeling may influence stress fracture risk.

The influence of NSAIDs on adaptive bone formation, a second important physiological response to heightened mechanical loading, is clearer than that of the effect of NSAIDs on targeted remodeling. Adaptive bone formation is a distinct physiologic response to mechanical loading. Through this process, mechanical signals generated from loading are translated into biochemical signals (a process called mechanotransduction) that results in recruitment of osteoblasts and *de novo* bone formation.[44] This new bone formation, independent of osteoclastic bone resorption, is a modeling response in bone [45] that can greatly improve the fatigue resistance of skeletal structure, particularly when it occurs on the periosteal surface, which is mechanically advantageous. For example, mechanical loading performed for three days per week for five consecutive weeks within the rat forelimb, resulted in only a modest amount of new bone formation but an impressive 107-fold increase in the fatigue resistance.[33] This study shows the importance of adaptive bone formation in reducing stress fracture risk through improvements in fatigue resistance.

NSAIDs, by blocking COX enzymes and therefore prostaglandin production, inhibit key secondary messengers in bone cell mechanotransduction. Prostaglandin E2, in particular, is generated by mechanosensitive bone cells in response to loading and is a key signaling mediator for bone formation.[32] Given the critical role of adaptive bone formation in improving the fatigue resistance of bone, interference with this response by NSAIDs may be a key mechanism contributing to increased stress fracture risk. Evidence for the interference of bone mechanotransduction and adaptive bone formation is largely derived from cell culture and animal studies.

Cell-based studies of NSAID effects on bone mechanotransduction and adaptive bone formation

Cellular studies are well suited for identifying mechanistic processes due to the ability to manipulate and control the local environment. In cell-based studies, NSAIDs have been shown to have dose-dependent effects on osteoblast activity,[25,46] largely via inhibition of osteoblast and osteoblast-like cell proliferation and differentiation.[47–52] Mechanisms underlying these anti-proliferative effects include induction of apoptosis/necrosis [47,48,51] and G0/G1 cell cycle arrest,[48] although cell cycle arrest has not always been a universal finding.[50] Moreover, celecoxib, valdecoxib, and a non-COX-inhibiting celecoxib derivative demonstrated the ability to suppress osteoblast differentiation, suggesting NSAIDs possess a mechanism(s) of action independent of COX inhibition.[53] Additional studies report that NSAIDs decrease alkaline phosphatase and type 1 collagen levels as well as the size of mineralization nodules within cell cultures.[51] Together, these reports suggest that NSAIDs may reduce the abundance of osteoblasts as well as their ability to produce new bone matrix.

Animal studies of effects of NSAIDs on adaptive bone formation

While cell culture studies may provide mechanistic evidence supporting suppression of bone formation activity by NSAIDs, these studies cannot provide data such as histomorphometry and mechanical testing to determine the phenotypic and structural consequences of these drugs following mechanical loading. To address these limitations, the effects of NSAIDs on load-induced bone formation have been studied utilizing a variety of small animal models. A summary of these animal studies can be found in Table 1A. In one of the first animal studies to investigate the effects of NSAIDs on adaptive bone formation, Pead and Lanyon [54] found that in the rooster ulna, a 40 mg/kg dose of indomethacin administered 1 h prior to a single axial loading event reduced bone formation in the NSAID-treated group compared to the untreated group. Their histomorphometric evidence was some of the first to show that prostaglandins are important for bone mechanotransduction and subsequent osteogenesis. Suppression of the adaptive bone formation response was most pronounced on the periosteal surface, suggesting that suppression of adaptive bone formation may occur at a mechanically stressed location on the bone.

Chow and Chambers [55] compared the impact of 2 mg/kg of indomethacin on bone formation in rats when administered either as a single dose or a daily dose for eight days. Additionally, the timing of the NSAID dose was compared in animals receiving the agent either before or after the mechanical loading of the vertebral bodies. They found that a single dose of indomethacin 3 h prior to, or 6 h following loading was sufficient to completely inhibit the bone formation response compared to vehicle. However, daily doses of indomethacin, whether administered before or after loading for the eight-day protocol, resulted in reduced bone formation similar to the single dose prior to loading. This latter observation has implications for chronic use of indomethacin during periods of heightened physical activity.

Four-point bending was used in a study by Forwood to compare the dose-dependent effects of the COX-1 specific inhibitor, indomethacin, to the COX-2 specific inhibitor, NS-398, in rat tibia.[56] NS-398 administration blocked adaptive bone formation on the endosteum at all the doses tested, while indomethacin only blocked formation at the highest dose, indicating that the COX-2 pathway is critical for lamellar bone formation. Woven bone formation, a common occurrence following fatigue damage in bone, was only suppressed by the highest dose of NS-398. Li *et al.* [57] utilized both axial loading and bending models in

Table 1. Summary of human and animal protocols examining NSAID effects on bone adaptation to mechanical loading.

	NSAID and dose	Population/groups	Intervention/methods	Relevant findings
A: Animal studies				
Pead *et al.* [54]	Indomethacin (40 mg/kg) 1 h before loading.	18 male Roosters.	Single bout of axial loading of the ulna, 5-day follow-up. Bone formation determined by histomorphometry.	Indomethacin prior to loading blocked periosteal osteogenic adaptation to loading.
Chow *et al.*[55]	Indomethacin (2 mg/kg/day) versus vehicle, 3 h before or 6 h after loading, single dose and daily doses.	100 female Wistar rats. 9 groups of 12.	Single bout of vertebral loading, 8-day follow-up. Bone formation determined by histomorphometry.	Indomethacin completely suppressed bone formation if administered before loading compared to vehicle. Formation was similarly suppressed if NSAID was administered after loading and daily for 8 days.
Forwood *et al.* [56]	Indomethacin or NS-398 (0.02, 0.2, or 2.0 mg/kg) 3 h before loading.	65 female Sprague-Dawley rats. 8 groups of 8 rats.	Single bout of 4-point tibial bending, 12-day follow-up. Bone formation determined by histomorphometry.	NS-398 blocked endocortical formation, Indomethacin partially blocked formation at highest dose. Woven bone formation in periosteal surfaces not affected by NSAID.
Li *et al.*[57]	Indomethacin, NS-398 (2 mg/kg oral) 3 h prior, NS-398 (10 mg/kg IP) 3 h, 30 min, and +30 min from loading.	56 female Sprague-Dawley rats. Two experiments – COX selectivity comparison and dose timing.	Single bout axial loading ulna and 4 point-bending on tibia, 12-day follow-up. Bone formation determined by histomorphometry.	NS-398 had greater suppression of loading-induced formation than indomethacin, and both greater than vehicle. Administration 3 h prior to exercise showed greater suppression than 30 min after. Formation rate not changed from vehicle if NS-398 administered after loading.
Sugiyama *et al.* [58]	NS-398 (5 mg/kg/d) 5 d per week for 2 weeks.	16 C57BL/6 mice in 2 groups.	Axial loading of tibia/fibula on 3 alternate days per week. Bone morphology determined by microCT.	No difference in cortical morphometry in loaded limbs between NSAID and vehicle injected mice. Slight decrease in trabecular bone volume to total volume at proximal tibiae.
Jain *et al.* [59]	Ibuprofen (45 mg/kg), daily during training.	113 female Sprague-Dawley rats into 6 groups.	High repetition, high frequency reaching and grasping task, 12 weeks training. Bone formation determined by histomorphometry and microCT on radius and ulna.	Ibuprofen abated training induced indicators of bone resorption. Formation markers largely unaffected by Ibuprofen.
Sherk *et al.* [60]	Ibuprofen (30 mg/kg), 1 h prior to treadmill session.	43 female Wistar rats in 4 groups.	Treadmill running, 5 days/week for 12 weeks. MicroCT on femur and tibia for bone morphology and 3 point bending for bone strength.	No differences in bone adaption to training between ibuprofen and vehicle groups.
Park *et al.*[20]	Aspirin (100 mg/kg) and Naproxen (10.9 mg/kg) daily through drinking water.	21 female C57BL/6 J mice in 3 groups.	6 bouts of axial forelimb loading over 2 weeks. Ulnar histomorphometry, microCT, 3 point bending, and serum measurements.	Naproxen decreased load-induced bone formation, bone toughness (due to decrease in post-yield deformation), and woven bone formation following stress fracture.
B: Human studies				
Kohrt *et al.* [61]	Ibuprofen (400 mg), taken before or after exercise versus placebo.	73 premenopausal females in 3 groups.	9 months, 3× week, weight-bearing exercise. BMD assessed by DXA.	NSAIDs taken 1 to 2 h before training may impair skeletal adaptive response. NSAID taken after exercise may enhance adaptive response.
Jankowski *et al.* [62]	Ibuprofen (400 mg), taken before or after exercise versus placebo.	189 male and females aged 60–75 years in 3 groups.	9 months, 3× week, weight-bearing exercise. BMD assessed by DXA.	No effect of exercise training or treatment in BMD.
Brewer *et al.* [63]	Naproxen sodium (440 mg) vs. placebo, before exercise.	23 college aged males in 2 groups.	6 weeks, 2× week, upper body progressive resistance training. Plasma PGF2α and BMC by DXA in forearm.	Slight decline in forearm BMC in both groups with training but no effect of NSAID treatment BMC. Naproxen reduced PGF2α response to acute exercise, but only at the onset of training.
Duff *et al.*[64,65]	Ibuprofen (400 mg) vs. placebo, administered after exercise.	90 postmenopausal females in 4 groups.	9 months, 3× week resistance training or stretching. Bone morphology assessed by DXA and pQCT.	No effect of Ibuprofen or training group in BMD assessed by DXA. 3% increase in Ward's region of hip in NSAID stretching group compared to placebo. Total BMC of distal radius determined by pQCT decreased by 1.5% in ibuprofen resistance training group compared to 0.6% increase in placebo group.

rat tibia and ulna to differentially stimulate formation in endocortical and periosteal surfaces. Similar to the results of Forwood's study, NS-398 treatment decreased endocortical mineralization (mineralizing surface/bone surface; MS/BS) in the tibia by 96% and periosteal MS/BS in the ulna by 37%. NS-398 was reported to have its greatest effect at suppressing bone formation when administered 3 h prior to loading compared to 30 min before, and had no effect when administered 30 min after loading. These studies indicate that NSAIDs, particularly those that inhibit COX-2 sufficiently close to the time of peak NSAID concentration, inhibit adaptive bone formation on both endocortical and periosteal surfaces of cortical bone following mechanical loading.

Park *et al.* [20] showed that administration of naproxen (10.9 mg/kg) through drinking water significantly impaired load-induced bone formation following six bouts of axial forelimb compression over two weeks as compared to aspirin or vehicle treatment. In addition to the sharp decrease in relative periosteal bone formation rate (−76%), naproxen was also associated with diminished whole bone toughness (−35%) and decreased thick collagen fibrils (−49%), which may contribute to increased stress fracture risk. Furthermore, this study demonstrated that bone repair following a preclinical ulnar stress fracture was inhibited by naproxen use. Unsurprisingly, stress fractured mice treated with naproxen or aspirin had greater limb use after injury than the control mice, underscoring the strong analgesic properties of NSAIDs for musculoskeletal injuries.

Not all studies have reported demonstrable suppression of adaptive bone formation by NSAIDs. For example, repetitive axial loading in female mice, three days per week, with or without NS-398 injected five days per week, had no influence on cortical bone formation over a two-week loading period as determined by microCT.[58] However, this study did report suppression of trabecular bone at the proximal tibia site, as NS-398 administration was associated with reductions in bone volume to tissue volume and trabecular number. However, no histological analyses were conducted. In another study, administration of ibuprofen, a commonly used non-specific COX inhibitor, was examined using a running training model in rats.[60] Exercise sessions 5 days per week for 12 weeks stimulated cortical bone formation, yet 30 mg/kg of oral ibuprofen 1 h prior to each exercise session failed to attenuate this response. It is unclear why suppressed adaptive bone formation was not observed in these studies, although it is possible that the dose of ibuprofen may have been too low to elicit an effect. Indeed, inhibition of COX-2 with ibuprofen requires a much higher concentration than indomethacin.[66] Another possibility is that the repetitive, uniaxial loading protocols may have failed to generate as great an adaptive response as other models, such as 4-point bending, and therefore, differences from NSAID administration may have been undetectable.

While the above studies largely focused on the adaptive formation response, one study in rats showed that a high-repetition/high-force task model was sufficient to stimulate bone resorption and decrease trabecular bone volume after 12 weeks of training.[59] Daily treatment of 45 mg/kg ibuprofen during training weeks 5–12 abated this response exhibited by post-training reduction in osteoclast response in ibuprofen-treated rats compared to non-treated rats. In addition, there were no changes in the osteoblast response with the ibuprofen treatment. Serum markers of formation and resorption also reflected these findings as markers of bone resorption were attenuated with ibuprofen treatment but formation was unaffected. These results support the concept that NSAID treatment may inhibit the bone remodeling pathway by inhibiting bone resorption.

In summary, studies of mechanical loading and NSAID administration in animals have generally resulted in attenuated or complete inhibition of the osteogenic response to loading.[20,54–57,67] Collectively, these studies also suggest some common themes, including: (1) the notion that NSAIDs inhibit adaptive bone formation on both the periosteal and endosteal surfaces; (2) NSAID administration prior to loading yields greater inhibition of adaptive bone formation; (3) COX-2 specific inhibitors yield the greatest suppression of formation; and, (4) NSAIDs appear to affect bone formation in a dose-dependent fashion, possibly secondary to their selectivity and potency towards COX-2.

NSAID suppression of adaptive bone formation in humans

Relatively few studies have examined the effects of NSAIDs on bone adaption to physical activity in humans compared to animal studies (Table 1B). In agreement with many of the animal studies, Kohrt *et al.* found that administration of 400 mg ibuprofen prior to weight-bearing exercise sessions (3×/week over 9-months) resulted in an impaired bone mineral density (BMD) adaptation in premenopausal women as assessed by dual-energy X-ray absorptiometry (DXA).[61] In contrast, they reported increased hip BMD when NSAIDs were consumed immediately following the exercise sessions compared to consumption of placebo immediately following exercise. This study highlights the importance of timing of NSAID administration. Consumption of ibuprofen, a non-selective COX inhibitor, resulted in an impaired BMD response only when given before exercise. These results suggest that inhibiting bone mechanotransduction with NSAIDs can suppress adaptive bone formation, as COX-2 is inducible, and is likely to be expressed during and after training sessions. In a similar study from the same research group, the same influence of ibuprofen on BMD with exercise in premenopausal women was not seen in older men and women, which the authors attributed to higher variability in BMD response, potentially leading to lack of adequate statistical power.[62]

When 400 mg of naproxen was administered to college-aged males prior to upper body resistance exercise performed twice a week over the course of six weeks, no effects of the NSAID on arm bone mineral content (BMC) assessed by DXA were observed compared to placebo trained .[63] In another report, Duff *et al.* [64,65] observed unchanged vertebral, hip, and femoral BMD as assessed by DXA after nine-months of resistance training in postmenopausal women who were either administered 400 mg ibuprofen or placebo

after the exercise session. However, when they used the more sensitive peripheral quantitative computed tomography (pQCT), changes in total bone content at the distal radius at the end of nine months of training were significantly different between NSAID-administered group (−1.5%) and the placebo group (+0.6%).

In summary, trials examining exercise and NSAID use in humans have reported minimal or no effects on adaptive bone formation. These findings however, may be from the available *in situ* imaging technologies available. Both DXA and standard pQCT likely lack the imaging resolution needed to capture the small but mechanically meaningful changes that can occur with mechanical loading. Future exercise trials in humans with NSAID consumption will benefit from utilization of high-resolution pQCT. Indeed, this technology has recently been used to capture quantifiable changes in adaptive bone formation following relatively brief periods of military training,[68,69] and may therefore provide the capability to capture suppression of adaptive bone formation in humans with NSAID use.

Summary and future directions

In summary, there is evidence for increased risk of stress fracture with NSAID prescription from population-level studies. There is also biological plausibility for a role of NSAIDs in inhibiting adaptive bone formation which is a critical preventative process in the etiology of stress fracture. Cell-based studies provide evidence for inhibition of osteoblast proliferation, differentiation, and mineralizing activity, and animal studies provide some of the strongest evidence of inhibition of adaptive bone formation with NSAIDs. While human exercise trials have not been as conclusive, they provide some evidence that NSAIDs inhibit adaptive bone formation, particularly if consumed prior to exercise. Introduction of higher resolution, non-invasive imaging technology will facilitate capturing the relatively small but mechanically meaningful changes in bone that occur with physical exercise,[68] and thus allowing a deeper examination of NSAIDs' influence on adaptive bone formation in humans.

Evidence supporting adverse effects of NSAIDs on adaptive bone formation and stress fracture risk is mounting, and many of these effects are also observed in fracture healing.[70] Treatment recommendations for fracture repair typically involve limiting NSAID consumption to minimally effective doses, for the shortest time possible, especially in populations at risk for delayed healing.[24–30] However, in terms of adaptive bone formation and stress fracture risk, much work still must be done before specific evidence-based recommendations for NSAID use can be made to military and athletic populations. Evidence from large prospective studies or randomized controlled trials in relevant, at-risk populations is lacking. Such studies will be important for establishing a causal relationship between NSAIDs and stress fractures. As NSAIDs are often used for pain relief, studies are also needed to identify potential analgesic substitutes, such as NSAIDs with a nitric oxide donor [71] or acetaminophen, which has been associated with lower stress fracture risk than NSAIDs.[21] Other potentially fruitful lines of research include determining the effects of NSAIDs on the targeted remodeling pathway, establishing the appropriate timing of NSAID administration before or after exercise, and identifying dose–response relationships between various NSAIDs and stress fracture risk. Finally, studies that identify the degree to which NSAIDs inhibit recovery from stress fracture will inform management and treatment algorithms that best support bone repair. Ideally, such algorithms will incorporate optimal NSAID dose and duration to maximize recovery. This will be of particular value when prescribing multiple and simultaneous treatment strategies, including non-pharmacologic interventions such as protection, rest, ice, compression, and elevation (P.R.I.C.E.). Completion of this work will provide health-care practitioners the necessary data to inform patient-centric recommendations that spare adaptive bone formation and reduce risk of stress fractures. The high prevalence of both NSAID use and stress fractures in military and athletic populations provides an impetus to identify and reduce risk in these groups and in the population at large.

AUTHORS' CONTRIBUTIONS

All authors participated in the conceptual development and writing of the paper.

ACKNOWLEDGEMENTS

The authors thank Colleen Castellani, Alyssa Geddis, Alexandra Kostaras, Graham Kulig, and Marinaliz Reynoso for their assistance in literature review and table preparation for this manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research supported in part by the United States Army Medical Research and Development Command.

DISCLAIMER

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army or the U.S. Department of Defense.

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