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Occupational Activities: Factors That Tip the Balance From Bone Accrual to Bone Loss

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BARBE, M.F. and S.N. POPOFF. Occupational activities: factors that tip the balance from bone accrual to bone loss. *Exerc. Sport Sci. Rev.*, Vol. 48, No. 2, pp. 59–66, 2020. *It is commonly assumed that beneficial adaptations in bone occur with vigorous exercise, yet any adaptive re/modeling in bone undergoing persistent overloading can be counteracted by superimposed inflammatory, compressive, and tensile loading–induced damage responses above thresholds of tissue fatigue failure and repair. This leads to a tenuous balance between achieving bone accrual and loss.* **Key Words:** repetitive overuse injury, repetitive motion injury, bone, anabolism, catabolism, work related

Key Points

- Responses in bone are complex and multifactorial. Yet unclear are load exposure thresholds and mechanisms that lead to pathological bone responses with persistent muscle contraction overloading of bone.
- It is commonly assumed that bone mass increases with all types of vigorous physical activity, yet persistent excessive loading with either exercise or occupational tasks can lead to diminishing returns in bone mass or quality and even induce microcracks or stress fractures.
- Repetitive overloading induces systemic and local inflammatory responses that can stimulate bone adaptation, repair, resorption, or further injury, based on superimposed processes in all involved tissues.
- Applied loads typically suppress sclerostin production, which releases the break on Wnt signaling and allows for bone formation; however, loading-induced matrix microdamage in which osteocyte apoptosis occurs enhances the release of both receptor activator of nuclear factor kappa-B ligand (RANKL) and sclerostin, changes that promote bone catabolism.

INTRODUCTION

In general, physical activity is considered to be beneficial for bone health because these activities can increase bone mass or help prevent bone loss typically seen with aging or estrogen deficiency. However, there is a point at which prolonged high-demand activities can tip the balance and induce adverse bone outcomes. It is well accepted that osteocytes function as the primary mechanosensing cells in bone and can respond to mechanical stimuli through molecular signals that can regulate osteoblastic bone formation and osteoclastic bone resorption (1). It is the balance between the opposing functions of osteoblasts and osteoclasts, which also are capable of regulating one another, that determines whether the net effect of mechanical loading results in bone accrual (anabolic effect), bone loss (catabolic effect), or maintenance of preexisting bone mass.

A key question to ask is, "What factors influence the point at which the interaction of repetition, force, and duration shifts from driving a net response of bone formation to bone resorption during muscle contraction–induced loading of bone" (Fig. 1). There are a multitude of factors that can influence the response of bone to mechanical loading, including, but not limited to, sex, age, genetic and epigenetic traits, hormonal status, serum mineral balance, nutritional status/diet, smoking status, emotional status (*e.g.*, stress/anxiety), and the presence of comorbidities that can affect bone health (*e.g.*, hypertension, obesity, hypercholesterolemia, diabetes) (Table) (2–4). Even when some factors are controlled, it is difficult to predict which factor or group of factors will prevail given their interwoven

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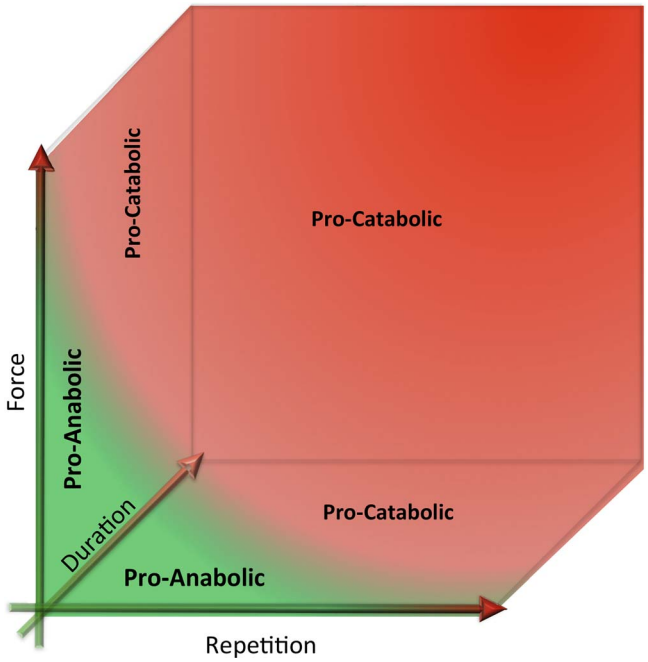

Figure 1. Schematic demonstrating that interactions of force, repetition, and duration of bone loading can elicit a pro-anabolic (bone accrual) response up to a point at which the combination of these factors exceeds a threshold (the transition region between the green and red zones), resulting in a net catabolic response due to tissue fatigue failure and damage (microcracks, osteocyte apoptosis). The point at which the threshold is crossed varies from one individual to another, and the factors that influence its location (*e.g.*, age, sex, genetic background) should be considered in future studies. The figure was created in consultation with Susan Fecho, M.F.A., Barton College.

complexity. Furthermore, the contributions of various stimuli generated by muscle on bones are still under investigation (5,6).

Because the responses of bone to exercise-related physical activity have been reviewed extensively (3,7–12), the focus of this contribution will primarily be on the less studied responses of bone to occupational-related physical activity. Many scientific questions remain to be answered to determine limits of high-demand occupational-related physical activity that would avoid bone catabolism and that would inform treatments and preventative approaches.

Physical Activities: Exercise Versus Occupational Tasks

Exercise is the deliberate performance of physical activity with the intent to improve performance/health/fitness. It is a subcomponent of physical activity. Because muscle and bone are biomechanically linked, most types of physical activities are considered beneficial to bone mass or quality, whether sports, planned exercise, or household work (6,12–14). It is commonly assumed that bone mass and quality increase with vigorous exercise and decrease as a result of unloading or reduced activity. Several studies show evidence of site-specific correlations between muscle activity in the form of grip strength and bone mineral density (BMD) in the radius of both nonathletes and athletes (15,16). Yet, there also are studies showing that increasing weight-bearing loads and muscle loading exercise to excessive levels is associated with diminishing returns in bone mass and quality and can even lead to increased stress fractures (7,9,17).

Unlike exercise, occupational-related physical activities usually provide no cardiovascular benefits (18) and may even promote myocardial infarctions in men with low levels of leisure time physical activity (19). Occupational-related physical activity involves repeated or sustained exertions of the body while often in biomechanically awkward postures. They include occupational computer work, hand tool use, and intense practice and playing of muscle instruments, in which there is prolonged positioning of the neck and shoulders in one position (20–23) or prolonged and sustained gripping and redundant movement of the thumb and digits (21,23–26). Occupational-related physical activity also includes manual material handling tasks that require lifting/lowering, pushing/pulling, and holding/carrying loads (27,28). Work-related musculoskeletal disorders (MSDs) encompass rotator cuff tears, tendinitis, arthritis, carpal tunnel syndrome, and more (25,29–31). These injuries are precipitated or aggravated by high repetitiveness, prolonged muscular exertions (particularly forceful exertions), chronic exposure to vibration of high intensity, or sustained awkward postures (25,32,33). Risk factors also include duration of exposure, female sex, aging, genetic traits (*e.g.*, interleukin-1 [IL-1] gene polymorphisms), smoking status, low serum 25-OH vitamin D levels, and diabetes (4,22,29,34). The interaction of cumulative exposure to multiple mechanical factors also needs to be considered as an additional risk factor (Fig. 1), as do other aspects of a particular occupation (32,35,36).

Neck and Shoulder Responses to Occupational Related Physical Activity

MSDs involving the shoulder accounted for 14.9% of all work-related MSDs in the United States in 2016, with heavy tractor-trailer truck drivers and laborers/material movers having a greater proportion of injuries affecting the shoulder than other occupations (37). Risk factors included frequent manual handling of loads, high-force highly repetitive work, working above shoulder level or other awkward postures and vibration (35,38), task duration (22), and female sex (39). Continuous low-intensity muscle contractions also increase the prevalence of neck-shoulder complaints and syndromes, including acromioclavicular syndrome (20,33,40). Miners that use vibration tools show increased frequency of radiologically detected shoulder lesions (40.7% of 152 miners) and lesions that included degenerative bone changes (34.5%), primarily in the acromioclavicular joint (17.8%) (41).

Forelimb and Hand Responses to Occupational Related Physical Activity

Although MSDs involving the arm and hand account for only 5.1% of all work-related MSDs (37), disorders of the hand

TABLE. Factors that favor bone anabolic versus catabolic responses

Pro-Anabolism (Accrual)	Pro-Catabolism (Loss)
Sex (male > female)	Sex (female > male)
Young adult	Aging
	Microcracks and osteocyte apoptosis
Decreased sclerostin–increased osteoblast activity	Increased sclerostin–decreased osteoblast activity
Decreased RANKL–increased osteoblast activity	Increased RANKL–decreased osteoblast activity
Somatosensory innervation	Nerve injury/compression
βAR antagonists	Increased sympathetic activity/βAR agonists
	Sustained inflammation — local and systemic
	Stress/anxiety

RANKL, receptor activator of nuclear factor kappa-B ligand.

and wrist constitute 40% and 13%, respectively, of such cases (42). Risk factors for wrist and hand MSDs include repetitive pushing, hand force, combined exposure to both force and repetition, sustained gripping (*e.g.*, computer or hand tool use), repetitive redundant movement of the thumb and digits (*e.g.*, typing or texting), sustained or repeated static loading of the weight of an instrument or tool, and use of vibrating tools (24–26,41,43). Continuous movement of a joint into end of range, for example, with repeated hyperextension of metacarpalphalageal joints, may be another causative factor due to enhanced inflammation in joint and tendon tissues (43,44). Individuals with prolonged heavy or one-sided hand workloads, or increased high-impact "jolting" of the hand show increased incidence of hand osteoarthritis, with higher incidence in females (29,30,45–47).

Carpal tunnel syndrome is a condition of median nerve compression that frequently presents in working aged adults, particularly in association with prolonged and highly repetitive flexion and extension of the wrist, especially when combined with forceful gripping (48). Patients with this syndrome show decreased areal BMD in distal forearm bones (*i.e.*, radius and ulna) and reduced bone in hand phalanges, assayed using quantitative ultrasound measurements (amplitude-dependent speed of sound, m s^{-1}) (49,50).

A Clinically Relevant Animal Model of Occupational Work

To explore underlying mechanisms of bone changes occurring with occupational tasks, we developed an operant and clinically relevant rat model of work-related MSDs. Rats are taught a reaching and lever bar grasping and pulling task (36,51–53). For this, they reach forward using their whole forearm into a shoulder-height portal to pull isometrically on a lever bar located outside the chamber at learned and defined reach rates ranging from two to four reaches min^{-1} and target forces of 15% to 55% of the rats' maximum voluntary pulling force (Fig. 2; see Video, Supplemental Digital Content 1 for demonstration, http://links.lww.com/ESSR/A52).

In this model, different osteogenic responses were seen with different force loads and repetition rates. Young adult rats performing the lever bar pulling task at the lowest level of demand, that is, a low-force low-repetition task for 12 wk (an LFLR task; defined as 15% maximum voluntary pulling force, two reaches min^{-1}, *i.e.*, 240 cycles d^{-1}, for 3 d wk^{-1}, which for 12 wk equals 8640 cycles total), show no changes in trabecular bone volume and no significant osteoblast or osteoclast responses compared with control rats (36). Yet, rats performing a low-force high-repetition task for 12 to 18 wk (an LFHR task; again 15% maximum voluntary force, yet now at 4 reaches min^{-1}, *i.e.*, 480 cycles d^{-1}, for 3 d wk^{-1}, which is 17,280 to 25,920 cycles total for 12 and 18 wk, respectively) show net adaptive bone changes, including greater increases in osteoblasts than osteoclasts and increased trabecular bone volume and formation in distal radial metaphyses (Figs. 3A, B) (36,51). The latter results are consistent with human and animal studies reporting bone anabolism in response to high-impact exercise and moderate loading levels (8,10–12,17).

In contrast, rats performing a high-force high-repetition task for 12 and 18 wk (an HFHR task; now at 55% maximum voluntary force, yet still 4 reaches min^{-1}, for 3 d wk^{-1}, which is 17,280 to 25,920 cycles total for 12 and 18 wk, respectively) show net bone catabolism, with significant increases in osteoclast numbers, significant increases in several inflammatory

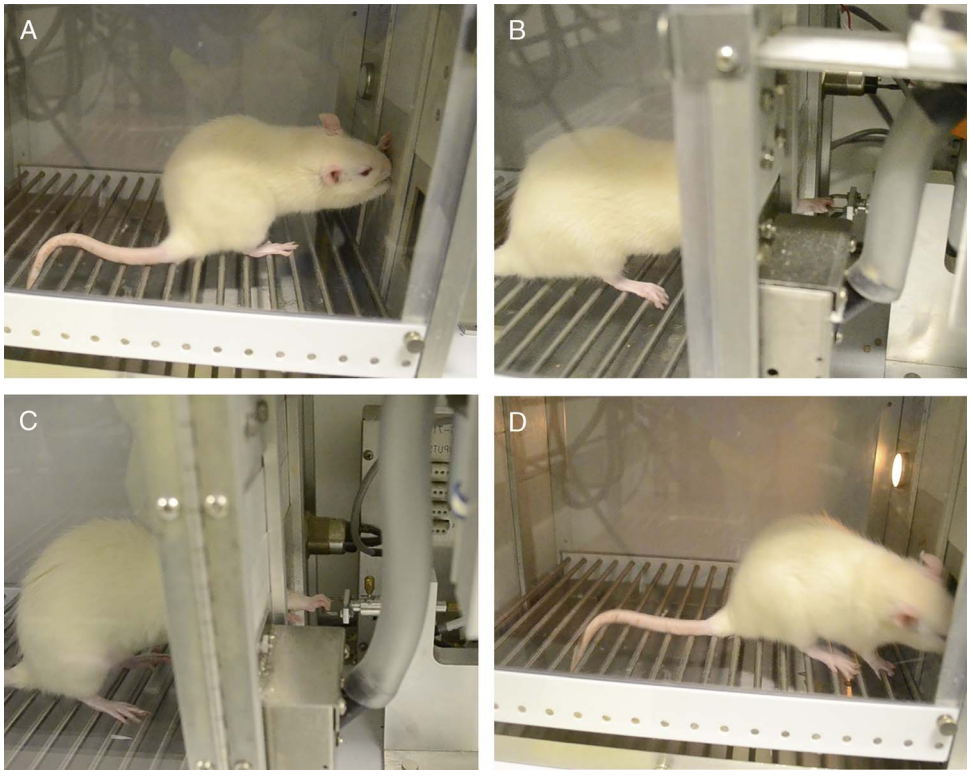

Figure 2. Image of rat performing the upper extremity reaching and grasping lever pulling task. A. Rat in an operant chamber with one limb extended into a portal located at shoulder height. B. Rat shown pulling on the lever bar, with digits four and five positioned in an ulnar position, indicative of ulnar deviation while pulling. C. Rat shown pulling in a neutral position. D. Rat retrieving a food reward.

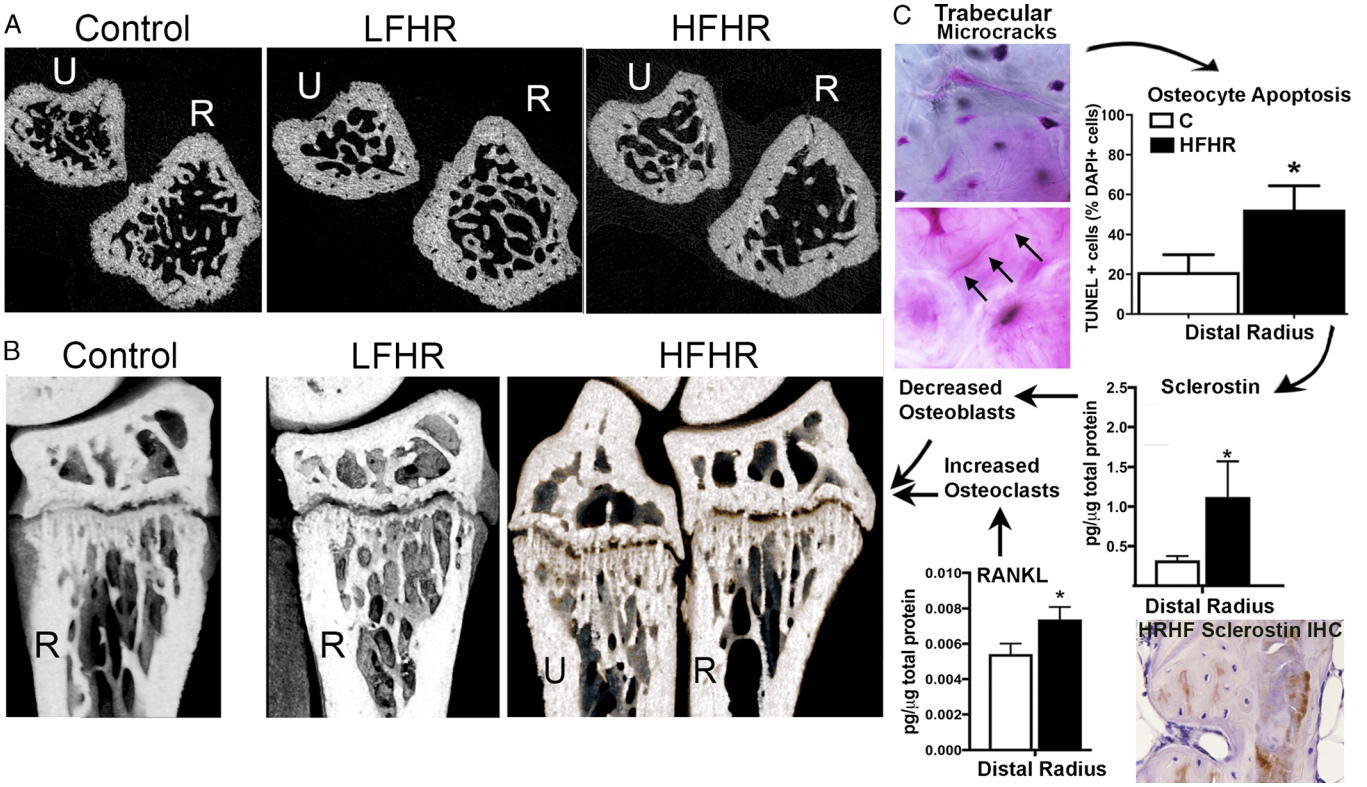

Figure 3. A and B. MicroCT images of ulnar (U) and radius (R) of control, 18-wk LFHR task, and 18-wk HFHR task rats. A. Transaxial images of the distal metaphyseal ulna and radius. Note the reduced numbers of trabeculae in HFHR rat radius. B. Sagittal images. C. Microcracks in the radial trabeculae (after basic fuchsin staining) of 18-wk HFHR rats lead to increased osteocyte apoptosis, sclerostin, and RANKL, which decreased osteoblast and increased osteoclasts numbers, respectively, compared with controls (C). (Adapted from (51). Copyright © 2019 Elsevier. Used with permission.)

cytokines (including tumor necrosis factor-α [TNFα]), trabecular bone volume loss, and cortical bone thinning in primarily the distal radius (Figs. 3A, B) (36,51,52). The radiocarpal cartilage of the wrist joint of HFHR rats also shows the onset of osteoarthritis (54), consistent with the earlier-mentioned human findings of increased incidence of hand osteoarthritis with hand-intensive tasks. The HFHR task responses are more consistent with human and animal studies showing net bone catabolism when the bone is not provided sufficient time to recover from mechanically induced microdamage that has accumulated with prolonged static or cyclic overloading (55,56).

Lumbar Vertebral Responses to Occupational Related Physical Activity

MSDs involving the back account for 38.5% of work-related MSDs in the United States (37). Occupational physical activities, such as carrying, lifting heavy weight while inclined, and awkward postures (*e.g.*, bending, twisting, squatting, and kneeling), are associated with a higher prevalence of recurrent low back pain (57,58). In professional drivers, whole-body vibration exposures contribute heavily to this risk (59), as do awkward postures while driving (60). Regarding bone, professional tractor drivers, urban taxi drivers, and helicopter pilots have increased exposure-dependent degenerative changes in the spinal column, *e.g.*, spondylolisthesis (61–64). The degenerative changes are thought to be due to enhanced mechanical overloading and shocks to the spinal column that increase internal lumbar vertebral load (compressive and shear peak forces) (59). Individual differences likely also alter ultimate stress values to the same load before rapid damage accumulation occurs in involved tissues, for example, differences in muscle mass, strength, kinematic strategies, and experience-driven differences in muscle recruitment patterns (27,65).

Lower Extremity Responses to Occupational Related Physical Activity

Although evidence is scarce that work-related physical activity can be beneficial to bone health, three studies have reported positive associations between occupational activity and areal hip/femoral BMD (66–68). Female nurses aged 47–48 yr had higher femoral neck BMD than female clerks, findings related to duration of standing at work, indicating that prolonged working in a sitting position may lower hip BMD (68), similar to findings of higher hip BMD in female postmenopausal agricultural workers than female office workers or housewives (66). Femoral neck and total hip BMDs were also found to be higher in men engaged in moderate work and travel-related physical activity, than inactive men (67). Similar relationships were not seen in work-active versus inactive women (67). These findings contrast with others showing no evidence that occupational physical activity is associated with higher hip BMD in either sex (69,70), and positive associations only with standing at 30 yr of age (70).

Yet, there is clear evidence that physical work activities can increase risk of knee osteoarthritis (45,71). Specifically, work-related and repetitive kneeling, bending, lifting, climbing, jolting of the legs, and whole-body vibration can cause or aggravate knee osteoarthritis (45,46,71). Obesity adds an additional risk of knee osteoarthritis, as well as subchondral tibial bone degeneration, in both workers and in general (45,72).

Potential Adaptive Re/Modeling May Be Countered by Other Superimposed Responses

Factors other than muscle size account for 12%–16% of the variations in differences in bone mass (73). Several studies have shown increased systemic and local inflammatory responses in humans engaged in occupational physical activity or frequent cell phone and keypad texting (43,74–76). Inflammatory responses can stimulate tissue adaptation, repair, resorption, or further injury based on superimposed processes in involved tissues. In bone, they may contribute to overuse-induced trabecular bone loss because increased inflammatory cytokines promote osteoclast activity and bone resorption (77). Involvement of inflammatory cytokines in repetitive overuse-induced bone loss has been confirmed with findings that anti-inflammatory treatments (ibuprofen and anti-TNFα) provided at peak points of inflammation improved trabecular bone volume and reduced osteoclast numbers and activity in rats performing the HFHR reaching and grasping task for 12 wk (52,78). Three-phase bone scintigraphy has been used to examine upper extremity bones of patients with occupational repetitive strain injury and demonstrated increased blood flow and pooling in wrist bones of affected limbs (79,80), suggestive of similar increases in inflammatory processes that might enhance osteoclastogenesis.

Mechanostat Theory Versus the Damage-Repair Theory

The mechanostat theory proposes that bones adapt their strength to keep the strain caused by physiological loads close to a set point (81) and, consequently, that physical activity typically increases bone adaptation in response to loading (81,82). Another theory, the damage-repair theory, was developed to explain catabolic changes in cortical bone and postulates that damage accumulates in the bone if the loading is so high that self-repair mechanisms cannot keep pace with the level of damage or overload-induced resorption (83). This damage-repair theory is relevant to trabecular changes seen in the rat model of repetitive reaching and grasping, in rats that performed the HFHR task for 18 wk (Fig. 3C) (51). These animals showed several catabolic indices in their distal radial metaphyses, including decreased trabecular bone volume, increased woven bone, microcracks, and osteocyte apoptosis, compared with control rats. The microcracks were likely the result of repeated high-force muscle compressive forces above fatigue failure thresholds for trabecular bone (51,82). The loss of trabecular bone volume has been shown to enhance brittleness and to increase fracture risk (84). Increased disorganization of trabecular patterning was also observed, a change that would further increase stress in trabeculae (47). Such responses are consistent with the damage-repair theory suggested previously for cortical bone (83) and now extended to trabecular bone. Such catabolic bone changes with high-demand tasks also are consistent with the fatigue-failure theory for MSD injuries (85).

Roles of RANKL and Sclerostin in Responsiveness to Bone Loading and Unloading

Osteocytes show metabolic responsiveness to bone loading and unloading (86) and have been implicated as the primary cells in bone that transduce mechanical signals into molecular signals capable of regulating bone formation and resorption (1). RANKL (Receptor activator of nuclear factor kappa-B ligand) is released by apoptotic osteocytes after loading-induced microdamage (87), thereby promoting increased osteoclast activity (88). This response is believed to encourage removal of damaged matrix by osteoclasts (87). It has been suggested that production of RANKL and osteoprotegerin (OPG), its receptor decoy, is dictated by the severity of damage disrupting the osteocytic network (89). Although osteocyte apoptosis and RANKL release are essential for bone re/modeling, a prolonged shift in the RANKL and OPG ratio toward more RANKL enhances osteoclastogenesis and net bone resorption (87).

Sclerostin also is expressed by osteocytes (90) and is a negative regulator of osteoblast differentiation, making it a potent inhibitor of bone formation (91). Sclerostin production typically decreases with physiological bone loading and increases with bone unloading (92,93). Applied mechanical loads usually suppress sclerostin production, a change that releases the inhibition of Wnt signaling and, thus, increases bone formation (86). On the contrary, loading-induced matrix microdamage in which osteocyte apoptosis occurs results in enhanced release of sclerostin into the bone matrix (91), changes that promote bone catabolism. Recombinant sclerostin upregulates RANKL production and increases osteoclast formation (88), changes that enhance bone resorption. In the rat model of repetitive reaching and grasping, when bones were loaded at high-force levels for 18 wk, loading-induced microdamage develops in the trabecular bone matrix (Fig. 3C) (51), through which the osteocytes extend their canaliculi (94). Subsequent osteocyte apoptosis triggered increased sclerostin and RANKL release into the bone matrix (Fig. 3C) (51), matching other studies demonstrating enhanced release of these factors after osteocyte apoptosis after microcrack damage (91). Thus, microdamage, sclerostin, and RANKL tip the balance from net bone formation (accrual of bone) to net bone resorption (bone loss) that occurs under extreme loading conditions.

Role of Nerves in Bone

As mentioned earlier, carpal tunnel syndrome is a condition of median nerve compression that frequently presents in workers. Patients with this syndrome show decreased areal BMD in distal forearm bones (49,50) that usually improves with surgical release of median nerves (50,95). Although yet unknown, median nerve compression may reduce neural growth factors provided to distal forearm bones, as found after spinal cord injury or chronic constriction injury of the sciatic nerve (96,97).

Studies have established that neurons communicate with cells in the bone microenvironment and regulate bone homeostasis (98). Both the periosteum and trabecular bone compartments contain a dense network of TrkA (the high-affinity receptor for nerve growth factor)–positive sensory fibers that are responsive to mechanical stimuli (99). These sensory neurons sense and respond to mechanical stimuli. A study in mice investigating the role of sensory neurons during forelimb axial loading demonstrated their importance in potentiating the anabolic response to mechanical stimuli to achieve maximal load-induced bone formation (100). It is generally believed that the somatosensory system plays a role in mediating the anabolic response of bone to physiological mechanical loading via the Wnt/β-catenin pathway.

In contrast, activation of the sympathetic nervous system (SNS) elicits a catabolic response in bone through an increase in bone resorption and a decrease in bone formation (101). Increased SNS activity stimulates the production of bone-resorptive cytokines, for example, RANKL and IL-6 (102,103). Although nerve fibers that are immunoreactive for various sympathetic markers, for example, vasoactive intestinal peptide, tyrosine hydroxylase, and neuropeptide Y, have been identified in bone (104), it appears that only a limited number of bone cells are in direct contact with sympathetic nerve terminals (105,106). Furthermore, beta-adrenergic receptors (βARs) (predominantly type beta 2 [β2]) are found on osteocytes, osteoblast, and osteoclasts (98). Studies have shown that βAR agonists trigger a bone catabolic response (increased bone resorption and decreased bone formation), whereas βAR blockade using antagonists has an anticatabolic effect, particularly in conditions when bone re/modeling is high, such as in young mice and estrogen-deficient bone loss (106,107).

Although somatosensory nerves are believed to play an important role in mediating the anabolic response of bone to physiological mechanical loading, the role of the SNS appears minimal under these circumstances (98,108). However, in cases in which the loading exceeds the beneficial threshold and results in tissue damage (*e.g.*, bone microcracks), hyperactivation of the SNS may tip the balance in favor of bone catabolism by overriding the positive effects of mechanical loading on bone. The advantageous effects of exercise on bone mass in rats can be suppressed by β2 agonists, thereby suggesting that the positive effects of physical activity can be overridden by activation of the SNS (107).

This is interesting in light of evidence of reduced skin temperatures in hands of individuals with advanced upper extremity MSDs, changes thought to reflect underlying dysfunction in peripheral sympathetic nerves (109,110). Although more work is needed to confirm this possible contribution, hyperactivation of sympathetic nerves may tip the balance toward bone loss, thereby negating the positive effects of mechanical loading on bone.

Key Questions That Need to Be Addressed (Future Perspectives)

The effects of repetitive high-demand activities on bones in human populations are not as well defined as in animal models. Longitudinal studies should be performed in young adult, mature, and aged humans to capture the effects of changing repair mechanisms, hormone levels, changes in metabolism, and inflamm-aging (the increase in inflammation occurring with aging) (111). We have shown that aged rats performing the same LFHR task for 12 wk as young adult rats develop greater levels of trabecular and cortical bone degradation, likely due to observed increases in systemic and tissue inflammatory cytokine responses occurring as a consequence of both aging and continued loading (53). Similar studies should be repeated in human populations, particularly in light of extended retirement times for workers (112).

Repair of biological tissues can be accomplished through the processes of inflammation and re/modeling, as long as the damage does not exceed the ability of tissues to repair.

Thresholds for damage need to be defined, as do rest and recovery allowances that would enhance tissue recovery and bone adaptation (*i.e.*, accrual). Current equations for repetitive occupational task thresholds were developed from 69 short-term psychophysical data tasks (each <4 wk in duration) and using physiological data from six studies demonstrating muscle fatigue after only 1 h (113). Duty cycle is the frequency of effort duration an individual worker is engaged in a repetitive task. Lowering duty cycles may increase the allowable maximum acceptable forces and enhance tissue recovery (113). Increasing periods of complete relaxation between work cycles also reduces health risks (114), supporting a need for further exploration of rest periods in loading models.

Future experiments also should consider the sexual dimorphism of bone (*e.g.*, structural or hormonal response differences) in their study design and data interpretation. Such studies would elucidate if male-female differences are from sex-linked biological factors versus gendered social dynamics, which might include differences in dress, occupation, physical activity, sun exposure, vitamin D synthesis, and weight-bearing activities in which the different sexes are typically engaged.

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