Aging and the Muscle-Bone Relationship

Aging-induced declines in muscle size and quality are thought to contribute to catabolic alterations in bone, but changes in bone with age also profoundly alter its response to muscle-derived stimuli. This review provides an overview of some of the alterations that occur in muscle and bone with aging, and discusses the cellular and molecular mechanisms that may impact these age-associated changes.

Over the next 10 years, the number of people in the world over the age of 65 is projected to increase on a percentage basis at a rate almost four times faster than that for the younger population (7). As the size of the older population increases, so does the occurrence of aging-related morbidities such as osteoporosis and sarcopenia. Bone fractures are directly linked to osteoporosis in aging adults, and in the U.S. the annual incidence of bone fractures in women exceeds the annual incidence of stroke, breast cancer, and heart disease combined (62). Hip fractures in particular are associated with significant morbidity and mortality, and of those suffering a hip fracture, roughly 40% will require nursing home care, and 20% will not walk again (24). Aging is not only associated with a loss of bone density and strength but is also associated with a reduction in muscle mass and strength referred to as sarcopenia. A consensus definition of sarcopenia has not been reached; however, most assessments involve declines in muscle functional capacity (e.g., strength) (11) and/or a morphometric measure (e.g., cross-sectional area, muscle mass). The muscle weakness that occurs with sarcopenia increases the risk for falling (38), which further increases the propensity for bone fracture.

Strong associations between muscle and bone size have been reported across the lifespan (16, 57). Since the late 1800s, it has been assumed that a causal relationship exists between muscle and bone and that this allometric scaling relationship is mechanical in nature (80–82). That is, muscle and bone are proportionally matched in their functional capacity and geometric structure. This relationship does, however, appear to change significantly with age. For example, the capacity for muscle to generate force declines with age, and the anabolic reponse of bone to muscle-derived stimuli also appears to be altered with age. In addition, muscle is now recognized to have paracrine and endocrine effects that may also influence bone independent of a mechanical relationship (26, 27). Here, we review some of the basic mechanisms by which muscle and bone are thought to interact throughout life, and how these may change with age, leading to bone loss and bone fractures. In The Mechanical Relationship Between Muscle and Bone, we discuss the mechanical relationship between muscle and bone, with particular emphasis on the role of muscle in affecting bone size and bone geometry. In Impact of Aging on the Muscle-Bone Relationship, we assess whether the muscle-bone relationship remains relatively constant with aging in both animals and humans. Cellular and Molecular Mechanisms Underlying Age-Related Changes in the Muscle-Bone Relationship addresses the cellular and molecular mechanisms linking bone and muscle that are altered with age and which negatively impact cross talk between the two tissues.

The Mechanical Relationship Between Muscle and Bone

The musculoskeletal system provides the mechanical framework for movement that is powered by contractions of skeletal muscles. To overcome the anatomical disadvantage associated with short lever arms, many muscles are required to produce high forces to generate movement. The muscle-generated loads applied to bone can far exceed external loads resulting from the body interacting with its environment (e.g., ground reaction forces) (19, 35, 46, 47, 54). Specifically, the utilization of instrumented proximal femoral prostheses have demonstrated that the forces produced during muscle contraction can account for >70% of the bending moments applied to the lower limb (46). Bone size and mechanical properties are, therefore, thought to allometrically scale to the magnitude of peak muscle forces (65) in response to mechanical loading (e.g., through increased or decreased use). Julius Wolff (“Wolff’s Law”) was the first to describe that bone changes its external shape and internal structure in response to mechanical loads imposed on the skeleton (80–82).

The inclusion of muscle as the primary source of mechanical loading was a central principle of the Utah paradigm of skeletal physiology and the mechanostat hypothesis (21, 22). Specifically,
healthy postnatal bone was proposed to adapt its structure and strength to the typical peak mechanical loads it experiences, which are applied via muscular contractions during exercise and/or a person’s activities of daily living (13, 21, 41, 45). Bone’s detection and transmission of mechanical loading stimuli by its resident cell populations is referred to as mechanotransduction, where the stimulus is the result of bone strain (i.e., the change in length per unit of original length) (4, 12, 15, 25, 42, 79). According to the mechanostat hypothesis, strain magnitudes experienced by mechanosensing cells in the tissue are compared against threshold values to determine whether feedback mechanisms and adaptive responses are necessary. Strains above 3,000 microstrain (με) typically trigger bone formation, whereas strains of <500 με trigger bone resorption. The dense network of osteocytes trapped within the mineralized bone matrix is the primary sensor of changes in bone loading, which occurs primarily through changes in fluid movement within the lacuno-canalicular system of bone. These changes in fluid movement in turn stimulate many downstream effects, including Wnt/beta catenin signaling that promotes the downregulation of sclerostin, a potent inhibitor of bone formation (5, 84). Muscle weakness or muscle atrophy is associated with bone loss, even in the absence of changes in load bearing. Specifically, muscle paralysis using botulinum toxin (botox) is observed to decrease bone mass even during hindlimb unloading, where the effects of paralysis on load bearing are removed (75). The mechanical communication between muscle and bone allows for anabolic/catabolic modifications to bone in response to loading that apparently attempt to maintain a constant relationship between the functional and structural capacities of the two tissues.

The long bones of the appendicular (limb) skeleton and shorter bones of the axial (spine) skeleton have a dense outer cortex and a spongy network of trabecular bone filling the vertebrae and the articular ends of long bones. Approximately 80% of the total mass of the skeleton is cortical bone, and, with aging, 70% of all bone lost is cortical (69). The nonvertebral (limb) skeleton is primarily cortical bone, and, of all fractures that occur, 80% are nonvertebral (69). Thus a key strategy for preventing bone fractures is to either prevent loss of cortical bone with aging or increase cortical bone formation with aging. The bone cortex has an outer periosteal layer that deposits bone peripherally, which ultimately increases the bone’s external diameter, overall cross-sectional area, and resistance to bending loads (FIGURE 1, A AND B). Notably, bone

**FIGURE 1.** Schematic representation of a long bone and dimorphism in bone cross-sectional geometry

A: schematic representation of a long bone indicating the outer periosteal surface (p) and inner endocortical surface lining the medullary cavity (e), with a dotted line showing cross section. B: schematic representations of long bone cross-sectional geometry in males vs. females at the level of the dotted line shown in A. Males typically have a wider bone cross section and outer radius (R), whereas females have a smaller outer radius but thicker bone cortex, leading to a shorter inner radius (r). As women age, bone is resorbed from the endocortical surface so that older women must increase R to compensate for an increasing r. Males have a larger R and so are at lower fracture risk even as r increases. C: increased muscle mass in males is associated with increased bone diameter, even in mice. Male mice (M) lacking myostatin show a greater increase in forelimb triceps brachii mass than female (F) knockout (KO) mice, and forelimb bone (radius) diameter is largest in M mice lacking myostatin (KO) compared with wild-type (WT) mice.
Muscle plays a critical role in the regulation of bone size. An excellent example of this association comes from the human upper limb, which is non-weight bearing and in the case of the non-dominant arm does not normally experience high mechanical loads. In older adults (~70 yr of age), the periosteal circumference of the radius from the non-dominant upper limb is strongly associated with forearm muscle cross-sectional area, such that greater muscle size is consistently associated with greater periosteal circumference (16). Notably, the association between bone size and muscle cross-sectional area is stronger than the association between bone size and body weight. A similar association is observed in adolescents (57), where cross-sectional area and strength of the non-dominant radius is more strongly associated with forearm muscle cross-sectional area than with fat mass. An interesting comparative example in this regard can be observed in hypermuscular mice lacking myostatin, where larger forelimb muscles in male and female knockout mice are associated with increased midshaft diameter of the radius (FIGURE 1C). In these mice, midshaft diameter of the radius is more highly correlated with triceps brachii mass ($r^2 = 0.64$) than with body weight ($r^2 = 0.31$).

Impact of Aging on the Muscle-Bone Relationship

If the relationship between muscle and bone is indeed mechanical, then the ratio of muscle to bone properties (i.e., functional capacity or size) should remain relatively constant across adulthood. That is, anabolic or catabolic changes within muscle and bone would be expected to occur in parallel. Alternative patterns of change to the muscle-to-bone ratio (i.e., an increase or decrease) with aging could suggest that the functional capacity and/or size of muscle and bone are capable of being mismatched. There have been a few trials in mice to test the mutability of Wolff’s Law and the mechanostat model by attempting to disrupt the scaling of mechanical properties in bone to those in muscle. Specifically, our group has investigated how the ratio of muscle function (i.e., peak isometric force assessed in vitro) to bone strength (i.e., ultimate load assessed by three-point bending) differs between young and aged mice with and without a genetic condition mimicking Duchenne muscular dystrophy (i.e., mdx mice) (FIGURE 2; Ref. 52). The muscle-to-bone ratio was not different between young and aged wild-type mice (FIGURE 2A). The ratio was, however, greater in aged compared with young mdx mice, with this being attributed to the active disease state in the young mice and muscle strength subsequently being impaired (52). In the aged mdx mice, muscle

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A Muscle Disease

![A Muscle Disease](image)

B Exercise

![B Exercise](image)
strength had normalized, and the muscle-to-bone ratio was increased such that it was not different from that of wild-type mice (52).

We and others have also assessed the effects of physical activity/training (78) and estrogen deficiency (77, 78) on the muscle-bone relationship. In the study by Warren et. al. (78), this was done by assigning female mice to voluntary wheel running or sedentary groups, either with or without ovariectomy surgery. Mice that took part in wheel running as a form of exercise, had higher muscle-to-bone ratios compared with sedentary mice (FIGURE 2B) (78). This suggests that physical activity has the potential to disrupt the muscle-to-bone ratio, which would not be predicted by Wolff’s Law. The removal of estrogen by ovariectomy for 30–60 days, however, did not disrupt the muscle-bone relationship (77, 78). Overall, these animal studies suggest that physical activity and muscle disease can create transient mismatches in the muscle-to-bone ratio, and perhaps that the influence of estrogen in mediating this response may be minimal.

To better assess the impact of aging on the muscle-bone relationship in humans, we conducted a systematic review (Table 1). The bone outcome measure desired for a study’s inclusion was bone mechanical strength, but because this is never reported, surrogates for bone strength were permitted. These surrogates included: estimates of bone strength (i.e., strength strain index), bone area (i.e., cortical bone area or cross-sectional area as determined by MRI or computed tomography), and bone mass [i.e., bone mineral content (BMC) or bone mineral density (BMD)] determined by DXA. The preferred muscle outcome measure was contractile strength, but measures of muscle anatomical dimensions (i.e., cross-sectional area or width) or mass were also permitted as a substitute. Studies were excluded if 1) the studied muscles or muscle groups were not in close proximity to bone that was studied or 2) insufficient data were available to calculate the ratio of muscle to bone outcome measures for each age group (i.e., only the correlation between the bone and muscle measures was reported, subjects were grouped based on age plus factors other than age). Fifteen studies met the inclusion and exclusion criteria. Mean muscle-to-bone ratios were calculated for each age group by dividing the reported mean muscle outcome measure by the corresponding mean bone outcome measure; standard deviations for these ratios were calculated using propagation of errors from the muscle and bone outcome standard deviations. Analysis of the ratio data was possible for all studies with the exception of Meema et al. (i.e., sample sizes lacking) (50), and thus for this study, the aging pattern for the muscle-to-bone ratios is only described qualitatively.

Table 1 summarizes the 39 muscle-to-bone ratios from the 15 studies included in the systematic review. The ratio remained unchanged with aging in 19 of the 39 ratios, whereas 15 ratios decreased with age and 5 ratios increased (Table 1). To illustrate the variability among studies in the age-related ratio changes, three studies are discussed here in greater detail. These studies are those with the largest sample sizes, age ranges, and number of age groups compared (3, 50, 51). Atlantis et al. (3) was the largest study included in the analysis, and quantified muscle masses and BMC by DXA in over 1,000 men between the ages of 35 and 81 yr. The ratio of muscle mass to BMC decreased with aging in the arms but remained unchanged in the legs (Table 1). Melton et al. (51) provided raw data for 307 men and 345 women between the ages of 22 and 97 yr, which included lean mass of the arms and legs and a measure of femur bending strength index (i.e., flexural rigidity or EI) for each of the 652 participants (51). The muscle-to-bone ratio significantly decreased in men with aging but not in women (P = 0.14; Table 1). Meema et al. (50) reported bone mass of the radius and the width of the adjacent forearm musculature of the radius for 613 men and women across 11 different groups between the ages of 18–97 yr (FIGURE 3). Because the authors failed to report sample size for each of the 11 groups, this prevented running statistical analyses. However, it appears that the ratio increases with age in both men and women. Overall, these three studies highlight a high variability in how aging affects the muscle-to-bone ratio.

To determine whether a study’s research design (i.e., the measures used to assess bone and muscle, number of age comparison groups, and age range among groups) affected how the muscle-to-bone ratio changes with aging, a logistic regression and a proportional odds (cumulative logit) model was utilized. The odds of an increase in the muscle-to-bone ratio with aging was dependent on the measures used to assess bone and muscle. For example, an increase in the ratio was >10-fold more likely to occur in studies in which bone was assessed via strength or BMC compared with when it was assessed via cross-sectional area (CSA). Similarly, an increase in the ratio was >50-fold more likely to occur in studies assessing bone via BMD compared with assessing bone via CSA. In contrast, studies that involved “strength” for the muscle strength measurement were more more likely to result in a decrease in the muscle-to-bone strength ratio with aging than the studies that used “area” for the muscle strength measurement. The number of age-comparison groups used in a study was related to the probability of observing an increase in the ratio. For each
additional age group, the odds of observing an increase in the muscle-to-bone ratio with aging was reduced by half. These results indicate that study research design features do influence how the muscle-to-bone ratio changes with aging. However, for all of the research design features we considered, we found that they could account for no more than 30% of the variance in whether a muscle-to-bone ratio increased, decreased, or did not change with age.

### Table 1. Effect of aging on the muscle-to-bone ratio

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Subjects/Age Range (yr)/Sample Size</th>
<th>Muscle Measure</th>
<th>Bone Measure</th>
<th>Effect of Aging on the Muscle-to-Bone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heikkinen et. al., 1984 (30)</td>
<td>Men/31-75/142</td>
<td>KE strength (isometric)</td>
<td>Calcaneous BMD</td>
<td>Decreases</td>
</tr>
<tr>
<td>Hyakutake et. al., 1994 (34)</td>
<td>Men/20-89/109</td>
<td>KE strength (90 deg/s)</td>
<td>Femur BMD</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td>Women/20-79/231</td>
<td>KE strength (90 deg/s)</td>
<td>Femur BMD</td>
<td>Decreases</td>
</tr>
<tr>
<td>Calmels et. al., 1995 (9)</td>
<td>Women/44-87/101</td>
<td>KE strength (30 deg/s)</td>
<td>Femur BMD</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td>KE strength (180 deg/s)</td>
<td>Femur BMD</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Humphries et. al., 1999 (33)</td>
<td>Peri- and post-menopausal women/45-65/96</td>
<td>KE strength (isometric)</td>
<td>Lumbar spine BMD</td>
<td>No change</td>
</tr>
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<td>Ryan et. al., 2004 (66)</td>
<td>Men/25-70/25</td>
<td>KE strength</td>
<td>Femur BMD</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Women/26-68/19</td>
<td>Leg press strength</td>
<td>Femur BMD</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KE strength</td>
<td>Femur BMD</td>
<td>Trend for decrease</td>
</tr>
<tr>
<td>Sherk et. al., 2009 (70)</td>
<td>Men/18-64/68</td>
<td>Leg press strength</td>
<td>Femur BMD</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DF/PF CSA (pQCT)</td>
<td>Tibia SSI</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DF/PF CSA (pQCT)</td>
<td>Tibia cortical BMC</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DF/PF CSA (pQCT)</td>
<td>Tibia cortical area</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DF/PF CSA (pQCT)</td>
<td>Tibia cortical density</td>
<td>No change</td>
</tr>
<tr>
<td>Rice et. al., 1989, (61)</td>
<td>Men/25-90/20</td>
<td>EF CSA (CT)</td>
<td>Humerus CSA</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE CSA (CT)</td>
<td>Humerus CSA</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF CSA (CT)</td>
<td>Tibia CSA</td>
<td>Decreases</td>
</tr>
<tr>
<td>Overend et. al., 1992 (53)</td>
<td>Men/19-77/24</td>
<td>KE CSA (CT)</td>
<td>Femur CSA</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KF CSA (CT)</td>
<td>Femur CSA</td>
<td>No change</td>
</tr>
<tr>
<td>Klein et. al., 2002 (43)</td>
<td>Men/20-90/33-44</td>
<td>EF/EE CSA (MRI)</td>
<td>Radius cortical area</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FF/FE CSA (MRI)</td>
<td>Ulna Cortical Area</td>
<td>Trend for Decrease</td>
</tr>
<tr>
<td>McNeil et. al., 2009 (48)</td>
<td>Men/23-91/39</td>
<td>Total Leg Muscle CSA (CT)</td>
<td>Tibia CSA</td>
<td>Decreases</td>
</tr>
<tr>
<td>Horber et al., 1997 (32)</td>
<td>Men/20-81/60</td>
<td>Arm lean muscle mass</td>
<td>Arm BMC</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>Pre and post-menopausal women/20-79/59</td>
<td>Leg lean muscle mass (DXA)</td>
<td>Leg BMC</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm lean muscle mass (DXA)</td>
<td>Arm BMC</td>
<td>Trend for Increase</td>
</tr>
<tr>
<td>Melton et. al., 2006 (51)</td>
<td>Men/20-93/307</td>
<td>Leg lean muscle mass (DXA)</td>
<td>Leg BMC</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Women/21-97/345</td>
<td>Arm/leg lean muscle mass (DXA)</td>
<td>Femur EI strength</td>
<td>Decreases</td>
</tr>
<tr>
<td>Atlantis et. al., 2008 (3)</td>
<td>Men/35-81/1,068</td>
<td>Arms muscle mass (DXA)</td>
<td>Femur EI strength</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Legs muscle mass (DXA)</td>
<td>Legs BMC</td>
<td>No change</td>
</tr>
<tr>
<td>Sanada et. al., 2009 (67)</td>
<td>Women/20-76/138</td>
<td>Arm lean muscle mass</td>
<td>Arm BMC</td>
<td>Increases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg lean muscle mass</td>
<td>Leg BMC</td>
<td>Increases</td>
</tr>
<tr>
<td>Meema et. al., 1973 (50)</td>
<td>Men/18-97/305</td>
<td>Muscle width of adjacent musculature</td>
<td>Radius bone mass</td>
<td>Increases*</td>
</tr>
<tr>
<td></td>
<td>Women/18-90/308</td>
<td>Muscle width of adjacent musculature</td>
<td>Radius bone mass</td>
<td>Increases*</td>
</tr>
</tbody>
</table>

The review involved three steps. In step 1, using the search terms “muscle, bone, and aging” with delimitations to human studies and the English language, 1,097 articles were identified. Article titles and abstracts were reviewed in step 2 to confirm that measures of bone and muscle functional capacity and/or structure were outcome measures in the studies, and that an assessment of aging was apparent; 119 studies met these criteria. In step 3, the following inclusion criteria for aging, bone, and muscle were applied during a full-text examination of the studies. A study’s assessment of aging was deemed acceptable if a comparison was made across two or more age groups with an average age difference of at least 20 yr. KE, knee extensor muscles; BMD, bone mineral density; KF, knee flexor muscles; DF, dorsi flexor muscles; PF, plantar flexor muscles; CSA, cross-sectional area; SSI, strength strain index; EF, elbow flexor muscles; EE, elbow extensor muscles; FF, forearm flexors; FE, forearm extensors; BMC, bone mineral content; EI strength, flexural rigidity. *Statistical analyses were not performed on muscle-to-bone ratio due to missing sample sizes.
highlights the potential for existence of one or more non-mechanical muscle-bone relationships.

**Cellular and Molecular Mechanisms Underlying Age-Related Changes in the Muscle-Bone Relationship**

The data reviewed above indicate that mismatches can occur between muscle and bone emanating from age-associated structural and/or functional changes in one tissue vs. another. Such dissociations are also observed with exercise and aging, where it is well known that exercise can significantly enhance bone mass and strength in young animals but not in older, adult animals, even when controlling for the duration and intensity of exercise (18, 55). There are likely a number of mechanisms that underlie this dissociation (FIGURE 4).

First, there are changes in bone with aging that likely attenuate its response to muscle-derived stimuli. Osteocytes trapped within the mineralized matrix of bone are the key mecanostransducers in bone tissue, and osteocyte number and density decline with age, resulting in an increased number of empty lacunae in bone (8). These age-associated changes in the lacunocanalicular system of bone ultimately impair the bone signaling network (8, 74) and may deleteriously impact the diffusion of important growth factors and signaling molecules to target cells (FIGURE 4). On the other hand, a greater density of empty osteocyte lacunae has also been observed closest to the periosteal surface (29), and so periosteal expansion with increasing age could be related to an absence of osteocytes secreting the anti-osteogenic factor sclerostin. There are also changes in the periosteum that occur with aging that may limit the potential of muscle to increase bone size. Periosteum has been observed to become thinner and less cellular with age in rodents and other mammals (17), aged rodent periosteal cells show an impaired regenerative capacity and impaired response to parathyroid hormone (83), periosteal osteoblasts demonstrate an impaired capacity to proliferate in response to mechanical loading (49), and human periosteal cells demonstrate a lack of spontaneous cartilage formation in vitro after age 30 (14). Aged osteoprogenitor cells also show an attenuated response to growth factors (FIGURE 4). For example, the dose of IGF-1 required to elicit a mitogenic response in aged osteoprogenitor cells is much greater than that required for younger cells (71).

There are well documented changes in muscle that occur with aging, including an overall decrease in myofiber size, a decline in the number of excitable motor units within muscle, and the gradual infiltration of muscle with fatty tissue (73). There are also pronounced degradative changes in the neuromuscular junction with aging, which is known to contribute to synaptic loss (10) and may be related to oxidative stress and mitochondrial dysfunction (37). All of these changes will alter the contractile behavior of aged muscle, which as noted above could be an important mechanistic link between muscle and bone formation (FIGURE 4). One of the most exciting new developments in the area of muscle-bone interactions is the recognition that skeletal muscle secretes a variety of peptides collectively termed myokines (56), and a number of these myokines are well recognized as having positive effects on bone formation (26–28), as well as inhibitory effects on osteoblast differentiation (40). Importantly, muscle contraction stimulates the release of myokines both in vivo and in vitro (60, 68). IGF-1 expression in skeletal muscle tissue is elevated with muscle contraction (1), and circulating levels of IGF-1 are also increased with resistance exercise (63). Recent experiments also have shown that conditioned medium...
from whole muscle explants stimulated in vitro can prevent the death of osteocytes when exposed to glucocorticoids (36), suggesting again that muscle contraction leads to the release of myokines that are beneficial for bone. Muscle contraction may also suppress the expression of factors that can inhibit the bone formation. For example, myostatin (GDF-8) expression is downregulated following concentric and eccentric muscle contractions (31), and myostatin suppresses the proliferation of bone marrow-derived stem cells in vitro (6).

Aging has been shown to reduce the anabolic effects of resistance exercise on muscle protein synthesis (23) and thus could potentially affect myokine synthesis and secretion. The effect of myokines on bone may be systemic as well as local, since elevated secretion of muscle-derived IL-15 not only decreases body fat but also increases whole-body bone mineral content (59). Another potential alteration in muscle with aging is that the myokine secretory profile may be altered. Aged human myoblasts, for example, show increased levels of TGF-β1 secretion in vitro compared with younger myoblasts (2), although it is not known how aging alters the secretion of other myokines with muscle contraction. In addition, aging is generally associated with a preferential denervation of fast-twitch fibers along with reinnervation of some of those fibers by α-motoneurons from slow motor units (58). It is not known how this could effect myokine secretion, but single fiber maximal isometric force production, either absolute or normalized to cross-sectional area, is not consistently different between slow- and fast-twitch fibers in older humans (e.g., Refs. 20, 72). It is well recognized that the bone marrow cavity accumulates fat with age (64), and it is certainly possible that increased bone marrow adipogenesis may attenuate the effects circulating myokines on endocortical (endosteal) osteoprogenitor cells (FIGURE 4). It should be noted that many of the associations between myokines and bone formation are more correlative and hypothetical rather than mechanistic. For example, although TGF-β1 and IL-6 are both well established myokines, their size may prevent their diffusion through the periosteum (44).

Studies need to be performed to determine how muscle-specific alteration of myokine expression and/or targeted changes in myokine receptors in osteoprogenitor cells impact bone modeling and remodeling.

Summary and Conclusions

Aging is associated with the development of sarcopenia in skeletal muscle and osteoporosis in bone; however, it is not fully understood how the relationship between the two tissues is impacted by aging. Our experiments in mice and our review of human studies demonstrate that the relationship between muscle and bone size and strength changes significantly with age, so that a potential mismatch occurs between these tissues. There are pronounced cellular and molecular changes in bone and muscle cells with age that likely underlie these observations. Such changes include the loss of osteocytes in bone matrix.

FIGURE 4. Schematic cross-section at the midshaft of a long bone diaphysis showing a summary of age-associated changes in muscle and bone

Muscle changes (red) include decreased fiber size, atrophy of fast-twitch fibers, fatty infiltration of muscle tissue, loss of motoneurons, and degradation of the neuromuscular junction (NMJ), all of which can negatively impact force production and potentially the secretion of myokines. Changes in bone (black) include decreased cellularity in the periosteum, loss of osteocytes in bone matrix due to senescence, fatty infiltration of bone marrow, and attenuated periosteal response to growth factors and parathyroid hormone (PTH). All of these changes can impair the capacity of bone to respond to anabolic stimuli.
and a decline in the proliferative capacity of osteoprogenitors in the periosteum, which attenuate the response of bone to muscle contraction and normal mechanical stimuli. Loss of motoneurons, reduced fiber size due to decreased muscle protein synthesis and increased degradation from atrogens, and perhaps fatty infiltration in muscle with age all negatively impact the contractile machinery and force-generating capacity of aged muscle. These data indicate that a therapeutic approach for improving bone health will require targeting both muscle and bone; that is, the changes in bone discussed above suggest that improvements in muscle function with age are unlikely to elicit an adequate anabolic stimulus in bone. Rather, strategies to enhance the anabolic capacity of periosteum in conjunction with therapeutics to increase the force- and power-generating capacity of aged muscle could significantly improve musculoskeletal health and function in the elderly.

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