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Mechanical Factors and Bone Health: Effects of Weightlessness and Neurologic Injury

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Abstract

Bone is a dynamic tissue with homeostasis governed by many factors. Among them, mechanical stimuli appear to be particularly critical for bone structure and strength. With removal of mechanical stimuli, a profound bone loss occurs, as best observed in the extreme examples following exposure to space flight or neurologic impairment. This review provides an overview of the changes in bone density and structure that occur during and after space flight as well as following neurologic injury from stroke and spinal cord injury. It also discusses the potential mechanisms through which mechanical stimuli are postulated to act on bone tissue.

Keywords

bone density; weightlessness; spinal cord injury; stroke; mechanical stimuli

Introduction

The importance of mechanical loading on bone health has long been recognized. In 1892, Julius Wolff [1] published his seminal work *Das Gesetz der Transformation der Knochen* (“The Law of Bone Transformation”), in which he postulated that bone adapts its external shape and internal structure in response to the mechanical forces it is required to support, a concept that has become known as *Wolff’s law*. More than a century later, several advances have been made in further understanding the principles that govern the role of mechanical factors in bone health. Bone is dynamic tissue, and its adaptive response to its environment is fundamentally complex, as it is influenced not only by mechanical stimuli but also by hormonal and metabolic factors, among others, which together result in a net effect on bone homeostasis. Nevertheless, the critical role mechanical factors play in bone homeostasis is well-illustrated by the skeletal changes observed following the apparent loss of mechanical stimuli to bone during exposure to the microgravity, or “weightless,” environment of space flight and following neuromuscular impairment from neurologic injury (eg, stroke or spinal cord injury). In each situation, there is a rapid onset of profound bone loss in the “unloaded” skeleton, yet key differences are also observed, which may be due to the type of mechanical stimuli being altered in each case. In this review, the changes in bone density and structure

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that occur during and after space flight, as well as following neurologic injury from stroke and spinal cord injury are highlighted to illustrate the potential mechanisms through which mechanical stimuli are postulated to act on bone tissue.

Overview of Mechanical Stimuli and Bone

The primary mechanical factors that govern bone homeostasis remain a source of debate but include mechanical forces that act on the skeleton through impact with the ground or other surfaces and through skeletal muscle contractions [2]. Increasing evidence indicates that mechanical stimuli that can affect bone metabolism are transmitted to bone at the cellular level through alterations in fluid flow in the porous spaces of bone (lacuna-canalicular network) and changes in intramedullary pressure [3–5, 6•]. The sensitivity of bone tissue to mechanical stimuli is additionally influenced by age, hormone levels, and other metabolic factors [7]. Furthermore, the response of bone tissue to mechanical stimuli is dependent on factors such as the magnitude, duration, and rate of stimuli [7]. Dynamic or cyclic stimuli seem to be more anabolic to bone than static stimuli [7]. As bone will accommodate to routine loading, periods of rest between cycles of mechanical loading are necessary to restore bone mechanosensitivity [7]. However, with prolonged withdrawal of mechanical stimuli, there is a rapid onset of bone resorption. The adaptive response of bone tissue to mechanical stimuli is clearly quite complex and carefully orchestrated.

Bone Health and Space Flight

The physiologic changes to the human body during exposure to the microgravity environment of space flight lead to several alterations in mechanical stimuli across the skeleton. The load-bearing forces experienced by the lower extremities are no longer present, muscles atrophy, and a cephalic fluid shift occurs due to the loss of gravitational forces. All likely contribute to the pattern of changes observed in bone across the skeleton in microgravity.

Bone Metabolism Following Short-Duration Exposure to Microgravity

In the initial manned flights by cosmonauts on board Vostok 2 and 3, a 1-day and approximately 4-day flight, respectively, an increase in urinary calcium excretion was observed, suggesting increased bone resorption [8, 9•]. These findings were confirmed on subsequent missions in the Russian and US space programs. On the 18-day flight of Soyuz 9, both cosmonauts on board had increased in-flight urinary calcium excretion as well as loss of bone density observed [8]. Among some of the Apollo astronauts, whose missions generally lasted less than 2 weeks, there was a net loss of calcium and loss of bone density measured at the calcaneus, although not at the radius or ulna [8, 9•]. Studies performed in astronauts on board some of the Skylab missions (which lasted 28–84 days) identified an immediate increase in urinary and fecal calcium excretion despite exercise countermeasures [8, 9•]. Data gathered during these missions further demonstrated that bone loss was greatest in weight-bearing bones, with significant losses occurring at the calcaneus, but not at the radius [8, 9•].

Bone Loss Following Long-Duration Exposure to Microgravity

Bone turnover and longitudinal bone density measurements following long-duration exposure to microgravity are available primarily from crew members (cosmonauts and astronauts) aboard Mir and, since 1999, the International Space Station (ISS). Most crew members have had less than 1 year of consecutive exposure to microgravity. Changes in bone turnover markers were consistent with earlier observations of an increase in bone resorption markers, with little change in bone formation markers [10]. A net loss of calcium in-flight of similar magnitude to that observed in earlier studies from Skylab was also observed [10].

Bone density was measured primarily by dual-energy x-ray absorptiometry (DXA) before and after space flight in cosmonauts and astronauts on Mir and ISS ($n = 60$; mean duration in space, 176 ± 45 days), with rates of bone loss showing considerable variability between individuals as well as among different bone sites [9•]. Bone loss was again observed to occur predominantly in the lower extremities and spine [9•]. Overall, 43% of crew members experienced a loss of 10% or greater at one skeletal site or more, while 92% experienced a minimum of 5% loss [9•]. In the microgravity environment of space, it is estimated that bone density is lost at a rate of 1% to 2% per month involving the lower extremities and spine, with little change in the upper extremities [9•, 11].

Quantitative CT (QCT) has now been performed at peripheral sites of the radius and tibia among cosmonauts before and after 1 to 6 months of exposure to space flight [12] and at the spine and hip on some crew members before and after 4 to 6 months on ISS [13, 14]. These newer imaging modalities assess bone density in trabecular and cortical compartments of bone and provide information on bone geometry and structure, which contribute to bone strength. Vico et al. [12] confirmed that there were no structural differences pre- and postflight at the radius in cosmonauts. However, at the weight-bearing tibia, there was greater cancellous than cortical bone loss that occurred as early as after 1 month of exposure to microgravity [12]. Similarly, Lang et al. [13] identified a significantly higher trabecular bone loss at the proximal femur than previously appreciated, in addition to cortical thinning. Cortical bone loss appeared to be through endosteal resorption without periosteal apposition [13]. These changes resulted in significant decrements in compressive and bending strength at the time of return to Earth [13]. Keyak et al. [15••] converted the QCT images of the proximal femur to finite element models to estimate proximal femur strength and reported that losses in proximal femur strength following long-duration space flight exceeded what was estimated by DXA. Based on the finite element models, there was a 5% per month decrease in proximal femur strength as estimated for stance loading [15••], which is in contrast to the 0.4% to 1.8% loss per month in bone density at the hip based on DXA measures. The structural changes to bone in microgravity seem to have greater impact on bone strength than was previously recognized. These results also imply that exercise countermeasures on ISS during these times were ineffective in preventing bone loss from microgravity exposure. These more detailed measurements have permitted greater insights into the structural changes in bone density that occur with space flight. They also have been informative on further understanding the changes in bone strength following long-duration space flight.

Bone Recovery Following Long-Duration Exposure to Microgravity

Bone density also has been measured longitudinally on crew members following their return from long-duration space missions on Mir or ISS. Based on measures from 45 crew members serving on Mir or ISS, it was estimated that their bone density would return to preflight levels within 3 years following a 4- to 6-month mission [16]. These data indicate that the period of recovery for bone, even in a 1G environment, is much greater than the duration over which the bone loss occurred. Furthermore, considerable variability in recovery was noted among crew members, with some showing a slower rate of recovery than others [16]. There were also different rates of recovery depending on the site of bone, with some of the slowest recovery noted at the trochanter of the hip [16]. Factors contributing to this variability in recovery remain unclear but may relate to nutritional factors, age, genetics, or differences in physical activity levels, among others.

Although results on recovery of bone density from DXA-based measures after long-duration space flight appear encouraging, results based on QCT measurements from a small sample of ISS crew members indicate that bone structure and strength may still be compromised [14]. Based on QCT measures at the hip, the increases in bone density after 12 months from landing appear to relate to an increase in bone mass without much improvement in bone strength indices [14]. Adaptation of the proximal femur to reloading entailed an increase in bone size through periosteal apposition and an incomplete recovery of volumetric bone mineral density [14]. Although these findings support the evidence in the aging literature for periosteal apposition as a compensatory response for bone loss [14], they also suggest that bone structure, and potentially bone strength, may not be completely restored after long-duration space missions.

In summary, there are limited data available to date on whether bone loss will continue at an accelerated pace with longer consecutive exposure to microgravity, or whether the loss of bone will gradually reach a new homeostasis. Data following return from long-duration space flight suggest that reloading of the skeleton in the 1G environment can stimulate bone formation with improvement in bone density lost during space flight. However, the increase in bone density seems to reflect an increase in size of bone from periosteal apposition, perhaps as a compensatory response following bone loss or due to the effects of reloading. The time to recover bone density back in a 1G environment is considerably longer than the time to lose it in microgravity. Whether significant improvement in bone strength indices will occur over time is still undetermined.

Mechanisms for Bone Loss in Microgravity

The mechanism by which bone tissue is regulated due to unloading in microgravity remains unclear but is likely multifactorial. The loss of load-bearing activity on the lower extremities may be a contributing factor to the predominant loss of bone observed there. Although significant muscle atrophy occurs, it is seen in the upper and lower extremities [17], yet bone density is unchanged in the upper extremities. On the other hand, fluid shifts and alterations in skeletal perfusion may play a key role in microgravity-induced bone loss. Growing evidence indicates that load-induced fluid flow in the lacuna-canalicular network is an important signal that influences bone cell metabolism and adaptation [4, 5]. Nitric oxide

and prostaglandin E₂, mediators of adaptive bone formation, increase in a dose-dependent manner to pulsatile fluid flow in bone cultures [18, 19]. Alterations in interstitial fluid flow in bones are also related to change in intramedullary pressure. Adult bone marrow contains mesenchymal stem cells that contribute to the regeneration of tissue, such as bone, by differentiating into osteoblasts [6•]. Mesenchymal stem cells have been shown to respond to mechanical signals such as hydrostatic (intramedullary) pressure, fluid flow–induced shear stresses, and viscosity of their microenvironment [6•]. Microgravity induces a cephalic fluid shift and thereby changes the hydrostatic pressures the body usually encounters in the gravity environment on Earth. These alterations in hydrostatic pressure, and thereby skeletal perfusion, are a leading potential explanation for the changes in bone density noted in microgravity, which predominantly occur in the lower extremities, not the upper extremities [3, 20–22]. In the hind limb–suspended rat model (animal model analogue of space flight), femoral and tibial perfusion were reduced, and, subsequently, blood flow to the femoral shaft and marrow, as measured by radiolabeled microspheres, was diminished [23]. Conversely, blood perfusion increased to the humerus, clavicle, and mandible [23]. Changes in bone mass corresponded to the changes in perfusion, with loss of bone mass noted in the tibia and femur, and yet a net increase in bone mass in the mandible [23]. These findings parallel observations noted in human bedrest studies. In a 17-week, 6-degree, head-down, tilt bedrest study (ground-based analogue of space flight), LeBlanc et al. [24] demonstrated bone loss to be greatest in the bones of the lower extremities, pelvis, and lumbar spine, but interestingly, bone mass appeared to be increased in the skull.

Furthermore, decreased fluid flow has been demonstrated with decreased intramedullary pressure [25]. Therefore, decreases in hydrostatic pressures seen in microgravity, leading to decreased intramedullary pressure, may decrease fluid flow shear stresses on osteocytes, resulting in increased bone loss. Because vigorous exercise has not demonstrated substantial prevention of urinary calcium excretion or lower extremity bone loss in microgravity, the reduced hydrostatic pressure may contribute to decreased mechanosensitivity of bone tissue to exercise-induced loads. That being noted, based on 6-degree, head-down, tilt bedrest studies, resistive exercises were reported to be beneficial for bone density in the lower extremities [26]; exercise countermeasures in microgravity may have failed to date, possibly due to the lower resistive forces achievable in microgravity. Of note, Whedon in 1949 reported that fluid shift and axial loading in an oscillating bed during bedrest reduced hypercalciuria by 51% [27]. Issekutz reported in 1966 that 3 h/d of quiet standing during bedrest significantly reduces urinary calcium, implying a decrease in bone resorption [27]. Further work on the role of intramedullary pressure changes and fluid shifts in bone mechanosensitivity would be of importance.

Collectively, these studies and observations support the hypothesis on fluid shifts and hydrostatic pressure changes playing a critical role in bone mechanotransduction and subsequent bone remodeling, which in turn may explain how the cephalic fluid shifts contribute to the selective bone loss that occurs during exposure to microgravity. Nevertheless, other physiologic changes that occur in microgravity could further aggravate the bone loss from unloading of the skeleton, including low vitamin D levels [28], oxidative stress [28–30], radiation exposure [31], acidosis [32], and possibly low sex steroid levels

[33]. All have potential implications for the long-term effects of microgravity exposure on bone metabolism.

Bone Health After Neurologic Injury

Bone loss following neurologic injury occurs predominantly in the affected paretic limb. Changes in muscle mass and strength as well as load-bearing activities are thought to contribute to bone density changes observed following neurologic injury. The unaffected limbs can experience an increase in bone density, presumed to be related to compensation from overuse, or a decrease in bone density, presumed to be related to generally decreased overall activity and thereby loading.

Bone Loss After Stroke

The pattern of bone loss observed in stroke patients is generally limited to the paretic side and is more evident in the upper extremities than in the lower extremities. The rates and pattern of bone loss following stroke are limited because most longitudinal studies do not have follow-up longer than 1 year. Bone loss starts within days of vascular brain injury and progressively worsens until 3 to 4 months after stroke [34•]. Bone loss then seems to proceed at a slower pace until 1 year after stroke [34•]. Loss of bone density is worse on the paretic side, especially in the upper extremity. During the first year after stroke, the upper extremity paretic side can lose up to 17% of bone density, whereas the nonparetic upper extremity can show an increase in bone density [34•]. In the lower extremity, the paretic side can lose up to 14% of bone density at the proximal femur [34•]. In contrast, a loss of up to 4% in bone density was observed in the nonparetic proximal femur [34•].

In a cross-sectional study, peripheral QCT was used to measure bone density and structure on the paretic—and nonparetic—upper (mid-shaft radius) and lower (tibia) extremities of 63 men and women on average 5 years after their stroke [35, 36]. The mid-shaft radius on the paretic side had significantly lower cortical thickness, cortical area, and cortical bone density than the nonparetic side, but there was no difference in total bone area between sides [35]. These findings suggest that the paretic upper extremity undergoes endosteal resorption without periosteal apposition [35].

In contrast, results at the tibia suggested a gender difference. In men, the tibia on the paretic side had thinner cortex and a larger marrow cavity than the tibia on the nonparetic side, whereas total bone area was not different between sides, suggesting increased endosteal resorption on the paretic side but no difference in periosteal apposition [36]. In women, cortical thickness and total bone area were significantly smaller on the paretic side compared with the nonparetic side, but the marrow cavity was similar between the two sides [36]. The authors suggested these observations related to periosteal resorption on the paretic side [36]; however, they may instead signify similar endosteal resorption between sides, with greater periosteal apposition on the nonparetic side. Given the cross-sectional nature of the study, the actual changes occurring are unknown. Whether hormonal factors contribute to the gender differences observed in the load-bearing lower extremity following stroke is also unclear.

The tonic muscle activity associated with spasticity could have theoretical protective effects on bone as compared with flaccid paralysis. Although some have observed spasticity having a beneficial effect on extremity lean muscle mass and bone density [37], others have not [35, 36], reporting instead that muscle weakness and increased muscle spasticity were associated independently with decreased cortical thickness and density [35].

Mechanisms for Bone Loss After Stroke

The pathogenesis of bone loss following stroke is multifactorial, with immobilization, duration of paresis, and loss of muscle function all likely playing key roles. Other factors, such as endocrine disorders, nutritional deficiencies, and medications, further contribute to bone loss after a stroke [34•]. The overall pattern of bone changes after a stroke seems consistent with the fact that the upper extremity function in the paretic arm is greatly diminished, resulting in bone loss, and as a consequence, the nonparetic arm is used more as compensation, leading to an increase in bone mass [34•]. In the lower limbs, the reduction of gait speeds and activity leads to decreased habitual skeletal loading in both lower extremities, although the paretic lower limb may be more affected due to decreased weight bearing and muscle mass [34•, 38]. The role of spasticity in changes in bone after a stroke remains unclear.

Bone Loss After Spinal Cord Injury

Bone loss is detected as early as 6 weeks following spinal cord injury [39]. The pelvis and lower extremities are predominantly affected in paraplegics, whereas bone loss is noted in the upper and lower extremities of tetraplegics [40, 41]. Bone loss is greater in trabecular bone than it is in cortical bone. In a prospective study of acute paraplegics and tetraplegics who had bone density measures at the radius using peripheral QCT, no changes in bone density at the radius were detected in paraplegics, but in tetraplegics, there was a 28% reduction in trabecular and a 3% reduction in cortical bone density at the radius after 12 months [41]. There was also a significant decrease in tibial trabecular and cortical bone density after 12 months of 15% and 7%, respectively, with no differences in the extent of loss between paraplegics and tetraplegics [41]. Based on cross-sectional data, it was estimated that bone loss occurs exponentially following spinal cord injury, then reaches a steady state after 3 to 8 years. Compared with a reference population of healthy individuals, those with spinal cord injury had lower cortical area and cortical thickness but similar total cross-sectional area at the femur and tibia shaft [42]. These data suggest there is endocortical resorption without periosteal apposition. In paraplegics who had suffered their injury more than 8 years earlier, cross-sectional area of the radius was significantly increased by 13% relative to controls, while cortical thickness was found to be 2% greater than that of controls but did not reach statistical significance [42]. Cortical thickness at the radius in tetraplegics, in contrast, was reduced [42].

The role of muscle spasticity in bone density following spinal cord injury remains controversial, just as it does following stroke. Although some studies suggest that spasticity following spinal cord injury is associated with a lower rate of loss in bone density, others have not been able to establish a relationship [39].

In a 2-year prospective study of 54 individuals following spinal cord injury, paraplegics and tetraplegics who performed passive daily standing of 1 hour or more per day for at least 5 days per week had less bone density loss in the lower extremities and pelvis after 2 years compared with those who did not perform standing (25% vs 34% loss in the lower extremities and 15% vs 21% loss in the pelvis, respectively) [43]. The main reason for not standing related to patient and family motivation, not severity of disability [43].

Mechanisms for Bone Loss After Spinal Cord Injury

Loss of mechanical stimuli from weight-bearing activities and muscle contraction following spinal cord injury likely contributes to the bone loss observed, but other factors are also important. Several neuroendocrine changes occur following spinal cord injury, such as calcium imbalance, alterations in the parathyroid-hormone-vitamin D axis, and decreased sex steroid levels, all of which could aggravate bone loss [44]. Furthermore, alteration in neural innervation of bone following spinal cord injury may play a role. The periosteum and bone marrow have both sympathetic and sensory fibers present. Some suggest that the sympathetic nervous system contributes to bone metabolism, especially in association with other hormonal factors [44, 45]. Others suggest that disruption of sympathetic innervation following spinal cord injury may lead to disordered vasoregulation, thus affecting bone remodeling [44].

Strategies in the Management of Bone Loss Following Mechanical Unloading

Given the rapid onset of significant bone loss uniformly observed following conditions of mechanical “unloading” in microgravity and with neurologic injury, strategies to attenuate and ideally prevent bone loss are necessary. Despite the evidence for removal of mechanical stimuli in contributing to rapid bone loss, few interventions to simulate mechanical stimuli have been successful in preventing bone loss in these population groups.

To date, exercise countermeasures have been unable to mitigate bone loss during space flight [9•], but there are ongoing efforts to improve exercise prescriptions and delivery. Due to mission constraints, controlled trials are challenging to undertake. There is currently no evidence available on the use of osteoporosis drug therapies during or following space flight.

The evidence for bone loss management strategies after a stroke [46, 47] and spinal cord injury [48, 49] have been reviewed recently. Only one randomized controlled trial examined the role of exercise in bone health after a stroke and did note beneficial effects of exercise intervention on bone density and structure in the paretic limb compared with controls [46, 47]. Bisphosphonates attenuate bone loss after a stroke in randomized controlled trials and may decrease fracture risk [46].

Few randomized controlled trials have been performed examining the effects of nonpharmacologic and pharmacologic therapies following spinal cord injury [48, 49]. Some interventions designed to increase mechanical stimuli to bone, which include weight-bearing exercise regimens, functional electronic stimulation, and pulsed electromagnetic fields, have

demonstrated some (yet no conclusive) benefits in attenuating bone loss following spinal cord injury, with interventions introduced early after injury perhaps demonstrating better efficacy [48, 49]. Based on results from a recent randomized controlled trial studying alendronate, bisphosphonates administered early following acute spinal cord injury may attenuate bone loss at the hip [50].

Cost-effective recommendations for the use of bone density or other modalities to monitor bone health and evidence-based guidelines for management of bone loss following long-duration space-flight or neurologic injury from stroke or spinal cord injury are needed. Concurrent hormonal or metabolic risk factors for bone loss should be identified and treated. Use of novel strategies to deliver mechanical stimuli to bone is being explored, including the use of whole body vibration, but evidence is currently lacking on their efficacy in these specific populations. Newer drug therapies being developed for osteoporosis management, including anabolic agents, may hold promise in these population groups. Well-designed controlled trials will be necessary to help address best practice recommendations on management of bone health during and after space flight as well as following neurologic injury.

Conclusions

Loss of mechanical stimuli, as observed following exposure to microgravity, stroke, or spinal cord injury, leads to an accelerated loss of bone. In microgravity, bone loss occurs predominantly in the lower extremities and spine, but not in the upper extremities, despite an intact neuromuscular control and movement of all limbs. After stroke and spinal cord injury, significant bone loss occurs in the paretic limbs. The unaffected limb can sometimes see an increase in bone density and structure presumably due to overuse from compensation. Despite the different mechanisms contributing to bone loss in each situation, bone loss seems to occur predominantly in trabecular more than cortical bone, and there also appears to be increased endosteal resorption without periosteal apposition. These findings suggest that the stresses and strains needed to maintain bone homeostasis affect trabecular and endosteal cortical bone, with resorption in these areas when stimuli are removed. In contrast, it appears that periosteal apposition occurs in response to reloading or increased loading, as observed during the months after return from space flight, or in the unaffected limbs in stroke or spinal cord injury. These observations of bone density and structure changes following extreme examples of mechanical unloading provide insight into the critical role of mechanical stimuli on bone homeostasis and underscore the important clinical implications of both physical inactivity and exercise on bone health.

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