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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-
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 sensorimotor declines, as are inflammation-linked fibrotic and degenerative/degradative tissue 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 ± 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.](http://dx.doi.org/10.5772/66480)
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 immunoeexpression in spinal cords of normal control rats, which showed an almost absence of IL-1-beta immunoeexpression (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 down-
stream mediator of TGFB-1’s effects on matrix protein production [49–53]. Strong links be-
tween 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 sec-
ondary 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 osteoarthri-
tis 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 associ-
ated 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 com-
pared 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 mac-
rophages, cyclooxygenase immunopositive cells, and inflammatory cytokine levels were
detected in the distal radius, ulna, and carpal bones (the latter shown in Figure 7F, G), sup-
porting 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 through 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); *p < 0.05 and **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.

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.

Acknowledgements

Research reported in this publication was supported by the National Institutes of Health, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, under Award Numbers AR056019 and AT009350 to MFB.

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References

[1] Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646–56. Epub 2004/01/09. PubMed PMID: 14710506; PubMed Central PMCID: PMC2572542.

[2] Bureau of Labor Statistics. Nonfatal occupational injuries and illnesses requiring days away from work, 2011. http://www.bls.gov/news.release/osh2.nr0.htm News Release USDL-12-2204, November 8, 2012. 2012.

[3] HSE. The Health and Safety Executive Statistics 2010/11.http://www.hse.gov.uk/statistics/overall/hssh1011.pdf. 2011.

[4] Horton R. GBD 2010: understanding disease, injury, and risk. Lancet. 2012;380(9859):2053–4. Epub 2012/12/19. doi: 10.1016/S0140-6736(12)62133-3. PubMed PMID: 23245595.

[5] Punnett L, Wegman DH. Work-related musculoskeletal disorders: the epidemiologic evidence and the debate. J Electromyogr Kinesiol. 2004;14(1):13–23. Epub 2004/02/05. doi: 10.1016/j.jelekin.2003.09.015. PubMed PMID: 14759746.

[6] Hauret KG, Jones BH, Bullock SH, Canham-Chervak M, Canada S. Musculoskeletal injuries description of an under-recognized injury problem among military personnel. Am J Prev Med. 2010;38(1 Suppl):S61–70. Epub 2010/02/13. doi: 10.1016/j.amepre.2009.10.021. PubMed PMID: 20117601.

[7] Barbe MF, Gallagher S, Massicotte VS, Tytell M, Popoff SN, Barr-Gillespie AE. The interaction of force and repetition on musculoskeletal and neural tissue responses and sensorimotor behavior in a rat model of work-related musculoskeletal disorders. BMC Musculoskelet Disord. 2013;14(1):303. Epub 2013/10/26. doi: 10.1186/1471-2474-14-303. PubMed PMID: 24156755.

[8] Gallagher S, Heberger JR. Examining the interaction of force and repetition on musculoskeletal disorder risk: a systematic literature review. Hum Factors. 2013;55(1):108–24. Epub 2013/03/23. PubMed PMID: 23516797.

[9] Bureau of Labor Statistics. Prevention of work-related musculoskeletal disorders. http://www.bls.gov/news.release/pdf/osh2.pdf. 2014.

[10] Stephens AS, Stephens SR, Morrison NA. Internal control genes for quantitative RT-PCR expression analysis in mouse osteoblasts, osteoclasts and macrophages. BMC Research Notes. 2011;4:410. Epub 2011/10/15. doi: 10.1186/1756-0500-4-410. PubMed PMID: 21996334; PubMed Central PMCID: PMC3204251.

[11] World Health Organization. Workers’ health: global plan of action 2007. Available from: http://www.who.int/occupational_health/publications/global_plan/en/.

[12] Clarke J. Organizing the approach to musculoskeletal misuse syndrome. Nurse Pract. 2001;26(7 Pt 1):11–5, 9–25. PubMed PMID: 11494933.
[13] Lashuay N, Burgel B, Harrison R, Israel L, Chan J, Cusac C, et al. We spend our days working in pain: a report on workplace injuries in the garment industry. Final Report for the California Wellness Foundation, Oakland: Asian Immigrant Women Advocates Oakland, CA: Asian Immigrant Women Advocates; 2002 [cited 2016 October 1].

[14] Anthony MJ, Martin EG, Avery AM, Williams JM. Self care and health-seeking behavior of migrant farmworkers. J Immigr Minor Health. 2010;12(5):634–9. Epub 2009/04/25. doi: 10.1007/s10903-009-9252-9. PubMed PMID: 19390972.

[15] Beebe FA, Barkin RL, Barkin S. A clinical and pharmacologic review of skeletal muscle relaxants for musculoskeletal conditions. Am J Ther. 2005;12(2):151–71. Epub 2005/03/16. PubMed PMID: 15767833.

[16] Curatolo M, Bogduk N. Pharmacologic pain treatment of musculoskeletal disorders: current perspectives and future prospects. Clin J Pain. 2001;17(1):25–32. Epub 2001/04/06. PubMed PMID: 11289086.

[17] Krause N, Scherzer T, Rugulies R. Physical workload, work intensification, and prevalence of pain in low wage workers: results from a participatory research project with hotel room cleaners in Las Vegas. Am J Ind Med. 2005;48(5):326–37. Epub 2005/09/30. doi: 10.1002/ajim.20221. PubMed PMID: 16193494.

[18] Boeuf-Cazou O, Lapeyre-Mestre M, Niezborala M, Montastruc JL. Evolution of drug consumption in a sample of French workers since 1986: the 'Drugs and Work' study. Pharmacoepidemiol Drug Saf. 2009;18(4):335–43. doi: 10.1002/pds.1713. PubMed PMID: 19180587.

[19] Graham B. Nonsurgical treatment of carpal tunnel syndrome. J Hand Surg Am. 2009;34(3):531–4. Epub 2009/03/05. doi: 10.1016/j.jhsa.2009.01.010. PubMed PMID: 19258153.

[20] Jarvik JG, Comstock BA, Kliot M, Turner JA, Chan L, Heagerty PJ, et al. Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial. Lancet. 2009;374(9695):1074–81. Epub 2009/09/29. doi: 10.1016/S0140-6736(09)61517-8. PubMed PMID: 19782873.

[21] Martin BI, Levenson LM, Hollingworth W, Kliot M, Heagerty PJ, Turner JA, et al. Randomized clinical trial of surgery versus conservative therapy for carpal tunnel syndrome [ISRCTN84286481]. BMC Musculoskelet Disord. 2005;6:2. Epub 2005/01/20. doi: 10.1186/1471-2474-6-2. PubMed PMID: 15656907; PubMed Central PMCID: PMC546190.

[22] O’Connor D, Marshall S, Massy-Westropp N. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Cochrane Database Syst Rev. 2003;(1):CD003219. Epub 2003/01/22. doi: 10.1002/14651858.CD003219. PubMed PMID: 12535461.

[23] Shi Q, MacDermid JC. Is surgical intervention more effective than non-surgical treatment for carpal tunnel syndrome? A systematic review. J Orthop Surg Res. 2011;6:17. Epub 2011/04/12. doi: 10.1186/1749-799X-6-17. PubMed PMID: 21477381; PubMed Central PMCID: PMC3080334.
[24] Verdugo RJ, Salinas RA, Castillo JL, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. Cochrane Database Syst Rev. 2008;(4):CD001552. Epub 2008/10/10. doi: 10.1002/14651858.CD001552.pub2. PubMed PMID: 18843618.

[25] Rainsford KD. Ibuprofen: A Critical Bibliographic Review. Philadelphia, PA: Taylor and Francis Limited; 1999.

[26] Miller SB. Prostaglandins in health and disease: an overview. Semin Arthritis Rheum. 2006;36(1):37–49. doi: 10.1016/j.semarthrit.2006.03.005. PubMed PMID: 16887467.

[27] Byl NN. Learning-based animal models: task-specific focal hand dystonia. ILAR Journal/ National Research Council, Institute of Laboratory Animal Resources. 2007;48(4):411–31. Epub 2007/08/23. PubMed PMID: 17712226.

[28] Topp KS, Byl NN. Movement dysfunction following repetitive hand opening and closing: anatomical analysis in Owl monkeys. Mov Disord. 1999;14(2):295–306. Epub 1999/03/26. PubMed PMID: 10091624.

[29] Sommerich CM, Lavender SA, Buford JA, J JB, Korkmaz SV, Pease WS. Towards development of a nonhuman primate model of carpal tunnel syndrome: performance of a voluntary, repetitive pinching task induces median mononeuropathy in Macaca fascicularis. J Orthop Res. 2007;25(6):713–24. Epub 2007/02/24. doi: 10.1002/jor.20363. PubMed PMID: 17318891.

[30] Barbe MF, Elliott MB, Abdelmagid SM, Amin M, Popoff SN, Safadi FF, et al. Serum and tissue cytokines and chemokines increase with repetitive upper extremity tasks. J Orthop Res. 2008;26(10):1320–6. Epub 2008/05/09. doi: 10.1002/jor.20674. PubMed PMID: 18464247.

[31] Fisher PW, Zhao Y, Rico MC, Massicotte VS, Wade CK, Litvin J, et al. Increased CCN2, substance P and tissue fibrosis are associated with sensorimotor declines in a rat model of repetitive overuse injury. J Cell Commun Signal. 2015:1–18. doi: 10.1007/s12079-015-0263-0.

[32] Gao HG, Fisher PW, Lambi AG, Wade CK, Barr-Gillespie AE, Popoff SN, et al. Increased serum and musculotendinous fibrogenic proteins following persistent low-grade inflammation in a rat model of long-term upper extremity overuse. PLoS One. 2013;8(8):e71875. Epub 2013/09/10. doi: 10.1371/journal.pone.0071875. PubMed PMID: 24015193; PubMed Central PMCID: PMC3756034.

[33] Bove GM, Harris MY, Zhao H, Barbe MF. Manual therapy as an effective treatment for fibrosis in a rat model of upper extremity overuse injury. J Neurol Sci. 2016;361:168–80. doi: 10.1016/j.jns.2015.12.029. PubMed PMID: 26810536; PubMed Central PMCID: PMCPMC4729290.

[34] Barr AE, Barbe MF. Pathophysiological tissue changes associated with repetitive movement: a review of the evidence. Phys Ther. 2002;82(2):173–87. Epub 2002/02/22. PubMed PMID: 11856068; PubMed Central PMCID: PMC1550512.
[35] Barbe MF, Barr AE, Gorzelany I, Amin M, Gaughan JP, Safadi FF. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. J Orthop Res. 2003;21(1):167–76. Epub 2003/01/01. doi: 10.1016/S0736-0266(02)00086-4. PubMed PMID: 12507595; PubMed Central PMCID: PMC1560095.

[36] Clark BD, Al Shatti TA, Barr AE, Amin M, Barbe MF. Performance of a high-repetition, high-force task induces carpal tunnel syndrome in rats. J Orthop Sports PhysTher. 2004;34(5):244–53.

[37] Barbe MF, Gallagher S, Popoff SN. Serum biomarkers as predictors of stage of work-related musculoskeletal disorders. J Am Acad Orthop Surg. 2013;21(10):644–6. Epub 2013/10/03. doi: 10.5435/JAAOS-21-10-644. PubMed PMID: 24084439.

[38] Adams SS, Bough RG, Cliffe EE, Dickinson W, Lessel B, McCullough KF, et al. Some aspects of the pharmacology, metabolism, and toxicology of ibuprofen. I. Pharmacology and metabolism. Rheumatol Phys Med. 1970;10:Suppl 10:9–26. Epub 1970/01/01. PubMed PMID: 5524289.

[39] Rani S, Barbe MF, Barr AE, Litivn J. Role of TNF alpha and PLF in bone remodeling in a rat model of repetitive reaching and grasping. J Cell Physiol. 2010;225(1):152–67. Epub 2010/05/12. doi: 10.1002/jcp.22208. PubMed PMID: 20458732.

[40] Jain NX, Barr-Gillespie AE, Clark BD, Kietrys DM, Wade CK, Litvin J, et al. Bone loss from high repetitive high force loading is prevented by ibuprofen treatment. J Musculoskeletal Neuronal Interact. 2014;14(1):78–94. PubMed PMID: 24583543; PubMed Central PMCID: PMC4067254.

[41] Kietrys DM, Barr AE, Barbe MF. Exposure to repetitive tasks induces motor changes related to skill acquisition and inflammation in rats. J Mot Behav. 2011;43(6):465–76. Epub 2011/11/18. doi: 10.1080/00222895.2011.627897. PubMed PMID: 22087754.

[42] Trappe TA, Carroll CC, Dickinson JM, LeMoine JK, Haus JM, Sullivan BE, et al. Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. Am J Physiol Regul Integr Comp Physiol. 2011;300(3):R655–62. Epub 2010/12/17. doi: ajpregu.00611.2010 [pii] 10.1152/ajpregu.00611.2010. PubMed PMID: 21160058; PubMed Central PMCID: PMC3064281.

[43] Krentz JR, Quest B, Farthing JP, Quest DW, Chilibeck PD. The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. Appl Physiol Nutr Metab. 2008;33(3):470–5. Epub 2008/05/08. doi: h08-019 [pii] 10.1139/H08-019. PubMed PMID: 18461099.

[44] Schafers M, Sorkin LS, Sommer C. Intramuscular injection of tumor necrosis factor-alpha induces muscle hyperalgesia in rats. Pain. 2003;104(3):579–88. Epub 2003/08/21. doi: S0304395903001155 [pii]. PubMed PMID: 12927630.
[45] Stauber WT, Clarkson PM, Fritz VK, Evans WJ. Extracellular matrix disruption and pain after eccentric muscle action. J Appl Physiol. 1990;69(3):868–74. Epub 1990/09/01. PubMed PMID: 2123179.

[46] Stauber WT, Knack KK, Miller GR, Grimmett JG. Fibrosis and intercellular collagen connections from four weeks of muscle strains. Muscle Nerve. 1996;19(4):423–30. Epub 1996/04/01. doi: 10.1002/mus.880190402. PubMed PMID: 8622719.

[47] Stauber WT, Smith CA, Miller GR, Stauber FD. Recovery from 6 weeks of repeated strain injury to rat soleus muscles. Muscle Nerve. 2000;23(12):1819–25. Epub 2000/12/05. PubMed PMID: 11102904.

[48] Willems ME, Miller GR, Stauber FD, Stauber WT. Effects of repeated lengthening contractions on skeletal muscle adaptations in female rats. J Physiol Sci. 2010;60(2):143–50. Epub 2010/01/07. doi: 10.1007/s12576-009-0078-y. PubMed PMID: 20052570.

[49] Smith CA, Stauber F, Waters C, Alway SE, Stauber WT. Transforming growth factor-beta following skeletal muscle strain injury in rats. J Appl Physiol. 2007;102(2):755–61. Epub 2006/10/28. doi: 10.1152/japplphysiol.01503.2005. PubMed PMID: 17068209.

[50] Nakama LH, King KB, Abrahamsson S, Rempel DM. VEGF, VEGFR-1, and CTGF cell densities in tendon are increased with cyclical loading: An in vivo tendinopathy model. J Orthop Res. 2006;24(3):393–400. Epub 2006/02/16. doi: 10.1002/jor.20053. PubMed PMID: 16479573.

[51] Shen W, Li Y, Zhu J, Schwendener R, Huard J. Interaction between macrophages, TGF-beta1, and the COX-2 pathway during the inflammatory phase of skeletal muscle healing after injury. J Cell Physiol. 2008;214(2):405–12. Epub 2007/07/28. doi: 10.1002/jcp.21212. PubMed PMID: 17657727.

[52] Garrett Q, Khaw PT, Blalock TD, Schultz GS, Grotendorst GR, Daniels JT. Involvement of CTGF in TGF-beta1-stimulation of myofibroblast differentiation and collagen matrix contraction in the presence of mechanical stress. Invest Ophthalmol Vis Sci. 2004;45(4):1109–16. Epub 2004/03/24. PubMed PMID: 15037576.

[53] Heinemeier KM, Olesen JL, Haddad F, Langberg H, Kjaer M, Baldwin KM, et al. Expression of collagen and related growth factors in rat tendon and skeletal muscle in response to specific contraction types. J Physiol. 2007;582(Pt 3):1303–16. Epub 2007/06/02. doi: jphysiol.2007.127639 [pii] 10.1113/jphysiol.2007.127639. PubMed PMID: 17540706; PubMed Central PMCID: PMC2075262.

[54] Daniels JT, Schultz GS, Blalock TD, Garrett Q, Grotendorst GR, Dean NM, et al. Mediation of transforming growth factor-beta(1)-stimulated matrix contraction by fibroblasts: a role for connective tissue growth factor in contractile scarring. Am J Pathol. 2003;163(5):2043–52. PubMed PMID: 14578203; PubMed Central PMCID: PMC1892432.
[55] Guo F, Carter DE, Leask A. Mechanical tension increases CCN2/CTGF expression and proliferation in gingival fibroblasts via a TGFbeta-dependent mechanism. PLoS One. 2011;6(5):e19756. Epub 2011/05/26. doi: 10.1371/journal.pone.0019756 PONE-D-11-01727 [pii]. PubMed PMID: 21611193; PubMed Central PMCID: PMC3096639.

[56] Yu F, Chou CW, Chen CC. TNF-alpha suppressed TGF-beta-induced CTGF expression by switching the binding preference of p300 from Smad4 to p65. Cell Signal. 2009;21(6):867–72. Epub 2009/04/23. PubMed PMID: 19385047.

[57] Beddy D, Mulsoj J, Watson RW, Fitzpatrick JM, O’Connell PR. Expression and regulation of connective tissue growth factor by transforming growth factor beta and tumour necrosis factor alpha in fibroblasts isolated from strictures in patients with Crohn’s disease. Br J Surg. 2006;93(10):1290–6. Epub 2006/07/14. doi: 10.1002/bjs.5431. PubMed PMID: 16838391.

[58] Rani S, Barbe MF, Barr AE, Litvin J. Periostin-like-factor and Periostin in an animal model of work-related musculoskeletal disorder. Bone. 2009;44(3):502–12. Epub 2008/12/20. doi: 10.1016/j.bone.2008.11.012. PubMed PMID: 19095091.

[59] Clark BD, Barr AE, Safadi FF, Beitman L, Al-Shatti T, Amin M, et al. Median nerve trauma in a rat model of work-related musculoskeletal disorder. J Neurotrauma. 2003;20(7):681–95. Epub 2003/08/12. doi: 10.1089/089771503322144590. PubMed PMID: 12908929; PubMed Central PMCID: PMC1550513.

[60] Fedorczyk JM, Barr AE, Rani S, Gao HG, Amin M, Amin S, et al. Exposure-dependent increases in IL-1beta, substance P, CTGF, and tendinosis in flexor digitorum tendons with upper extremity repetitive strain injury. J Orthop Res. 2010;28(3):298–307. Epub 2009/09/11. doi: 10.1002/jor.20984. PubMed PMID: 19743505; PubMed Central PMCID: PMC2807907.

[61] Abdelmagid SM, Barr AE, Rico M, Amin M, Litvin J, Popoff SN, et al. Performance of repetitive tasks induces decreased grip strength and increased fibrogenic proteins in skeletal muscle: role of force and inflammation. PLoS One. 2012;7(5):e38359. Epub 2012/06/08. doi: 10.1371/journal.pone.0038359. PubMed PMID: 22675458; PubMed Central PMCID: PMC3364991.

[62] Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am. 2008;34(3):531–59. Epub 2008/08/09. doi: S0889-857X(08)00045-8 [pii] 10.1016/j.rdc.2008.05.011. PubMed PMID: 18687271.

[63] Calfee RP, Leventhal EL, Wilkerson J, Moore DC, Akelman E, Crisco JJ. Simulated radioscapholunate fusion alters carpal kinematics while preserving dart thrower’s motion. J Hand Surg Am. 2008;33(4):503–10. Epub 2008/04/15. doi: S0363-5023(07)01104-5 [pii] 10.1016/j.jhsa.2007.12.013. PubMed PMID: 18406953.

[64] Martin JA, Buckwalter JA. Post-traumatic osteoarthritis: the role of stress induced chondrocyte damage. Biorheology. 2006;43(3-4):517–21. Epub 2006/08/17. PubMed PMID: 16912423.
[65] Bernard B. Musculoskeletal disorders and workplace factors. NIOSH Report 97–141 Cincinatti (OH): National Institute for Occupational Safety and Health 1997.

[66] Solovieva S, Vehmas T, Riihimaki H, Luoma K, Leino-Arjas P. Hand use and patterns of joint involvement in osteoarthritis. A comparison of female dentists and teachers. Rheumatology (Oxford). 2005;44(4):521–8. Epub 2005/02/25. doi: keh534 [pii] 10.1093/rheumatology/keh534. PubMed PMID: 15728421.

[67] Ding H, Solovieva S, Vehmas T, Takala EP, Leino-Arjas P. Hand osteoarthritis and pinch grip strength among middle-aged female dentists and teachers. Scand J Rheumatol. 2010;39(1):84–7. Epub 2010/02/06. doi: 10.3109/03009740903201834. PubMed PMID: 20132076.

[68] Dominick KL, Jordan JM, Renner JB, Kraus VB. Relationship of radiographic and clinical variables to pinch and grip strength among individuals with osteoarthritis. Arthritis Rheum. 2005;52(3):1424–30. Epub 2005/05/10. doi: 10.1002/art.21035. PubMed PMID: 15880347.

[69] Spies-Dorgelo MN, van der Windt DA, van der Horst HE, Prins AP, Stalman WA. Hand and wrist problems in general practice—patient characteristics and factors related to symptom severity. Rheumatology (Oxford). 2007;46(11):1723–8. Epub 2007/10/17. doi: kem253 [pii] 10.1093/rheumatology/kem253. PubMed PMID: 17938132.

[70] Driban JB, Barr AE, Amin M, Sitler MR, Barbe MF. Joint inflammation and early degeneration induced by high-force reaching are attenuated by ibuprofen in an animal model of work-related musculoskeletal disorder. J Biomed Biotechnol. 2011;2011:691412. Epub 2011/03/16. doi: 10.1155/2011/691412. PubMed PMID: 21403884; PubMed Central PMCID: PMC3051200.

[71] Rubin C, Turner AS, Muller R, Mittra E, McLeod K, Lin W, et al. Quantity and quality of trabecular bone in the femur are enhanced by a strongly anabolic, noninvasive mechanical intervention. J Bone Miner Res. 2002;17(2):349–57. Epub 2002/01/29. doi: 10.1359/jbmr.2002.17.2.349. PubMed PMID: 11811566.

[72] Gross TS, Srinivasan S. Building bone mass through exercise: could less be more? Br J Sports Med. 2006;40(1):2–3; discussion 2–3. Epub 2005/12/24. doi: 10.1136/bjsm.2004.016972. PubMed PMID: 16371481; PubMed Central PMCID: PMC1435732.

[73] Srinivasan S, Weimer DA, Agans SC, Bain SD, Gross TS. Low-magnitude mechanical loading becomes osteogenic when rest is inserted between each load cycle. J Bone Miner Res. 2002;17(9):1613–20. Epub 2002/09/05. doi: 10.1359/jbmr.2002.17.9.1613. PubMed PMID: 12211431; PubMed Central PMCID: PMC1435731.

[74] Bourrin S, Genty C, Palle S, Gharib C, Alexandre C. Adverse effects of strenuous exercise: a densitometric and histomorphometric study in the rat. J Appl Physiol. 1994;76(5):1999–2005. Epub 1994/05/01. PubMed PMID: 8063662.

[75] Amorim BJ, Etchebehere EC, Dalla Torre G, Lima Mdac, Santos Ade O, Ramos CD, et al. Low sensitivity of three-phase bone scintigraphy for the diagnosis of repetitive strain injury. Sao Paulo Med J. 2006;124(3):145–9. Epub 2006/11/23. PubMed PMID: 17119691.
[76] Al-Nahhas AM, Jawad AS, McCready VR, Kedar R. Detection of increased blood flow to the affected arm in repetitive strain injury with radionuclide and Doppler ultrasound studies. A case report. Clin Nucl Med. 1995;20(7):615–8. Epub 1995/07/01. PubMed PMID: 7554665.

[77] Al-Nahhas AM, Jawad AS, Norman A, McCready VR. 99Tcm-MDP blood-pool phase in the assessment of repetitive strain injury. Nucl Med Commun. 1997;18(10):927–31. Epub 1997/12/11. PubMed PMID: 9392793.

[78] Kulkarni RN, Bakker AD, Everts V, Klein-Nulend J. Mechanical loading prevents the stimulating effect of IL-1beta on osteocyte-modulated osteoclastogenesis. Biochem Biophys Res Commun. 2012;420(1):11–6. Epub 2012/03/07. doi: 10.1016/j.bbrc.2012.02.099. PubMed PMID: 22390927.

[79] Nanes MS. Tumor necrosis factor-alpha: molecular and cellular mechanisms in skeletal pathology. Gene. 2003;321:1–15. Epub 2003/11/26. PubMed PMID: 14636987.

[80] Erselcan T, Topalkara K, Nacitarhan V, Akyuz A, Dogan D. Carpal tunnel syndrome leads to significant bone loss in metacarpal bones. J Bone Miner Metab. 2001;19(5):317–20. Epub 2001/08/11. doi: 10.1007/s0077410190317. PubMed PMID: 11498735.

[81] Schorn D, Hoskinson J, Dickson RA. Bone density and the carpal tunnel syndrome. Hand. 1978;10(2):184–6. Epub 1978/06/01. PubMed PMID: 711001.

[82] Hasegawa Y, Schneider P, Reiners C. Age, sex, and grip strength determine architectural bone parameters assessed by peripheral quantitative computed tomography (pQCT) at the human radius. J Biomech. 2001;34(4):497–503. Epub 2001/03/27. PubMed PMID: 11266673.

[83] Desrosiers J, Hebert R, Bravo G, Rochette A. Age-related changes in upper extremity performance of elderly people: a longitudinal study. Exp Gerontol. 1999;34(3):393–405. Epub 1999/08/05. PubMed PMID: 10433393.

[84] Machida M, Takemasa T. Ibuprofen administration during endurance training cancels running-distance-dependent adaptations of skeletal muscle in mice. J Physiol Pharmacol. 2010;61(5):559–63. Epub 2010/11/18. PubMed PMID: 21081799.

[85] Soltow QA, Betters JL, Sellman JE, Lira VA, Long JH, Criswell DS. Ibuprofen inhibits skeletal muscle hypertrophy in rats. Med Sci Sports Exerc. 2006;38(5):840–6. Epub 2006/05/05. doi: 10.1249/01.mss.0000218142.98704.66. 00005768-200605000-00006 [pii]. PubMed PMID: 16672835.

[86] Ziltener JL, Leal S, Fournier PE. Non-steroidal anti-inflammatory drugs for athletes: an update. Ann Phys Rehab Med. 2010;53(4):278–82. 82–8. Epub 2010/04/07. doi: S1877-0657(10)00057-6 [pii]. 10.1016/j.rehab.2010.03.001. PubMed PMID: 20363203.

[87] Moore, R.A., S. Derry, and H.J. McQuay, *Cyclo-oxygenase-2 selective inhibitors and non-steroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk*. BMC Musculoskeletal Disord, 2007. 8: p. 73.
[88] Al-Saeed, A., *Gastrointestinal and Cardiovascular Risk of Nonsteroidal Anti-inflammatory Drugs*. Oman Med J, 2011. 26(6): p. 385–91.

[89] Barr, A.E. and M.F. Barbe, Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders. Journal of electromyography and kinesiology: official journal of the International Society of Electrophysiological Kinesiology, 2004. 14(1): p. 77–85.

[90] Page MJ, O'Connor D, Pitt V, Massy-Westropp N. Exercise and mobilisation interventions for carpal tunnel syndrome. Cochrane Database Syst Rev. 2012;6:Cd009899. Epub 2012/06/15. doi: 10.1002/14651858.cd009899. PubMed PMID: 22696387.

[91] Elliott R, Burkett B. Massage therapy as an effective treatment for carpal tunnel syndrome. J Bodyw Mov Ther. 2013;17(3):332–8. Epub 2013/06/19. doi: 10.1016/j.jbmt.2012.12.003. PubMed PMID: 23768278.

[92] Moraska A, Chandler C, Edmiston-Schaetzel A, Franklin G, Calenda EL, Enebo B. Comparison of a targeted and general massage protocol on strength, function, and symptoms associated with carpal tunnel syndrome: a randomized pilot study. J Altern Complement Med. 2008;14(3):259–67. Epub 2008/03/29. doi: 10.1089/acm.2007.0647. PubMed PMID: 18370581.

[93] Moraska A. Sports massage. A comprehensive review. J Sports Med Phys Fitness. 2005;45(3):370–80. Epub 2005/10/19. PubMed PMID: 16230990.
