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Ibuprofen as a Treatment for Work-Related Musculoskeletal Disorders: Effectiveness versus Caveats

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Additional information is available at the end of the chapter

Abstract

Work-related upper limb disorders (WMSDs), also known as repetitive strain injuries, affect a large subsection of the US population. These disorders are a significant source of injury, morbidity, loss of work, and pain. We have developed a rat model of upper extremity repetitive work at high forces, and observed exposure-dependent increased inflammatory responses in all tissues involved in performing the task. A 2- to 8-week regimen of oral ibuprofen provided to rats while they continued to perform a high-repetition high-force task ameliorated these inflammatory responses as well as several motor declines. Ibuprofen treatment also attenuated task-induced tissue fibrosis, cartilage degeneration, and bone osteopenia, indicating their link to inflammatory processes. However, ibuprofen did not significantly attenuate persistent nocifensive pain behaviors (reflexive grip strength results are presented) likely because of persistent increases in inflammatory cytokines in the spinal cord, suggestive of central sensitization. Since long-term ibuprofen use can induce a number of negative side effects, such as gastritis, multi-pronged approaches should be considered with anti-inflammatory drugs included for only short time periods.

Keywords: repetitive loading, work-related musculoskeletal disorders, repetitive strain injury, ibuprofen, osteopenia

1. Introduction

Overuse-induced musculoskeletal disorders (MSDs) are also known as overuse injuries, repetitive strain injuries. Diagnoses of upper extremity MSDs include muscle strain injuries, carpal and cubital tunnel syndromes, muscle myalgia/hyperalgesia, dorsal wrist tendinosis, lateral and medial epicondylopathies, rotator cuff tendinopathies, and more. These disorders often occur as a consequence of daily activities (both occupational and not), sports or military activi-

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ties, and are a leading cause of pain and physical disability [1–4]. Some cases become so severe that simple personal tasks, such as buttoning a shirt, become difficult to impossible. Acute trauma may be a causal factor in some WMSDs. Yet, many result from cumulative small amplitude forces occurring with overtraining, overexertion, repetitive activities, forceful actions, and prolonged static positioning [5–8]. Prevention is hampered by many problems [9, 10]. There remains a call for effective treatments for these often debilitating disorders [9, 11].

2. Current treatments for overuse—MSDs

The first line of treatment for workers in pain usually entails a prescription of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen [12, 13]. NSAIDs are the most commonly used (self-care and prescribed) for acute and chronic musculoskeletal pain [14–17]. A survey study of 941 workers found that 84% used NSAIDs, including ibuprofen, for pain [17]. Forty percent of 2213 French workers reported the regular use of ibuprofen in a 1-month period [18]. Back and shoulder injuries and other musculoskeletal strains are largely self-treated by migrant farm workers with rest and over-the-counter drugs, such as ibuprofen [14]. Rest, ice, compression, and elevation (termed RICE oftewn) are also often used to treat acute injuries. However, RICE has proved less effective for treatment of pain associated with chronic overuse—MSDs than NSAIDs. Splinting for carpal tunnel syndrome is less effective than surgical release or injections of steroids around the nerve [19–24], which are also not always effective [19–24].

3. Ibuprofen

Ibuprofen was introduced to the US market as a prescription drug to treat arthritic conditions in 1974, and subsequently became available over the counter in the United States in 1984. Despite its relatively short history as an over-the-counter medicine, it has quickly achieved popularity as a treatment for musculoskeletal and peripheral nerve pain, capturing up to a third of the over-the-counter analgesics market of the US by 2002. According to background information supplied by Wyeth Pharmaceuticals (a manufacturer of Advil, a brand name ibuprofen), this occurred principally because of its strong gastrointestinal (GI) safety profile that ibuprofen was approved for over-the-counter use. There are a wide variety of ibuprofen drugs available on the market as indicated in **Table 1**. Tablet, caplet, injectable, and topical forms are available. Negative side effects and major concerns will be discussed later in this chapter, although it should be noted that topical ibuprofen formulas are absorbed less into blood stream than oral forms, avoiding several side effects. However, as topical NSAID drugs are not systemic, they will not reduce inflammatory responses other than at the site of application.

Ibuprofen works by inhibiting both the constitutive cyclooxygenase (COX)-1 and the more inducible COX-2 enzyme. These enzymes catalyze the generation of prostanoids (prostaglandins PGE2 and PGF2a), prostacyclins, and thromboxanes [25, 26]. Inhibition of

these enzymes by ibuprofen prevents the conversion of arachidonic acid to prostaglandin H2, and in doing so blocks the prostaglandin-signaling pathway. Prostaglandins play an important role in pain and inflammatory signaling, as well as have roles in maintaining kidney function (mainly by regulating blood flow in the glomerular capsule) and the gut mucosa, and cardiovascular physiological processes [26].

Brand names

Ibuprofen Tablets and Caplets: Actiprofen Caplets (CA), Advil, Advil Extra Strength (CA), Advil Migraine, Anadin Ibuprofen (UK), Anadin Ultra (UK), Apo-Ibuprofen (CA), Arthrofen (UK), Brufen (UK), Cuprofen (UK), Extra Strength Motrin IB (CA), Hedex Ibuprofen (UK), Motrin, Motrin IB, Ibuprofen (CA), IBU

> **Active ingredient:** Ibuprofen (100–800-mg tables and caplets available).
> **Typical dose** is 200–400 mg/dose; Maximum amount is 800 mg/dose, or 3200 mg per day.
> **Use:** Reduction of fever, pain, or inflammation from headache, dental pain, menstrual cramps, rheumatoid arthritis, osteoarthritis, muscle aches, minor aches, and pain.
> **Note:** An anti-inflammatory dose is higher than an analgesic dose, and must be maintained for full effectiveness.

Ibuprofen PM Tablets: Advil PM, Motrin PM

> **Active Ingredient:** Ibuprofen (200 mg) and Diphenhydramine citrate (38 mg).
> **Typical dose** is two capsules at bedtime (also the maximum dose/day).
> **Use:** Occasional sleeplessness when associated with minor aches and pains.

Injectable Ibuprofen: Caldolor, Calprofen (UK), and more

> **Active Ingredient:** Ibuprofen (various doses available).
> **Typical dose**: Intravenous infusion of 100–800 mg dose, after dilution to 4 mg/ml or less per injection.
> **Use:** Reduction of fever; Management of mild to moderate pain, and moderate to severe pain as an adjunct to opioid analgesics.

Topical Ibuprofen: Ibuprofen Gel (US), Ibuleve gel (UK), Ibumousse (UK), Ibuspray (UK), and more

> **Active Ingredient:** Ibuprofen (various doses available).
> **Typical dose:** three to four times a day, or as directed by a doctor, with at least 4 h between applications.
> **Use:** Muscle or rheumatic pain, backache, neuralgia; sprains, strains and sports injuries; mild arthritis.
> **Note:** Absorbed less into blood stream when applied topically, so not thought to reduce fever or widespread inflammation as a consequence.

Table 1. Types of ibuprofen available.

A steady dose of ibuprofen is considered necessary to attenuate the increase in inflammation, rather than just analgesic. The dose used should be lower than the maximum limit for gastrointestinal toxicity. Those suggested maximum limits are indicated in **Table 1**.

4. An operant rat model of WMSD

Several animal models have been developed to study WMSDs and have shown that repetitive hand activities induce sensorimotor dysfunction [27–33]. A model developed in our

laboratory is a unique operant rat model of voluntary reaching and grasping (**Figure 1**; [7, 34]). Using this model, we are able to examine the effects of voluntary performance of repetitive low or high demand tasks on sensorimotor performance and musculoskeletal tissues [7, 30, 35]. This model is nonsurgical and involves performance of voluntary repetitive tasks to induce mechanical loading of forearm tissues. Specifically, adult rats are required to voluntarily and repetitively reach for, grasp, and isometrically pull a handle with one forelimb to obtain a food reward at various reach rates and force levels determined from studies on risk exposure for WMSDs to humans [7, 34]. Additionally, several functional outcomes are tested that are similar to those tested in patients, including forepaw (hand) sensitivity, grip strength, and median nerve conduction velocity.

Using this rat model, we have observed early exposure-dependent changes (duration and task level) in inflammatory responses in the form of increased macrophages and inflammatory cytokines in soft tissues involved in performing the repetitive task [7, 30, 32, 35, 36]. The greatest responses were observed in rats performing a high-repetition high-force (HRHF) task for 6–12 weeks, compared to lower demand tasks. Therefore, we picked this HRHF task regimen for experiments in which we tested the effectiveness of ibuprofen.
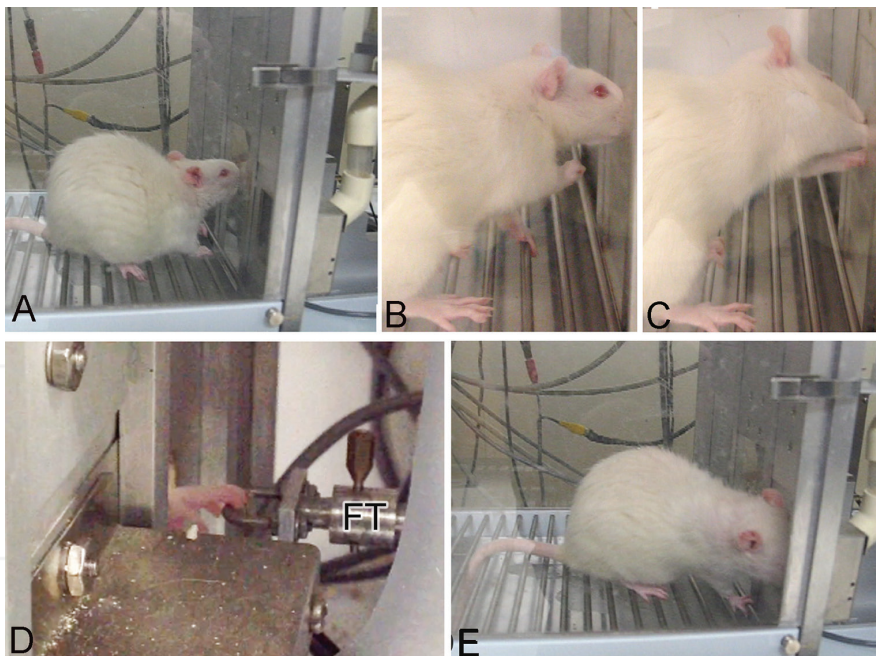

Figure 1. Rat performing HRHF repetitive reaching task. (A) Rat awaits auditory stimulus with snout in portal. (B and C) Rat reaches for force handle with right forepaw; left forepaw used for postural support. (D) Closer view, rat grasps and isometrically pulls force handle attached to force transducer (FT), until predetermined force threshold is reached and held for at least 50 ms. (E) Rat retrieves foot pellet reward by mouth from food trough.

5. Testing the effectiveness of ibuprofen treatment for WMSDs

We hypothesized that an underlying inflammatory mechanism is driving many of the sen-sorimotor declines, as are inflammation-linked fibrotic and degenerative/degradative tis-sue changes [37]. We explored this hypothesis by treating rats with systemic ibuprofen (i.e., oral) at anti-inflammatory doses. The design of these experiments is shown in **Figure 2**, and included normal controls (termed NC rats) and food-restricted-only controls (termed FRC rats). Rats were food-restricted to body weights of 5% less than age-matched normal controls to motivate them to work. Subsets of food-restricted rats were trained to high-force levels to determine the effects of training (10 min/day, 5 days/week, for 5 weeks) in which they learn to pull at high-force levels (1.25 Newton's which is approximately 60% of their maximum voluntary force) [7]. The trained-only rats are termed TRHF rats. Subsets of TRHF rats went on to perform a high-repetition high-force task regimen for 2 h/day, 3 days/week for up to 12 weeks. Task requirements were a reach rate of 8 reaches/min and a target force of $60 \pm 5\%$ of their mean maximum pulling force. HRHF rats had to grasp the force lever bar and exert an isometric pull at the target level for at least 50 ms to receive a food reward. Half of each group was administered ibuprofen (Children's Motrin Grape Flavored, Johnson & Johnson) in drinking water daily (a dose of 45 mg/kg body weight was used). This dose was lower than the maximum limit for gastrointestinal toxicity in rats, yet effective in reducing chronic inflammation [38]. The results of these experiments and the effectiveness (or lack thereof) are discussed below.
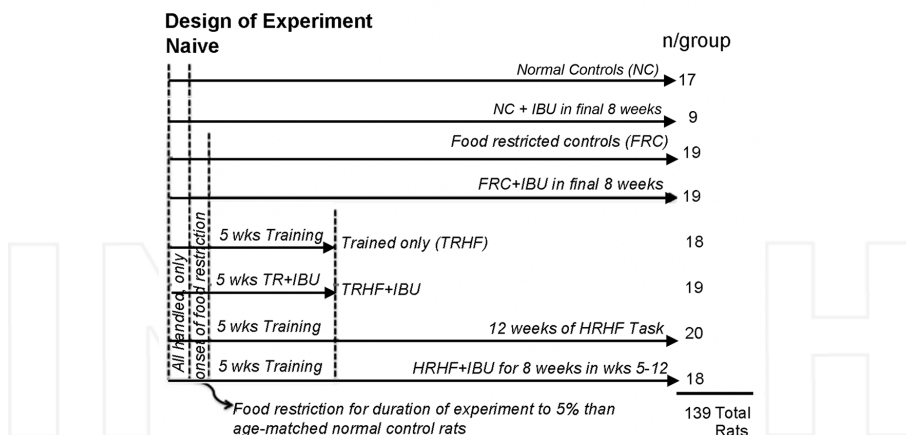

Figure 2. Experimental design. (A) Food restriction began after a 1-week period of daily handling. All rats but normal control (NC ± ibuprofen treatment) were food restricted to 5% less than weights of age-matched NC rats. NC and food-restricted control (FRC) rats rested until euthanasia at matched time points as HRHF rats. Trained and task rats underwent a 5-week training period (rats reached the HRHF level by last week of training). These trained-only rats (TRHF) were euthanized after training. Task rats performed a high-repetition high-force (HRHF) task for 12 weeks. NC+IBU and FRC+IBU rats received daily ibuprofen (IBU) treatment of 45 mg/kg of body weight in drinking water in the final 8 weeks, as did HRHF+IBU rats (arrow indicates the onset of ibuprofen treatment). TRHF+IBU rats received ibuprofen treatment prophylactically during training. The number of rats per group is shown at the far right.

5.1. Ibuprofen effectively reduced tissue inflammation induced by the HRHF task and voluntary motor abilities

Some mechanisms examined to date in our rat model include task-induced tissue injury, inflammation, and fibrosis, each of which contributed to declines in grip strength by producing discomfort or affecting biomechanical strength. Evidence of tissue injury was paralleled by inflammatory responses, such as increased pro-inflammatory cytokines in flexor digitorum muscles and tendons [30–32, 39], and increased macrophages in the median nerve at the level of the wrist (**Figure 3A, B**). Elevated levels of key pro-inflammatory cytokines, IL-1beta, and TNF-alpha were also observed in serum of rats that had performed a HRHF task for 12 weeks (12-week HRHF rats) (**Figure 3D, E**).

Treatment of rats performing a high-repetition high-force task with oral ibuprofen in weeks 5–12 of a 12-week task regimen significantly reduced macrophage numbers and inflammatory cytokines in tissues and serum (**Figure 3A, B, D**). Ibuprofen treatment also improved HRHF-induced declines in several voluntary work parameters, including reach rate, voluntary pulling force, and duration of voluntary performance (**Figure 4A, B**) [40, 41]. Similarly, the treatment of human subjects with ibuprofen before unaccustomed exercise improves muscle strength [42, 43]. The attenuation of voluntary reach abilities in HRHF+IBU rats in parallel with reduced numbers of macrophages in the median nerve (**Figure 3A**) [40] indicates that a task-induced neuralgia is contributing to voluntary motor declines seen in **Figure 4A and B**.

5.2. Ibuprofen treatment did not ameliorate HRHF-induced spinal cord sensitization or muscle hyperalgesia

However, reflexive grip strength was not rescued in 9- and 12-week HRHF+IBU rats (**Figure 4C**) [41]. This type of nocifensive motor behavior has been termed muscle hyperalgesia [44] and is a type of chronic pain. We postulate that ibuprofen did not rescue reflexive grip strength declines because it did not prevent inflammation-associated changes in the central nervous system. We stained cervical regions of the spinal cord for pro-inflammatory cytokine IL-1-beta levels using immunohistochemical methods and found that both untreated HRHF and HRHF+IBU animals expressed this cytokine in neurons and some glial cells at roughly the same frequency and intensity (**Figure 5A, B, D**). This was in sharp contrast to IL-1-beta immunoexpression in spinal cords of normal control rats, which showed an almost absence of IL-1-beta immunoexpression (**Figure 5C**). We postulate that ibuprofen, or other anti-inflammatory drug, would have to be provided earlier than week 4 prior to the onset of pain behaviors in order to be fully effective. Future studies need to consider these negative central nervous system changes to successfully treat chronic pain behaviors in subjects with WMSDs.

5.3. HRHF task-induced tissue fibrosis is effectively reduced by ibuprofen, indicative of an underlying inflammatory mechanism

Muscles undergo repetitive strain-induced fibrosis. Stauber and colleagues have shown that repeated muscle strains at fast velocities resulted in fibrotic myopathy with increased collagen content, collagen cross-links, and non-contractile tissues [45–48]. Factors and mechanisms of repetitive strain-induced fibrosis are still under investigation. They appear to involve transform-

ing growth factor beta-1 (TGFB-1) and connective tissue growth factor (CTGF), a key downstream mediator of TGFB-1's effects on matrix protein production [49–53]. Strong links between mechanical loading and increased TGFB-1 and CTGF protein levels in muscles and tendons *in vivo*, and in isolated fibroblasts and tenocytes, have been established [50, 52–55]. It is key to identify effective early or preventive treatments for such tissue fibrosis, as recovery from such tissue fibrosis is slow, even with complete cessation of strain or activity for up to 3 months [47].

CTGF production also appears to be regulated by pro-inflammatory cytokines, IL-1-beta, and TNF-alpha, which are also thought of as pro-fibrogenic cytokines [37, 56, 57]. Since we have observed that task-induced tissue inflammation precedes tissue fibrotic responses, including increased CTGF and collagen type 1 production [58–60], we next examined the effects of secondary ibuprofen treatment on fibrogenic processes in our rat model [40, 61]. In addition to successful reductions of tissue and serum inflammatory responses after ibuprofen treatment, we observed significant reductions in TGFB-1 and CTGF protein expression as well as collagen deposition in median nerves (**Figure 3A**) and flexor digitorum muscles of 6-week and 12-week HRHF+IBU rats (**Figure 6**) [40, 61]. These findings support an underlying inflammatory drive on at least some fibrogenic processes. This reduction in collagen deposition within and around tissue components of the upper extremity may also aid the return of function, such as the return of median nerve conduction velocity in median nerves of 12-week HRHF rats as shown in **Figure 3C**.

5.4. HRHF task-induced radiocarpal joint damage is ameliorated by ibuprofen treatment

Joint degeneration may occur for a number of reasons including joint trauma from increased repetition of joint loading, high impact joint loading, increased inflammatory processes (e.g., autoimmune), or pathological metabolic processes [62–64]. Radiocarpal and intercarpal joints of the wrist and hand, respectively, can show signs of increased incidence of hand osteoarthritis in individuals involved in intense (defined as long duration, high repetition, and/or high force) occupationally related physical activities [65–67]. A high incidence of radiographic of hand osteoarthritis has been identified in middle-aged female dentists and teachers [66, 67]. Several studies report that increasing radiographic severity of hand osteoarthritis is associated with reduced hand function and increased pain [66, 68, 69]. Therefore, the impact of hand osteoarthritis is considerable [68, 69].

After 12 weeks of performing the HRHF task, untreated task animals demonstrated evidence of joint inflammation (loss of proteoglycan staining as shown in **Figure 7B** as compared to controls in **Figure 7A**) [70]. This loss of proteoglycan staining in untreated 12-week HRHF rats is captured in the form of elevated Mankin histopathological scores (**Figure 7E**), a scoring system that also reflects a development of pannus and apoptotic cells in the joint cartilage. Each of these changes was indicative of task-induced joint degeneration. Serum biomarker testing revealed increased levels of a serum biomarker of collagen degradation, C1,2C (a marker of collagen type 1 and 2 degradation fragments produced by collagenase cleavage of type II collagen) in untreated 12-week HRHF rats [70]. Increased activated macrophages, cyclooxygenase immunopositive cells, and inflammatory cytokine levels were detected in the distal radius, ulna, and carpal bones (the latter shown in **Figure 7F**, **G**), supporting our hypothesis of an underlying inflammatory mechanism.
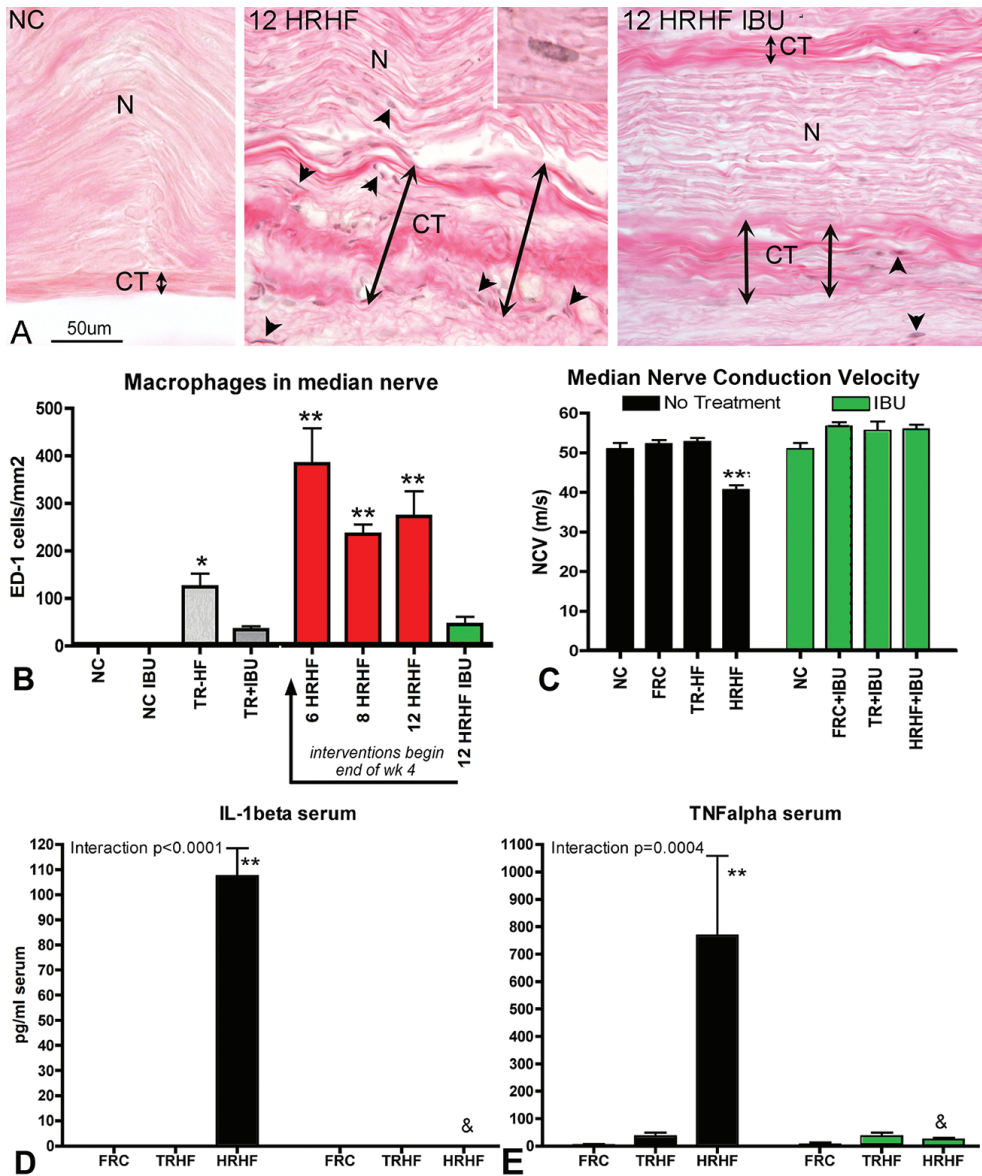
Figure 3. Median nerve inflammatory and fibrotic responses as well as systemic cytokine responses. (A) Photomicrographs showing increased activated macrophages in the median nerve of HRHF rats (detected immunohistochemically and denoted with arrowheads), and width of epineurial connective tissues (CT; (double arrows)) around the median nerve (N) at the wrist level. Eosin counterstain. (B) Mean number of activated macrophage in the median nerve decreased with ibuprofen treatment provided daily in task weeks 5–12. (C) Nerve conduction velocity (NCV) in meters/second (m/sec) declined in HRHF rats and was rescued by ibuprofen treatment that began after task week 4 (arrow) and that continued though task week 12. (D and E) IL-1-beta and TNF-alpha increased systemically (in serum) in untreated HRHF rats. These increases were ameliorated with 8 weeks of ibuprofen treatment. Symbols: $^{*}p < 0.05$ and $^{**}p < 0.01$, compared to NC or FRC rats; $^{\&}p < 0.05$, compared to untreated HRHF rats. Modified with permission from Jain et al. [40], and used by permission.
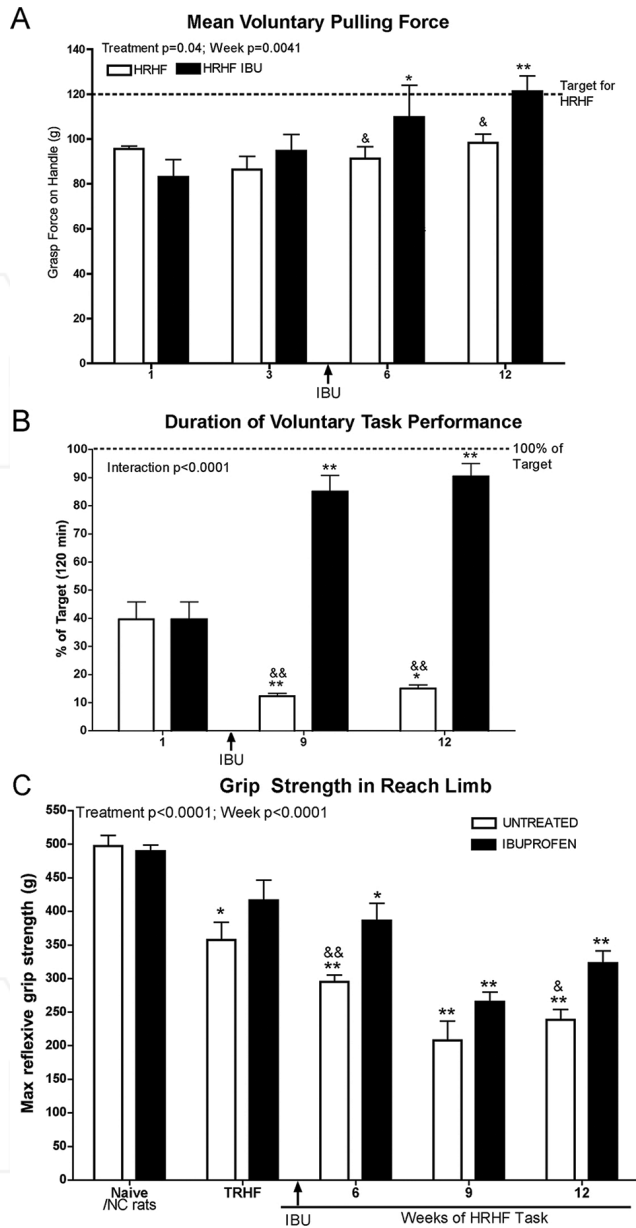
Figure 4. Voluntary and reflexive motor abilities. (A) Mean voluntary pulling force on the handle (percent of maximum pulling force) in grams. Across weeks of task performance, the mean voluntary pulling force was lower than target levels in untreated HRHF rats, yet met target levels in ibuprofen-treated rats (ibuprofen was provided in task weeks 5–12, with onset indicated by arrow). (B) Across the weeks, the duration of voluntary task performance decreased in untreated HRHF rats. By contrast, the duration was near target levels in HRHF+IBU rats in weeks 9 and 12. (C) Grip strength (maximum reflexive grip strength in grams) in the preferred reach limb decreased in both groups, compared to baseline naïve levels. Ibuprofen treatment only partially rescued this nocifensive motor behavior. $^*p < 0.05$ and $^{**}p < 0.01$, compared to week 1; $^&p < 0.05$ and $^&p < 0.01$, compared to target levels. Used by permission from Jain et al. [40] and Kietrys et al. [41].
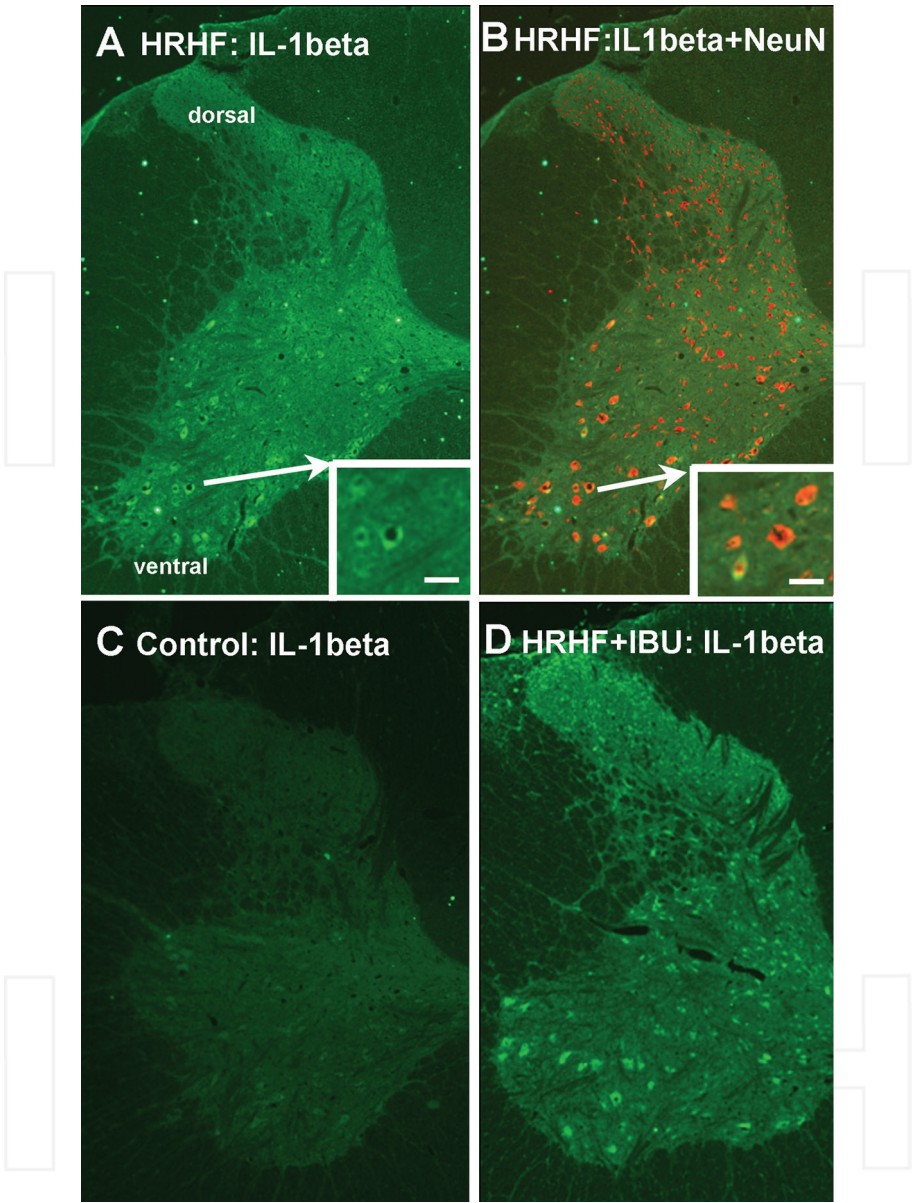
Figure 5. Inflammatory cytokine (IL-1-beta) immunoexpression was increased in neurons of spinal cords of both HRHF and HRHF+IBU rats, compared to NC rats, indicative of central sensitization (n = 4/group, images only shown). (A–D) IL-1-beta immunostained cells that are green in color were visible in spinal cord sections collected from the cervical region (since that region provides input to the median nerve innervating the hand and wrist). These cells were present in the intermediate and ventral horn regions of HRHF rats (A) but none were present in a control rats (C). The red color in panel is NeuN, a neuronal cell body marker. However, IL-1-beta immunostained cells were still visible in spinal cord sections of HRHF+IBU rats (D). Scale bar = 50 μm. Used by permission from Kietrys et al. [41].
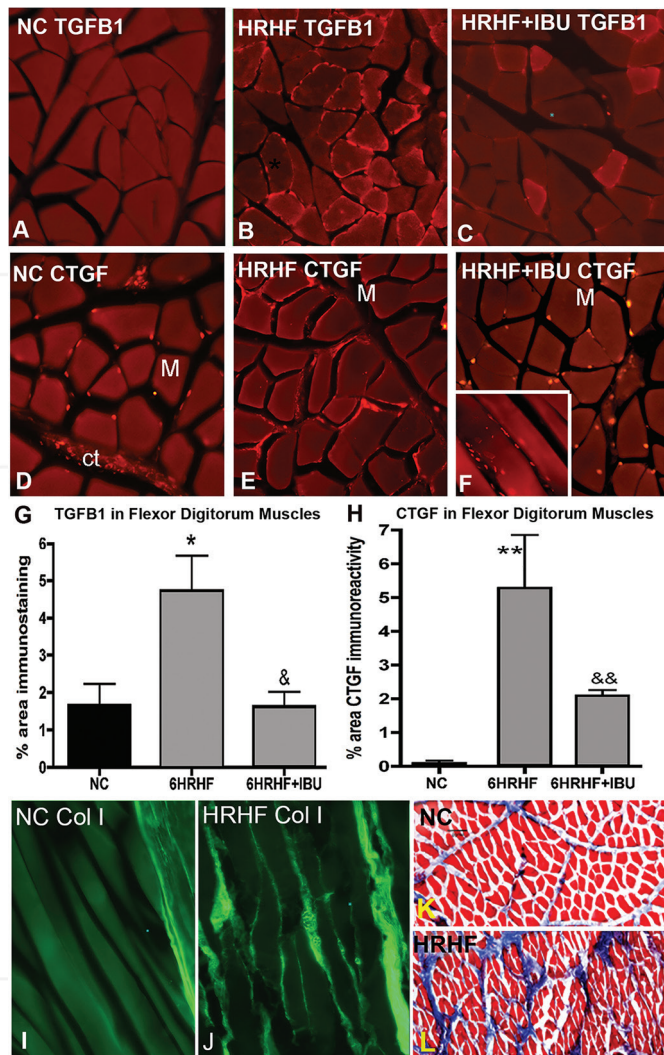
Figure 6. Fibrogenic protein levels (TGFB1, CTGF, and collagen type 1 (Col I)) were increased in forearm muscles of 6-week HRHF rats, increases that were reduced after a 2-week treatment with ibuprofen provided in task weeks 5 and 6. Cross sections of flexor digitorum muscle are shown. (A–C, G) TGFB1 staining was absent in muscles of normal control (NC) rats shown in panel A, high in muscles of untreated 6-week HRHF rats (visible as red staining at the edges of the myofibers in panel B), and reduced in muscles of 6-week HRHF rats treated with ibuprofen (panel C). (D–F, H) A small number of CTGF-immunostained cells (red in color) were present around myofibers in NC rats as shown in panel D, increased in muscles of untreated 6-week HRHF rats as shown in panel E, but reduced back to control levels in muscles of 6-week HRHF rats treated with ibuprofen as shown in panel F. (G&F) Quantification of percentage area of muscle with TGFB1 and CTGF staining. $^*p < 0.05$ and $^{**}p < 0.01$, compared to NC rats; $^{\&}p < 0.05$ and $^{\&}p < 0.01$, compared to untreated 6-week HRHF. Scale bars = 50 μm. (I, J) Collagen type 1 (Col I) immunostaining, green in color, is increased considerably between myofibers of 6-week HRHF rats compared to NC rats. These sections were cut longitudinally. (K,L) Another stain (a Masson's trichrome stain, which shows collagen as blue) also shows that collagen deposition is increased between myofibers of 6-week HRHF rats compared to NC rats. Used by permission from Abdelmagid et al. [60].

Eight weeks of ibuprofen administration reduced all of these changes, despite continued task performance (**Figure 7**). This latter finding indicates that the joint degenerative changes observed were a consequence of the inflammatory response induced by this high-repetition high-force task that was 12 weeks in duration. Each of these changes were attenuated by ibuprofen treatment, suggesting that such treatment is chondroprotective, at least during the early phases of cumulative loading-induced inflammation and degeneration in hand and wrist joints.
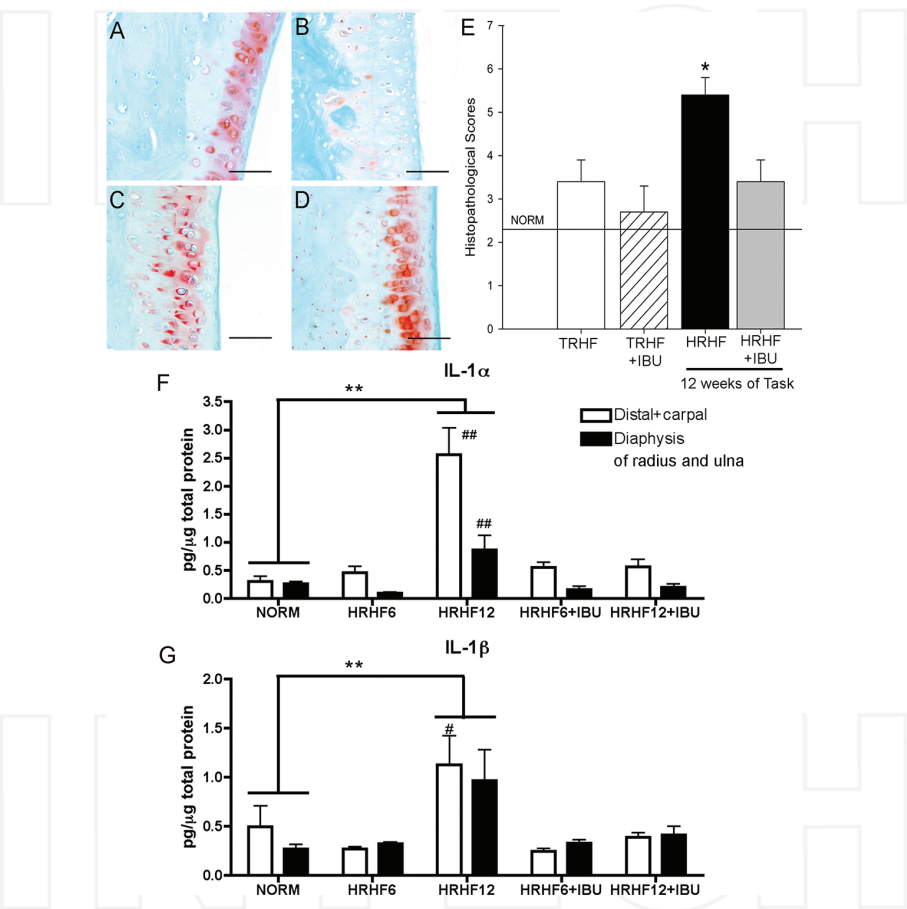

Figure 7. HRHF-induced degeneration of radiocarpal joint cartilage was attenuated by ibuprofen treatment. (A–D) Distal radii articular cartilage stained with safranin O and fast green from (A) untreated TRHF rat, (B) TRHF+IBU rat (trained controls receiving ibuprofen treatment prophylactically), (D) HRHF rats that performed the task for 12 weeks show dramatically reduced proteoglycan staining in the articular cartilage (red-pink safranin O staining), and (E) HRHF+IBU rats that performed the task for 12 weeks while receiving ibuprofen treatment (45 mg/kg body wt, daily, oral) in the last 8 weeks. (E) Histopathological Mankin scores for distal radius articular cartilage of the reach limb in TRHF, TR+IBU, HRHF, and HRHF+IBU rats. (F&G) Cytokine concentrations in wrist joint (distal radius, ulna, and carpal bones) and in diaphysis of the radius and ulna bones, tested using ELISA. Levels of (F) IL-1-alpha and (G) IL-1-beta are shown for each group. $^*p < 0.05$ and $^{**}p < 0.01$, compared to NC rats (terms NORM); $^{\ddagger}p < 0.05$ and $^{\ddagger\ddagger}p < 0.01$, compared to untreated 6-week HRHF. Modified with permission from Driban et al. [70], and used by permission.

5.5. Ibuprofen effectively ameliorated osteopenia by reducing task-induced cytokines and osteoclast activity in bones

Cyclical loading and high-force loads are known to affect bone quality [71–74]. However, only a few studies have examined changes occurring in upper extremity bones as a consequence of prolonged performance of occupational tasks. Bone scan studies of patients with upper extremity MSDs show increased blood flow and pooling (suggestive of inflammation) in affected bones, although the sensitivity and accuracy of the results were variable across studies [75–77]. We found that the performance of a HRHF task for 12 weeks reduced trabecular bone (**Figure 8A, B**) and cortical bone thinning in the radius and ulna in untreated HRHF rats (**Figure 8B**) [39, 40]. Bone levels of IL-1-beta, an inflammatory cytokine known to stimulate osteoclastogenesis and activity [78, 79], increased in involved distal forelimb bones (**Figure 8C**). This increase was matched by increased osteoclasts (**Figure 8C**) and increases in two serum biomarkers of bone degradation (Trap5b, band 5 tartrate-resistant acid phosphatase, and a biomarker of osteoclast activity and bone resorption, and CTX1, the C-terminal telopeptide of collagen type I cleaved by osteoclasts during bone resorption). Thus, a 12-week task at high-repetition high-force levels leads to a net loss of trabecular bone volume in the radius and ulna.
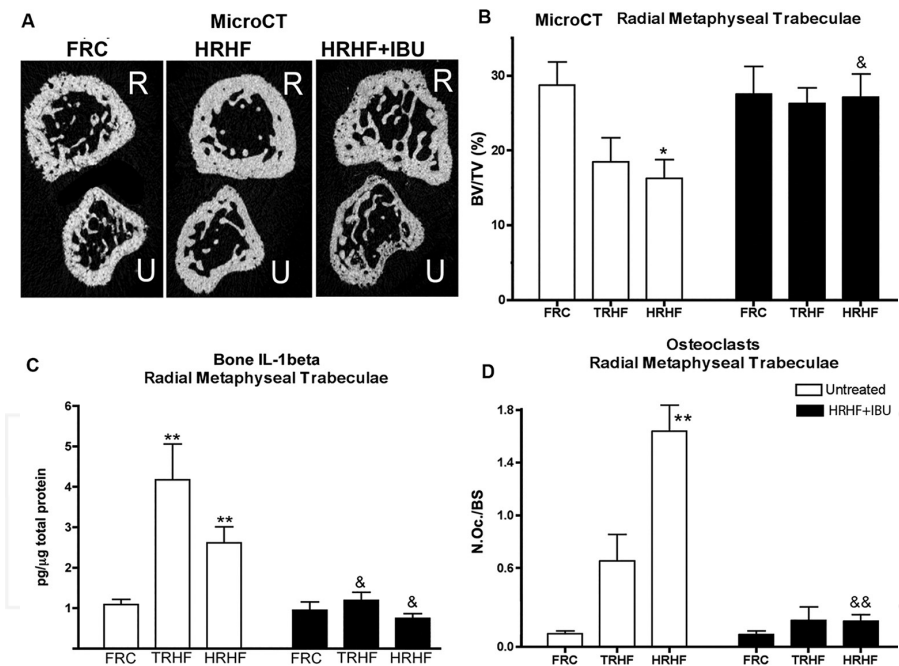

Figure 8. Microcomputed tomography (MicroCT), bone cytokines, and osteoclast numbers in distal radial trabecular region. (A) Representative transaxial microCT slices of the metaphysis of the radius and ulna (at 166 slices, 1.5 mm from the distal edge of their respective growth plate) from an FRC, 12-week HRHF, and 12-week HRHF+IBU rat. (B) MicroCT analysis of trabeculae of distal radius showing reduced trabecular bone volume (BV/TV) in HRHF rats that was rescued by ibuprofen treatment in task weeks 5–12. (C) IL-1-beta in forelimb bones (radius and ulna), tested using ELISA. $^{*}p < 0.05$ and $^{**}p < 0.01$, compared to FRC rats; $^{\&}p < 0.05$, compared to untreated HRHF rats. (D) Density of osteoclasts (N.Oc.), normalized to bone surface (BS), of distal radial metaphyseal trabeculae. Used by permission from Jain et al. [40].

Fortunately, systemic anti-inflammatory treatment with ibuprofen prevented these bone catabolic changes (**Figure 8**) [40, 70]. Eight weeks of continual ibuprofen treatment reduced bone inflammatory cytokine levels, and osteoclast numbers and activity, despite continued task performance. These results suggest that bone catabolism in the untreated HRHF rats was the result of increased inflammatory cytokines and their activating effects on osteoclasts. In summary, forearm bone osteopenia can be one consequence of prolonged high-intensity hand and wrist tasks. This increase in osteopenia and perhaps even fracture risk of workers performing this type of task is under-investigated in human and should be the focus of future studies.

A loss of bone mineral density has been reported in metacarpal bones and distal radius and ulna of patients with long-term carpal tunnel syndrome [80]. Surgical release treatment for carpal tunnel syndrome rescues this decline in distal forearm bone mineral density [81]. Those authors hypothesized that nerve-compression-induced muscle weakness led to bone loss as a consequence of reduced muscular loading on the bone [80], since the muscles involved in performing hand-grip actions produce forces on forearm bones [82, 83]. In our model, ibuprofen may be sparing bone volume by reducing osteoclastogenesis and activity as well as by reducing fibrotic nerve compression, thus sparing muscle activity and muscle-pulling forces on bones (refer to **Figure 3C** and **4A** again).

6. Caveats of ibuprofen use

Ibuprofen treatment is inexpensive and readily available over the counter. Yet, its use should be limited to short-term treatments (we have tested only up to 8 weeks). Ibuprofen medication may inhibit skeletal muscle hypertrophy and adaptation [42, 84–86], although a more recent study shows no effect of ibuprofen on muscle hypertrophy [43]. Long-term use of ibuprofen-related NSIADs could increase gastrointestinal bleeding, renal toxicity, risk of myocardial infarction, and hypertension [87, 88]. NSAIDs are also not always successful for long-term treatment of pain and dysfunction [16], similar to our results with reflexive grip strength.

7. New treatment directions

It is unlikely that a single drug will be effective in treating all WMSDs since their development is multi-factorial. Multipronged treatment should be developed that are individualized to the subject for complete reversal of WMSD-induced tissue inflammation/fibrosis/degeneration and recovery of function. **Figure 9** shows various points of interventional treatment, indicating that early treatment is needed to alter acute inflammatory responses, while chronic inflammatory responses are accompanied by several signs and symptoms of chronic pain and should be treated with secondary anti-inflammatory drugs such as ibuprofen or anti-tumor necrosis factor alpha drugs [89]. The latter drugs have yet to be tested in subjects with WMSDs, but have been tested in our animal model and show fair to strong efficacy [39, 61]. In subjects with chronic or persistent pain, negative neuroplasticity in the CNS, termed central

sensitization, may have occurred. Treatment options of such central sensitization should be explored carefully in future studies to reduce chronic pain. At the right side of this figure, we show the onset of fibrosis, which may compress and damage axons (such as in carpal tunnel syndrome), and tether tissues. We are currently exploring options of blocking fibrogenic-signaling pathways in our rat model.
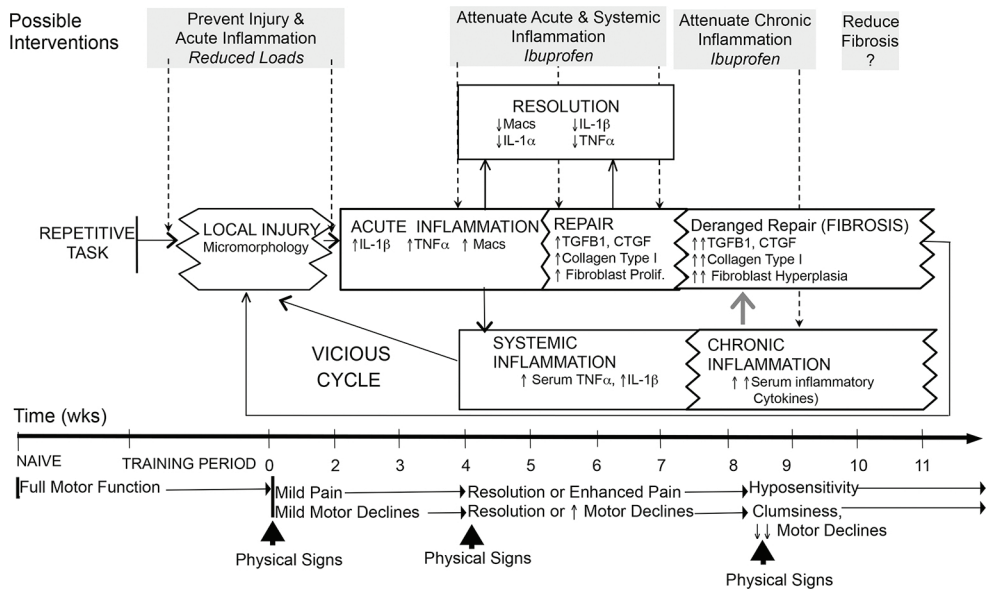

Figure 9. Summary of results and possible points of intervention indicated. Repetitive tasks can cause local injury and acute inflammation that could be prevented with reduced loads. Acute and chronic inflammation can be treated by prophylactic and secondary ibuprofen treatment at anti-inflammatory doses. Means to treat fibrosis are still under investigation as are most effective ways to rescue persistent sensorimotor declines. Abbreviations: CTGF = connective tissue growth factor; IL-1 = interleukin 1; Macs = macrophages; TNF = tumor necrosis factor; TGFB1 = transforming growth factor beta 1. Modified and used by permission from Barr and Barbe [89].

One new non-pharmaceutical direction may be modeled manual therapy. A recent review examined the effectiveness of exercise versus several types of mobilization methods for the treatment of carpal tunnel syndrome and concluded that there was only poor support [90]. However, two recent pilot studies examined massage therapy methods specifically and observed reduced symptoms of discomfort and increased strength post treatment in patients being treated for carpal tunnel syndrome [91, 92]. Another type of massage termed "sports massage' has been used to treat post-exertional muscle soreness, which is also known as delayed onset muscle soreness (DOMS). While the clinical utility of sports massage for DOMS is supported overall, a comprehensive review of the literature by Moraska in 2005 shows its effectiveness in some studies and a lack thereof in others [93]. Perhaps, this is because sports massage therapy treatment is typically short term. With regard to the use

of massage therapies for individuals with repetitive motion disorders, clinicians should be aware that these disorders are not acute in nature. Instead, repetitive motion disorders are the consequence of underlying tissue changes that take weeks to years. It is unlikely that a single, short-term treatment will be effective.

Because we could not identify any studies using manual therapies for WMSDs (other than carpal tunnel syndrome), we recently performed a study examining the effectiveness of modeled manual therapy (MMT) as a treatment for symptoms of discomfort, reduced grip strength, and increased tissue fibrosis occurring in forearms of rats performing a HRHF task for 12 weeks [33]. We began the MMT immediately post training to the high-force level, a time point when the rats began to display signs and symptoms consistent with WMSDs. Results were compared to untreated HRHF rats and to age-matched control rats. The MMT protocol included a mixture of manual therapy submodalities: gentle mobilization, skin rolling, and myofascial release (deep massage) of the forearm flexor compartment; joint mobilization of the wrist (gentle rotation and traction of the wrist); and stretching of the entire upper limb from the shoulder to the fingers. The therapy was provided 5 days per week for 12 weeks, while the animals performed the HRHF task for a food reward (as above, for 3 days/week, 2 h/day, in 30-min sessions). Compared to untreated HRHF rats, the HRHF rats receiving the MMT (called HRHF-MMT rats) showed significantly fewer behaviors suggestive of discomfort and had increased numbers of successful reaches. Grip strength had decreased significantly post training to the high-force levels, compared to the rats' naïve levels. However, the MMT protocol improved grip strength within 2 weeks of treatment, an improvement that continued through week 12 despite continued performance of the HRHF task by the HRHF-MMT rats. An examination of tissues post euthanasia showed decreased nerve and connective tissue fibrosis, and decreased collagen and TGF-B1 in the 12-week HRHF rats, compared to the untreated HRHF rats. These observations support further investigation of manual therapy as a preventative for repetitive motion disorders.

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