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Mechanical signals protect stem cell lineage selection, preserving the bone and muscle phenotypes in obesity

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Abstract

The incidence of obesity is rapidly rising, increasing morbidity and mortality rates worldwide. Associated comorbidities include type 2 diabetes, heart disease, fatty liver disease, and cancer. The impact of excess fat on musculoskeletal health is still unclear, although it is associated with increased fracture risk and a decline in muscular function. The complexity of obesity makes understanding the etiology of bone and muscle abnormalities difficult. Exercise is an effective and commonly prescribed non-pharmacological treatment option, but it can be difficult or unsafe for the frail, elderly, and morbidly obese. Exercise alternatives, such as low-intensity vibration (LIV), have potential for improving musculoskeletal health, particularly in conditions with excess fat. LIV has been shown to influence bone marrow mesenchymal stem cell differentiation toward higher-order tissues (i.e., bone) and away from fat. While the exact mechanisms are not fully understood, recent studies utilizing LIV both at the bench and in the clinic have demonstrated its efficacy. Here, we discuss the current literature investigating the effects of obesity on bone, muscle, and bone marrow and how exercise and LIV can be used as effective treatments for combating the negative effects in the presence of excess fat.

Keywords

osteoporosis; diabetes; vibration; exercise; musculoskeletal

Introduction

Obesity rates are rising worldwide, especially in the United States, where more than one-third (78.6 million) of adults and 17% of children are considered obese.¹ This overall prevalence is only projected to increase, reaching 42% by 2030.^{2,3} An increase in the morbidity and mortality associated with being obese, whether it is a result of nutrition (i.e., high caloric intake) or exacerbated by hormonal imbalances (i.e., estrogen deficiency in menopause), is a major clinical concern. Obesity is associated with a myriad of

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CTR is a founder of Marodyne Medical and BTT Health Systems, as well as the holder of several patents related to healthcare applications of low-intensity vibration and low-magnitude mechanical signals. The other authors have no competing interests to declare.

comorbidities, including type 2 diabetes,⁴ heart disease,⁵ stroke,⁶ metabolic syndrome,⁴ cancer,³ and increased susceptibility to infectious disease.⁷ In 2008 alone, these cumulatively resulted in obesity-related medical spending of approximately \$147 billion in the United States.⁸ Consequently, physicians are faced with new challenges in treatment, diagnosis, and prognosis as we continue to learn more about the epidemiology of the disease. Extensive research in the last few years has clearly shown that obesity is a condition of chronic and mild inflammation. The mechanism of obesity-induced inflammation is thought to originate in the adipose tissue, which accumulate and hypertrophy with higher energy intake and lack of exercise.^{9,10} This inflammation has also been associated with insulin resistance, the basis for the development of type 2 diabetes.¹⁰ In fact, 90% of patients with type 2 diabetes are considered overweight or obese.¹¹

Health complications due to altered endocrine and inflammatory function open the door to a range of chronic diseases. Growing evidence suggests that, in addition to these metabolic abnormalities, and in some cases as a results of the abnormalities, excess adipose tissue is linked with poor musculoskeletal health. It is reported that obese women face higher fracture-related morbidity than nonobese women and that there is a greater fracture incidence among diabetic versus healthy subjects.^{12,13} Obesity also leads to skeletal muscle insulin resistance, alterations in muscle size and composition,¹⁴ and the decline of muscular function in the elderly.¹⁵ As the obese population ages, it is imperative that musculoskeletal tissue systems are maintained, as age-related complications (i.e., osteoporosis and sarcopenia) increasingly wear on the skeleton. The extent to which excess fat influences these tissues is an area of study that requires further investigation to obtain a complete understanding of the negative consequences obesity imposes on bone and muscle.

It is essential that appropriate treatments are available and employed in the clinic, as the number of people affected by obesity and type 2 diabetes continues to rise and the costs for treatment invariably grow. Pharmacological agents, surgical procedures, and lifestyle interventions targeting diet and activity level are all options that can be effective but have limitations. Bariatric surgery successfully reduces adipose tissue and improves type 2 diabetes¹⁶ but is costly and invasive,¹⁷ making the procedure unfit for a large population. There are long-term and short-term U.S. Food and Drug Administration (FDA)-approved weight loss drugs, the majority of which are appetite suppressants,¹⁸ but these are often not void of side effects or do not maintain weight loss in the long term. Rosiglitazone is indicated for the treatment of type 2 diabetes and acts by sensitizing tissues to insulin; however, it has been associated with increased risk of cardiovascular disease, myocardial infarction, and heart failure.^{19,20} Other non-pharmacological interventions include dietary restrictions and increased physical activity; however, compliance is poor, and long-term weight loss is only achieved by a few.¹⁷ A low-cost, safe, and effective alternative that will be utilized by those with obesity remains an unmet need in the clinic. This review will focus on the impacts of obesity on bone and muscle tissues and the use of exercise and low-magnitude mechanical signals as an alternative and/or complement to existing treatment methodologies.

Impact of obesity on musculoskeletal tissue systems

Fat is an inhomogeneous tissue that contains a range of cell types, including adipocytes, fibroblasts, endothelial cells, immune cells, and adult stem cells (mesenchymal and hematopoietic) and their progenitors. In addition to storing energy, it is also an active endocrine organ that modulates adipokine (e.g., leptin, resistin, adiponectin) and inflammatory cytokine (e.g., TNF α , IL-6, TGF- β) release,²¹ affecting both local and systemic environments. Fat tissue plays a role in a range of physiological processes, including immune function,²² glucose homeostasis,²³ and energy balance.²⁴ Its signaling directly affects other tissue systems,²⁵ including bone and muscle. Osteosarcopenic obesity syndrome (OSO), a recently defined condition, encompasses both the skeletal (osteoporosis) and muscular (sarcopenia) complications associated with excessive fat mass (obesity).²⁶ Although OSO has thus far been primarily relevant to the elderly population, the whole-body impact of fat across age is important to consider. Not only does excess fat mass put increased physical loads on the musculoskeletal system, but its endocrine function also induces molecular challenges to bone and muscle. With greater research into the mechanisms of action on each system, we can work to develop preventative approaches to diseases, such as obesity, osteoporosis, diabetes, sarcopenia, and OSO.

Bone

It has been presumed that obesity would be associated with increased bone mass and concomitant protection against osteoporosis and fracture, achieved as an adaptive product of the increased skeletal loads imposed during locomotion.^{27,28} However, since non-load-bearing bones also show a similar response to obesity, this suggests that increased secretion of hormones and adipokines might also contribute to changes in bone mineral density (BMD).^{29,30} Still, more recent evidence suggests that obesity might negatively affect BMD and promote fracture risk. When evaluating the influence of increasing body fat in elderly patients with obesity, it was found that greater adiposity and adipokine levels were associated with reduced lean mass, lower BMD, and increased fracture risk.³¹ A clinical study assessing 400 obese women in relation to BMI and fracture risk found that even obese women with almost normal BMD had an elevated risk of fracture compared with obese women with higher BMD scores,³² suggesting that BMI does not always relate to fracture risk. Whether BMD is a predictor of fracture risk is still debatable. A meta-analysis performed by De Laet and colleagues concluded that the relationship between BMI and fracture risk is nonlinear and is dependent on the level of BMI. This analysis demonstrated that there is a marked increase in fracture risk with low BMI, but the relative risk for people with obesity and high BMI is not as clear.³³ Furthermore, there is growing evidence to indicate that the risks may also be site specific and mediated not only by BMD but also bone structure, geometry, and patterns of falling.³⁴ A study by Hsu *et al.*, which looked at a cohort of Chinese men and women, showed that non-spine fractures were higher in patients with a higher percentage of body fat.³⁵ Similarly, while obesity is shown to be protective against hip and pelvic fractures, it increases the risk of fracture at other anatomical sites, such as the humerus.^{36,37}

In vivo rodent models have allowed for further examination of the complex relationship between bone and fat. Wei *et al.* showed that diet-induced obese mice that develop higher BMD compared with control regular diet-fed mice present with impaired bone remodeling characterized by decreased bone resorption, low bone turnover, and decreased insulin signaling in bone-forming osteoblasts.³⁸ Some believe that the increased bone resorption overwhelms any positive effects that increased body weight may have, leading to eventual bone loss.³⁹ Other studies in diet-induced obese mice showed that bone responds in two phases, with an initial positive response, in which visceral fat expansion leads to increased bone mass, followed by a second negative phase, where prolonged exposure to obesity results in impaired bone formation and bone metabolism.⁴⁰ More specifically, deterioration of trabecular bone architecture occurs early and is followed by decreases in cortical bone density, suggesting that trabecular and cortical bone are differentially regulated in diet-induced obese mice.⁴¹

In addition to bearing weight and providing structural support, bone tissue is an endocrine target in which certain processes and properties (e.g., bone remodeling, mass, and material properties) are regulated by adipokine release, such as leptin from fat tissue.^{42,43} Leptin secretion, determined by the amount of body fat, is differentially related to bone depending on whether it acts centrally or peripherally. Central effects of leptin have been shown to have negative impacts on bone formation,⁴⁴ while peripheral leptin has been shown to promote osteoblastogenesis and suppress osteoclastogenesis.^{45,46} While increases in abdominal adiposity are in large part the primary contributors of adipokines and hormones to bone health in obesity, a rise in bone marrow adiposity, also seen in obesity, could potentially have more direct impacts, especially on trabecular bone health.⁴⁷

Bone marrow niche

The bone marrow is a unique environment that modulates many systems, including bone and blood. It provides cellular niches that support the proliferation, self-renewal, and maintenance of stem cells, specifically hematopoietic (HSC) and mesenchymal (MSC) stem cells (Fig. 1).⁴⁸ This dynamic environment also has access to a complex network of vasculature, allowing for exchange of endocrine signals and passage of cells into circulation,⁴⁹ influencing the total body system. In the marrow there is a concentrated population of MSCs that has the potential to differentiate into bone, fat, skeletal muscle, and cartilage cell lineages,⁵⁰ highlighting the therapeutic potential of these stem cells for tissue regeneration.⁵¹ Characterization of MSCs has been difficult owing to varying surface markers and differentiation potential, reliant upon species and strain of the host from which the cells are isolated.⁵² MSCs are even functionally different within the bone shaft itself, having distinct niches dependent on proximity to bone surfaces.⁵³ Minimum characterization requirements include self-renewability, plastic adherence, and ability to differentiate into fat, bone, and cartilage lineages and are identified through a panel of cell surface markers: (CD105⁺ CD90⁺ CD73⁺ and CD45⁻ CD34⁻ CD11b⁻ CD19⁻ HLA-DR⁻).⁵⁴ MSCs play critical roles in the marrow space, particularly in HSC homeostasis, expressing HSC maintenance genes and providing better homing capabilities for HSCs following lethal irradiation in mice.⁵⁵ MSCs also regulate T cells⁵⁶ and play a role in immunomodulation, influencing B-cells, natural killer cells, and dendritic cells.⁵⁷ MSC function relies in part on

local cues from the marrow microenvironment,⁵⁵ and, considering the important regulatory role of MSCs within the bone marrow space, disruption of the niche is likely to influence MSC lineage commitment and neighboring cell populations.

In the development of obesity, the expansion of fat depots is mediated through fat pad remodeling and adipocyte lineage commitment via MSC differentiation.⁵⁸ Adipogenic differentiation is primarily driven by the expression of PPAR and C/EBP gene families^{59,60} and can occur in non-adipose tissues, including the marrow space. MSC function in this niche can be influenced by both local and systemic adipokine release and from the physical encroachment of adipocytes.⁶¹ Concurrent with increases in total body and visceral adiposity, high-fat diet models of obesity in rodents show increased marrow fat,^{47,62} increased commitment to adipogenesis, and alterations in MSC differentiation potential.⁶³ MSC differentiation is also regulated by the Wnt signaling pathway,^{64–66} and it is understood that osteoblastogenesis and adipogenesis in the marrow generally maintain an inverse relationship. Adipocyte commitment is often associated with reduced bone formation, as seen in models of microgravity,^{67,68} ovarian hormone depletion,^{69,70} and aging.⁷¹ Through Wnt signaling or other osteogenic signaling pathways, it is plausible that MSC commitment to adipogenesis in the obese state can be controlled.

MSC populations also reside in tissues outside of the marrow⁷² and vary in functional capabilities depending on origin.⁷³ However, MSCs derived from bone marrow and adipose tissue have been shown to share similar gene profiles and phenotypes, in both humans and mice.^{73,74} Bone marrow–derived MSCs can migrate and engraft in tissues outside of the bone and differentiate into tissue-specific cell types (e.g., myoblasts and adipocytes) under physiological conditions or if these cell populations solely originate from resident progenitors. Work in animal models has demonstrated bone marrow cell migration that is also influenced by both diabetes and rosiglitazone.^{75,76} Similarly, Ryden *et al.* showed that the obese condition influences bone marrow cell migration and behavior in humans. Following bone marrow and blood stem cell transplantations, there was increased donor cell engraftment in the fat pads of obese individuals compared with nonobese subjects.⁷⁷ This work suggests that fat pad—and perhaps other tissue—formation and function is not derived solely from local progenitor pools and that bone marrow–derived cells and/or bone marrow–derived MSCs play a role in these tissues.

Obesity-induced MSC differentiation toward the adipogenic lineage leads to characteristic fat depots in the marrow cavity. Bone marrow adipose tissue (MAT) is distinct in comparison to white and brown fat depots.⁷⁸ While development of a fatty marrow is a known consequence of aging and osteoporosis, the obese condition accelerates the fatty marrow phenotype, as has been demonstrated in both rodent and human marrow.^{79,80} A plausible reason for MAT deposition is an abnormally high commitment of MSCs into adipocytes due to biased lineage commitment towards adipogenesis and the inability to differentiate into other cell types, such as the osteoblastogenic lineage. This inverse bone and fat relationship has been seen in models of osteoporosis⁸¹ but is not so clear in obesity models. Nevertheless, high levels of MAT observed in the aged population,^{82,83} obesity,⁸⁴ and postmenopausal women⁸⁰ have the potential to alter marrow homeostasis and crowd resident marrow cell populations, including immune and stem cells, and may have negative

effects on hematopoiesis resulting from paracrine signaling.⁸¹ This is an area of heavy research as we continue to learn more about the role of MAT in the pathogenesis of obesity.

Bone marrow hematopoietic stem cells give rise to all blood cells in the body and have been largely studied in the context of metabolic disorders owing to the impacts on the immune system. People with obesity have an increased risk and greater severity of various infections and illnesses, suggesting an immune system that is inferior to that of people without obesity.^{85,86} To a degree, this is a result of the development of chronic systemic inflammation, releasing increased proinflammatory cytokines into circulation, such as IL-1, IL-6 and TNF- α , that then promote a cascade of immune cell responses.⁸⁷ Similar changes, including inflammation and compromised stem cell populations, can also be seen within the bone marrow niche as fat encroaches into that space.⁸⁷⁻⁸⁹

Rodent models of obesity, including diet-induced, leptin/leptin receptor knockout, and estrogen-deficient models, have expanded our understanding of the impacts of excess fat on immune systems, specifically hematopoiesis and bone marrow HSCs. Studies have shown that 16 weeks on a 60% kcal high-fat diet as well as in the *ob/ob* mouse leads to increased HSC progenitor populations concurrent with increased leukocytosis.^{90,91} Interestingly, short-term, 1-week exposure to the same diet results in a transient reduction in primitive HSCs followed by a later increase.⁹¹ Several studies also reported on the imbalance of mature leukocyte (i.e., blood cell) populations caused by obesity. For example, some reported that long-term exposure to high-fat diet leads to aging of the thymus concurrent with defective T cell production.⁸³ Similarly, a different study showed a suppression of bone marrow B lymphopoiesis concurrent with deterioration of trabecular bone mass in obese mice.⁸² Other studies with diet-induced obesity have shown expansion of circulating and marrow leukocytes, including lymphocytes, data that are more consistent with reports of circulating leukocytes in obese humans.^{92,93} The collective literature on the adaptive immune cell populations in obesity are, however, inconsistent and warrant further research. Nevertheless, the general consensus is that white adipose tissues in obesity are permissive and recruit macrophages from the circulation and bone marrow, fueling the chronic inflammatory state.^{90,94}

It is believed that obesity might also influence immunity through direct alterations to the HSC and HSC progenitors that maintain the mature immune populations. In fact, HSC behavior has been shown to be primed by states of obesity-induced chronic inflammation to bias lineage commitment and their proliferative and self-renewal capabilities. More specifically, LSK⁺ HSCs from mice on a 45% kcal high-fat diet show reduced proliferation when removed from their obese *in vivo* environments. When these same obese HSCs were transplanted into a lean animal, they exhibited reduced reconstitution capabilities.⁹⁵ Additionally, when repopulating a lean, irradiated animal, obese HSCs have a biased differentiation towards myeloid cell types.⁹¹ These studies suggest that, once the HSC and/or HSC progenitor is primed by the disease state, its altered behavior cannot be reversed, even when transplanted into a lean host environment. Thus, considering the complex signaling cascades initiated by adipose tissue and obesity-related factors (e.g., cytokines, hormones), the obese condition may alter bone marrow stem cell behavior,

including their migration and contributions of bone marrow–derived cells to tissues outside of the bone.

Skeletal muscle

Fatty infiltration of muscle tissue (myosteatosis) is a strong indicator of decreased muscular function and mobility⁹⁶ and is likely to be accelerated by a systemic fat insult. Changes in muscular composition, specifically increased non-contractile tissue, directly affect the muscle tissue⁹⁷ and significantly alter overall functional capabilities of muscle.

Intramyocellular lipid and ectopic adipocytes are found in a range of conditions with decreased muscle mass and strength, including aged muscle,⁹⁸ disuse,⁹⁹ and muscular dystrophies, such as Duchene muscular dystrophy (DMD).¹⁰⁰ Fatty muscle has also been identified in the pathogenesis of obesity¹⁰¹ and linked to poor muscular mechanical properties¹⁰² and insulin resistance.¹⁰³ Importantly, myosteatosis accelerates with age, and fatty infiltration in the thigh muscle is associated with increased risk of hip fracture in the elderly.¹⁰⁴ Diet-induced obesity in the mouse has also led to impaired muscular regenerative capabilities following injury, specifically impaired satellite cell function and delayed myogenic gene expression.¹⁰⁵

Intermuscular adipocytes likely originate from fibro/adipogenic progenitors (FAPs), which readily differentiate into adipocytes, lack myogenic potential, and are influenced by cues in the muscular niche.^{106,107} Mesenchymal progenitors,⁷³ pericytes,¹⁰⁸ satellite cells,^{109,110} and PDGFR α ⁺ PW1⁺ interstitial cells (PICs)¹¹¹ have also been identified as muscular stem cell populations having adipogenic potential. Local increases in adipogenesis and alterations in the muscular niche could negatively regulate muscle regeneration through altering stem cell function, proliferation, or differentiation. Controlling adipogenic differentiation in skeletal muscle may be achievable through upregulation of the Wnt signaling pathway,^{112,113} similar to mechanisms occurring within the bone marrow cavity.¹¹⁴

The accumulation of fat metabolites within the muscle results in metabolic abnormalities, including interrupted insulin signaling⁹⁶ and glucose transport activity.¹¹⁵ Elevated levels of intramyocellular lipids are a direct indication of insulin sensitivity and/or resistance,¹¹⁶ which is commonly seen in obesity and can lead to type 2 diabetes. Insulin resistance has long been thought to develop via increased fatty oxidation leading to inactivation of pyruvate dehydrogenase activity and reduced glucose oxidation.¹¹⁷ However, a recent hypothesis suggests that muscular insulin resistance results from the accumulation of lipids within the muscle cells and activation of the θ isoform of protein kinase C (PKC- θ),^{118,119} inhibiting insulin signaling and glycogen synthesis. The metabolite responsible for the activation of the PKC- θ pathway is believed to be diacylglycerol (DAG), a fat intermediate that is a precursor to triglycerides. Previous studies showed transient increases in DAG due to lipid infusion in the skeletal muscle of both rats¹²⁰ and humans,¹²¹ and elevated DAG concentrations were found in humans that are obese and have type 2 diabetes.¹²¹ While data suggest that DAG leads to insulin resistance, it should be noted that DAG plays a complex role in the muscle, and higher concentrations of this metabolite do not necessarily translate to impaired insulin signaling. For example, total myocellular DAG content was found to be greater in well-trained athletes who also had higher insulin sensitivity compared with obese, sedentary

adults.¹²² This echoes the “athlete’s paradox:” well-trained endurance athletes often have higher levels of skeletal muscle adiposity in the form of triglycerides.¹²³

Combating obesity with mechanical signals

Exercise as a treatment modality

Exercise is a desirable treatment modality for obesity and type 2 diabetes because it is a non-pharmacological means of catabolizing fat tissue and building muscle and bone. A strong musculoskeletal system is imperative for preventing falls and fractures, particularly in the elderly and for maintaining quality of life. The public health recommendation of physical activity for adults is to perform a minimum of 150 min of moderate-intensity aerobic exercise per week (or other variations) to achieve health benefits.¹²⁴ Various exercise regimes, from walking to high-intensity exercise, have been clinically shown to provide health benefits related to the prevention or treatment of obesity and type 2 diabetes and building muscle and bone tissues.^{125–127}

Nevertheless, exercise is often not effective as a weight loss intervention. While short-term weight loss may be achieved through exercise, patients often relapse and regain the weight that was lost. Importantly, regular physical activity is critical for maintaining long-term weight loss,¹²⁸ which will in turn prevent the recurrence of obesity-related health complications. Compliance with exercise intervention is a major concern,⁸⁹ and it is often the case that this intervention is considered too strenuous or time-consuming for patients to incorporate this type of treatment into a permanent lifestyle change. Lastly, successful exercise interventions in the clinic are often coupled with dietary restrictions,¹²⁹ making it difficult to tease apart the benefits of exercise from diet. While exercise is seemingly effective in catabolizing fat and building muscle and bone, its effectiveness in long-term weight maintenance is likely to require a simultaneous healthy diet.

Epidemiological studies have shown that exercise can prevent and improve obesity and related complications, including diabetes. A study by Helmrich *et al.* showed that, among 5990 male students, the risk of developing diabetes was reduced by 6% for every 500-kcal increase in weekly exercise over a period of 14 years.¹³⁰ Exercise also protects from cardiovascular disease, reduces blood pressure and bad cholesterol, improves insulin sensitivity,¹³¹ and protects from non-alcoholic fatty liver disease,¹³² which are all complications associated with obesity. Interestingly, weight loss interventions, including diet-induced interventions or bariatric surgery, have been shown to induce bone loss in overweight and obese patients.^{133,134} It should be noted that the inclusion of exercise training with these weight loss programs significantly ameliorated bone loss in this population.¹³⁵

The influence of exercise on bone has been extensively shown in both rodent and human models to improve skeletal outcomes that are affected by obesity and diabetes, including bone mineral density and structural, material, and biomechanical properties.^{136,137} More recently, voluntary exercise has been shown to influence the bone marrow microenvironment in diet-induced obese mice, mainly by reducing fat accumulation in the bone marrow.⁶² Interestingly, while exercise reduced MAT in these obese mice, it simultaneously increased

bone mass. When challenged by PPAR- γ agonists, such as rosiglitazone, which induces MAT in mice, exercise was also able to suppress MAT and induce bone formation.¹³⁸ This was also observed in ovariectomized rats given access to treadmill running: a reduction in MAT and prevention of bone loss.¹³⁹ While this inverse bone-to-fat relationship has been observed in several models, it is not always the case, as evidenced in certain mouse strains, such as C3H mice, which experience an increase in both bone and MAT.^{78,140} However, while there was a suppression of PPAR- γ , master regulator of adipogenesis, they did not observe an increase in RUNX2, master regulator of osteoblastogenesis, indicating that this relationship might not always be one-to-one. These data suggest that marrow health can be mitigated by exercise when challenged not only by diet but also by hormonal and pharmacological insults.

The effects of exercise on bone marrow stem cells in obesity are, however, not fully understood. A recent study reported that exercised lean mice exhibit increased bone marrow MSCs concurrent with enhanced osteogenic differentiation potential and inhibition of adipogenic properties.¹⁴¹ Similarly, MSCs isolated from lean mice that underwent climbing exercise had limited adipocyte differentiation and increased osteogenic potential.¹⁴² One study investigated the response of obese bone marrow hematopoietic cells to exercise and have found that obese animals have a suppressed immune response to high-intensity bouts of exercise compared with lean animals; however, the effects on HSCs are still not understood.¹⁴³ With greater knowledge of the exact influence of fat burden on these bone marrow stem cells, we can begin to ask more questions about how exercise might be used to change their behavior, particularly in the obese condition.

The effects of exercise on skeletal muscle are also well-established, benefiting muscular composition and glucose metabolism. Exercise is anabolic to muscle¹⁴⁴ and reduces both muscular fat content in humans^{101,145} and muscle triglycerides in animal models of high-fat diet.¹⁴⁶ Importantly, the reduction of ectopic lipid is associated with improved insulin resistance,¹⁴⁵ which aids in curbing the progression of glucose intolerance. Aerobic exercise combined with weight loss was effective in reducing lipid in the thigh muscle and improving glucose tolerance in aged men.¹⁴⁷ Duncan *et al.* also demonstrated that improved insulin sensitivity in humans can be achieved through exercise without any weight loss.¹⁴⁸ Additionally, a *lack* of physical activity is associated with increased intermuscular adipose tissue in humans with type 2 diabetes,¹⁴⁹ emphasizing the importance of exercise at any level in maintaining musculoskeletal health and preventing the onset of type 2 diabetes. In addition to muscle and bone, exercise can have profound impacts on other load-bearing tissues. Exercise is commonly prescribed by clinicians to alleviate the symptoms of osteoarthritis;¹⁵⁰ however, the intensity of the exercise can be a concern, because extreme loads can have detrimental consequences on cartilage health.¹⁵¹ Strenuous treadmill running in rats and cyclic loading of tibias in mice, for example, have been shown to induce cartilage degeneration in the knee.^{152,153} Likewise, the absence of mechanical stimulation, such as in cases of extended bedrest, has been shown to induce cartilage thinning.¹⁵⁴ Moderate exercise, however, in the form of cycling, rope skipping, and light jogging, has been shown to improve knee cartilage glycosaminoglycan content in patients at high risk of developing knee OA.¹⁵⁵ As with bone and muscle, previous research suggests that obesity induces degenerative changes in cartilage tissue. Although the mechanism by which obesity induces

cartilage degeneration is still unclear, research suggests that altered joint biomechanics and elevated secretion of proinflammatory cytokines and adipokines contribute to increased osteoarthritis risk.¹⁵⁶ With regard to using exercise as an intervention, wheel running was shown to reduce the progression of osteoarthritis in obese mice while also disrupting the clustering of inflammatory cytokine expression compared with sedentary animals fed a high-fat diet.¹⁵⁷

Low-intensity vibration as an exercise surrogate or adjunct therapy

While exercise may in many cases be a desirable method for treating metabolic disorders, certain groups of people may require safer or less strenuous alternatives. The elderly or those with osteopenia, sarcopenia, or osteoporosis are at great risk of falls¹⁵⁸ and fracture.¹⁵⁹ The recommended moderate-intensity exercise may be undesirable as it may precipitate a fall and fracture, and such events in the elderly population can significantly reduce quality of life, both socially and physically.^{159,160} Those who suffer from motion-restricting musculoskeletal disorders or severe musculoskeletal pain may find a less intensive alternative to exercise attractive, and patients who are morbidly obese may be bedridden or otherwise physically incapable of exercise owing to physical limitations.

Although mechanical signals delivered through high-impact (strains > 1000 $\mu\epsilon$, or 0.1% strain) exercises with fewer cycles (< 1000 cycles per day), such as resistance training, are anabolic to the skeleton, studies show that low-impact signals (strains < 100 $\mu\epsilon$) delivered over many repeating cycles (> 1×10^5) might also impart similar benefits.¹⁶¹ Low-intensity vibration (LIV) is a low-magnitude (< 1 g where g is earth's gravitational field at 9.81 m/s^2), high-frequency (30–90 Hz) mechanical signal typically delivered through the lower extremities that gets transmitted through the skeleton. LIV biases stem cell differentiation toward osteoblastogenesis and away from adipogenesis, making this intervention a noninvasive means of building bone and muscle and preventing the formation of fat—and giving it the potential to be used as a surrogate for exercise. Compared with many exercise regimes, LIV can be less time-consuming and easier to use and has the potential to increase compliance. LIV is typically delivered in brief (< 30 min) bouts five to seven days a week and only requires a person to stand on the plate for the duration of the treatment. Most importantly, the delivery of LIV is safe for up to several hours of use each day, as designated by the International Standards Organization.¹⁶² LIV does not put people at risk of fracture in the same way that moderate-intensity exercise may, and, unlike high-intensity vibration, LIV is not damaging to the skeleton nor does it cause musculoskeletal pain.

In humans, LIV has been an effective therapeutic intervention for a variety of musculoskeletal disorders, including building trabecular bone in the tibia of children with Duchenne muscular dystrophy,¹⁶³ reducing low back pain,¹⁶⁴ preventing bone loss¹⁶⁵ and increasing muscular strength and function^{166,167} in postmenopausal women, improving balance¹⁶⁸ in patients who underwent bed rest, and increasing both muscle and bone mass in young women with low bone mineral density.¹⁶⁹ These clinical trials successfully utilized LIV intervention without any severe adverse events and targeted a range of musculoskeletal conditions in different age groups. The anabolic potential of LIV has also been demonstrated in animal models through increasing the cross-sectional area of muscle fibers,¹⁷⁰ preserving

trabecular bone loss,^{171,172} and biasing MSC differentiation toward osteoblastogenesis.¹⁷³ Considering bone, fat, and muscle tissues all arise from a common progenitor, these studies support the idea that LIV can be utilized as a protection mechanism in the presence of a high-fat environment through promoting bone and muscle anabolism and preventing adipogenesis.

LIV in models of obesity

The influence of whole-body vibration on MSCs and its ability to bias the stem cell away from adipogenesis provides the foundation for a new focus of investigation involving the prevention of obesity and type 2 diabetes.¹⁷³ While still a relatively new area of research, much of the literature has largely focused on *in vitro* and rodent models. There are currently a variety of vibration protocols with different frequencies, magnitudes, and durations being tested for medical applications; however, our focus here is on the use of lower-intensity vibration protocols utilizing low magnitudes and high frequencies for short exposure durations.

One of the earliest reports of LIV's influence on obesity used a high-fat diet-induced obesity model in C57BL/6 mice to show that 12 weeks of LIV ($0.2 \times g$, 90 Hz, 15 min/day) treatment reduced subcutaneous and visceral fat in the obese animals concurrent with increased bone marrow MSCs with decreased adipogenic differentiation capability.¹⁷³ Further testing in a similar animal model was able to show that LIV ($0.2 \times g$, 90 Hz, 15 min/day) had the ability to restore bone mass and bone marrow and peripheral immune populations (B and T cells) that were initially depleted by the high-fat diet.⁸² More recently, evaluation of bone, muscle, and fat systems with vibration was performed in an ovariectomized mouse model, which displayed both a systemic fat burden and osteopenia. These studies showed that LIV ($0.2\text{--}0.3 \times g$, 90Hz, 15–30 min/day) was able to partially protect against estrogen-deficient bone loss and reduce the presence of adipocytes or adipogenic gene expression in bone marrow and muscle tissues.^{70,174}

Whole-body vibration of different intensity but relatively low magnitude ($0.13\text{--}0.68 \times g$, 5.6–13 Hz) was shown to improve exercise performance and fatigue while also preventing fat accumulation in obese mice.¹⁷⁵ Vibration treatment was also tested and proved positive in a more severe obesity model. Application of vibration ($0.5 \times g$, 45 Hz, 60 min/day) for 12 weeks in female *db/db* mice ameliorated insulin resistance, showing the potential for the treatment of type 2 diabetes.¹⁷⁶ In male *db/db* mice, McGee-Lawrence *et al.* showed that 3 months of whole-body vibration is comparable to the effects of treadmill exercise for that same duration, specifically in mitigating adipocyte hypertrophy in visceral fat pads, attenuating insulin resistance, and increasing skeletal muscle fiber diameter and serum osteocalcin levels.¹⁷⁷ A recent clinical evaluation of overweight prepubertal boys demonstrated that 10 weeks of whole-body vibration ($1.9\text{--}6.2 \times g$, 30–40 Hz, 3–20 min/day) with dynamic lower and upper body training improved their bone mineral content and bone mineral density through a reduction in bone-resorptive activity.¹⁷⁸ These studies highlight the potential of low-intensity whole-body vibration for treatment of obesity-related complications; however, they also highlight the considerable uncertainties regarding the

mechanisms of these mechanical signals, especially in the complicated pathogenesis of obesity.

Preliminary data in our lab has shown that low-intensity vibration stimulates increased cartilage thickness in high-fat animals compared to high-fat diet controls, presumably leaving these animals better equipped to endure the potential onset of obesity-induced osteoarthritis.¹⁷⁹ Our results contrast with recent research that reports that repeated exposure to low-intensity vibration induced marked degeneration of murine knee joints, including meniscal tears and focal damage to the cartilage surface within the medial joint compartment.¹⁸⁰ Of the numerous small animal models^{70,82,171,174,181,182} and human studies^{164,168,183–185} that have utilized LIV, no damage to connective tissues, including bone, cartilage, tendon, intervertebral disc, muscle, or ligament, has been observed. It is important to note that CD-1 mice were used in this study, and when repeated in the C57BL/6 strain, no joint degeneration due to LIV was observed.¹⁸⁶ Therefore, genetic differences may be a source of contrasting results and warrant further investigation.

While recent evidence is promising, LIV is a subtle signal that is not always effective in improving or maintaining the musculoskeletal system. Whole-body vibration treatment given to an elderly (> 80years) population resulted in no reversal of poor bone mineral density,¹⁸⁷ and mechanical intervention in general is thought to be less effective in older populations owing to the decreased number and responsiveness of stem cells to mechanical signals. Slatkowska *et al.* also saw no improvement in bone outcomes in postmenopausal women subject to vibration treatment for 12 months;¹⁸⁸ however, these subjects did not all have osteoporotic bone at the start of the study. Severe systemic burdens, such as menopause or obesity, may alter cell responsiveness to mechanical signals and thus the ability of LIV to bias stem cell differentiation away from adipogenesis.

It should also be noted that animal models of obesity, especially in the mouse, vary significantly and are likely to lead to inclusive findings regarding the effectiveness of vibration. There are a range of mutations and dietary models that affect metabolism and the musculoskeletal system differently, all which are limited when modeling obesity after humans. Two of the most common and robust genetic strains include mutations in the leptin hormone (*ob*) and leptin receptor (*db*) genes. There are a range of other transgenic models targeting the *tubby*, *Carboxypeptidase E*, *Mc3r*, *Mc4r*, and *Pomc* genes, among others, and obesity can also be induced via pharmacological agents (e.g., gold thioglucose model). Dietary approaches typically include diets high in carbohydrates or fat, which can originate from various sources (e.g., animal lard, plant oils, beef tallow, coconut fat, fish oil) and vary in fat fraction (20–60%).¹⁸⁹ High-fat diets in the range of 40–60% kcal from fat are commonly used models and mimic the progression of insulin resistance and glucose intolerance seen in humans.¹⁹⁰ Data from transgenic strains or mutation models must be interpreted with care, since it may be unclear whether the cause was the genetic background or the obese phenotype, and there is certainly a difference between the effects of diet versus the effects of obesity on the body system. The effectiveness of vibration treatment in improving bone and muscle maybe reliant on the initial condition of the subjects, chosen animal models, or methods of analysis, and LIV may be more effective in humans and animals that have a pre-existing detriment.

Summary: mechanism of LIV and implications

While it is understood that a mechanical signal of low magnitude ($< 1 \times g$) is necessary for the safe application of vibration, there is currently no consensus on the signal parameters that are most beneficial in improving bone or muscle tissues or biasing stem cell differentiation. It is likely that the frequency, magnitude, and duration of exposure is specific to the target tissue—the signal most anabolic to bone in postmenopausal osteoporosis may differ from the signal most anabolic to muscle in the obese condition. The incorporation of a refractory period is a parameter of recent interest that may be more important in influencing cellular outcomes than the signal magnitude, frequency, or total duration of exposure. Previous work in rats shows that a refractory period incorporated between bouts of the dynamic loading of bone allows for the restoration of mechanosensitivity and ultimately leads to increased bone formation.¹⁹¹ Other groups also found that incorporating a rest period between loads resulted in a heightened cellular response.^{192,193} Work by Sen *et al.* demonstrated that a 3-h refractory period was more successful in suppressing MSC adipogenesis *in vitro* than either a 1-h period or the absence of a refractory period.¹⁹⁴ Allowing a period of rest may enable appropriate cellular adaptations to become more sensitive to or more primed for responding to the mechanical signal. This idea can also be translated to exercise in humans—*when* you exercise rather than *how* you exercise may be a determining factor in your body response.

While the mechanism by which LIV influences bone, muscle, and fat is not completely understood, biased differentiation towards the osteoblastic lineage resulting from mechanical stimulation is thought to come at the expense of MSC differentiation towards adipogenesis (Table 1).^{173,195,196} Recent work regarding the understanding of how MSCs recognize a low-magnitude mechanical cue and transform the signal into a behavioral adaptation has shown that the signal elicits an acute cellular response and reorganization of focal adhesions and the cytoskeleton.^{197,198} Uzer and colleagues showed that LIV activates a coupling between the cell nucleus and cytoskeleton (termed the LINC complex) that initiates intracellular signaling.¹⁹⁸ Recent studies also suggest that LIV may bias stem cell differentiation through sclerostin (SOST), which regulates adipogenesis through inhibiting Wnt signaling.⁶⁶ Vibration has been shown to suppress SOST both in culture and *in vivo*.^{199,200} Additional research is needed to gain a complete understanding of the mechanosensitive signaling pathways triggered by LIV and the consequential stem cell behavior. Understanding the mechanism of LIV-biased stem cell differentiation and the implications of the signal parameters—whether it is magnitude, frequency, duration of exposure, or incorporation of a refractory period— will allow for optimized treatment and the development of targeted therapies.

In summary, low-magnitude mechanical signals show potential to be used as an adjunct therapy or alternative to more expensive, invasive, or strenuous treatment methods. Importantly, the use of this exercise surrogate is particularly valuable for patients that suffer from musculoskeletal pain, frailty, or physical limitations due to obesity. Through biasing MSC differentiation and influencing the bone marrow space, LIV can alter obesity related complications, including impaired immunity, ectopic fat formation in muscle and bone

tissues, and insulin resistance, ultimately delaying the onset of type 2 diabetes or even improving the existing condition.

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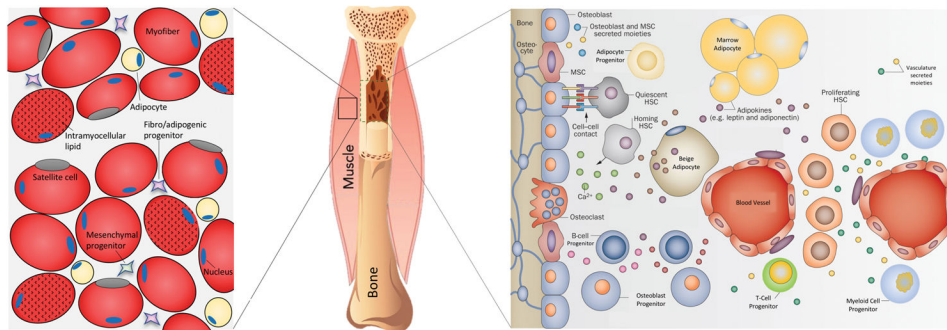


Figure 1. Schematic (adapted from Ref. 49) depicts the bone marrow cellular niche (right) and muscle cellular niche (left). The bone marrow is a dynamic heterogeneous environment and home to mesenchymal and hematopoietic stem cells. Mesenchymal stem cells regulate bone and fat systems in the marrow and support the hematopoietic niche. Hematopoietic stem cells regulate blood and immune cells, which can be compromised by obesity. The skeletal muscle microenvironment comprises multinucleated myofibers and stem cells, including satellite cells, mesenchymal progenitors, and fibro/adipogenic progenitors. Obesity results in increased intramyocellular lipid accumulation within myofibers and increased local adipocytes, likely through mesenchymal or fibro/adipogenic progenitor differentiation. This change is paralleled in the marrow, where increased marrow adipose tissue is characteristic of conditions with excess adiposity. Maintaining healthy levels of fat in bone and muscle may be achieved through mechanical stimulation intervention and biasing stem cell differentiation away from adipogenesis.

Table 1

Summary of the bone, muscle, and marrow systems in response to obesity and the impacts of exercise and LIV in the presence of excess fat

	Obesity/adipose burden	Exercise	LIV
Bone	<ul style="list-style-type: none"> - Decreases bone resorption³⁸ - Leads to low bone turnover³⁸ - Short-term diet-induced obesity (DIO) leads to increased bone mass⁴⁰ - Long-term DIO leads to impaired bone formation⁴⁰ - Trabecular bone deterioration occurs before cortical bone⁴¹ - Peripheral leptin promotes osteoblastogenesis and suppresses osteoclastogenesis^{45,46} - Central leptin negatively affects bone formation⁴⁴ 	<ul style="list-style-type: none"> - Improves bone mineral density, bone structure, and biomechanics in rodents and humans^{136,137} - Ameliorates bone loss in patients who have undergone bariatric surgery or other weight loss¹³⁵ 	<ul style="list-style-type: none"> - Restores bone mass in DIO⁸² - Protects from bone loss in OVX^{174,70} - Reduces bone-resorptive activity¹⁷⁷ - 10 weeks of vibration treatment improved bone mineral density and bone mineral content in overweight prepubertal boys¹⁷⁸ - Whole-body vibration treatment showed no improvement in bone in elderly population and postmenopausal women^{187,188}
Muscle	<ul style="list-style-type: none"> - Myosteatosis is an indication of decreased muscular function and mobility^{96, 97} - Fatty muscle is linked to poor mechanical properties and insulin resistance^{102,103} - DIO in the mouse impairs muscular regenerative capabilities following injury¹⁰⁵ 	<ul style="list-style-type: none"> - Reduces muscular fat content in humans^{101,145} - Reduces thigh muscle lipid content and improves glucose tolerance in humans when combined with weight loss¹⁴⁷ - Improves insulin sensitivity¹⁴⁸ - Reduces muscle triglycerides in high-fat diet animal models¹⁴⁶ - Anabolic to muscle in obese adults¹⁴⁴ 	<ul style="list-style-type: none"> - Increases muscular strength and function in postmenopausal women^{166,167} - Increases cross-sectional area of muscle fibers in mice¹⁷⁰ - Reduces adipogenic gene expression in the muscle of OVX mice¹⁷⁴ - Improves insulin resistance in <i>db/db</i> mice^{176,177} - Increases fiber diameter in <i>db/db</i> mice¹⁷⁷
Bone marrow	<ul style="list-style-type: none"> - Increases marrow adipose tissue^{62,47,79,80,82-84} - Long-term DIO leads to increased HSC progenitors^{90,91} - Short-term DIO leads to transient reduction followed by increase in HSC progenitors⁹¹ - Decreases and/or increases in B and T cells^{82,87, 92,93} - Increases recruitment of BM macrophages to white adipose tissue^{90, 94} - Primes BM HSCs to promote inflammation⁹¹ 	<ul style="list-style-type: none"> - Reduces MAT in DIO^{62,139} - Reduces PPAR-γ expression¹³⁶ - Increases BM MSCs with increased osteogenic potential in DIO¹⁴¹ - MSCs from exercised mice have limited adipocyte differentiation¹⁴² 	<ul style="list-style-type: none"> - Increases BM MSCs with decreased adipogenic potential in DIO¹⁷³ - Restores BM B and T cells in DIO⁸²