

Effect of Spaceflight and Microgravity on the Musculoskeletal System: A Review

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ABSTRACT

With National Aeronautics and Space Administration's plans for longer distance, longer duration spaceflights such as missions to Mars and the surge in popularity of space tourism, the need to better understand the effects of spaceflight on the musculoskeletal system has never been more present. However, there is a paucity of information on how spaceflight affects orthopaedic health. This review surveys existing literature and discusses the effect of spaceflight on each aspect of the musculoskeletal system. Spaceflight reduces bone mineral density at rapid rates because of multiple mechanisms. While this seems to be recoverable upon re-exposure to gravity, concern for fracture in spaceflight remains as microgravity impairs bone strength and fracture healing. Muscles, tendons, and entheses similarly undergo microgravity adaptation. These changes result in decreased muscle mass, increased tendon laxity, and decreased entheses stiffness, thus decreasing the strength of the muscle-tendon-enthesis unit with variable recovery upon gravity re-exposure. Spaceflight also affects joint health; unloading of the joints facilitates changes that thin and atrophy cartilage similar to arthritic phenotypes. These changes are likely recoverable upon return to gravity with exercise. Multiple questions remain regarding effects of longer duration flights on health and implications of these findings on terrestrial medicine, which should be the target of future research.

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The private expansion of space travel and its future potential have been developing at a rapid rate. The National Aeronautics and Space Administration (NASA) has been sending humans to space for decades. However, in recent years, there has been a push for longer distance, longer duration spaceflights including returning to the moon and exploring the inner solar planets such as Mars. Furthermore, commercial spaceflight and space tourism are becoming increasingly popular as companies such as SpaceX, Virgin Galactic, and Blue Origin seek to increase access to space travel for the general population. With more humans gaining access to spaceflight and longer duration missions scheduled, it is more important than ever to

understand the effects of microgravity on the musculoskeletal system. Therefore, this study seeks to examine the current state of knowledge of the effect of spaceflight and microgravity on various aspects of orthopaedic health.

Bone Mineral Density

Decreased bone mineral density (BMD) is a notable risk factor of orthopaedic morbidities ranging from increased risk of fracture to adverse surgical outcomes requiring complex primary or revision procedures.^{1,2} As a result, it is vital to understand the effect of space travel on BMD.

Findings from astronauts who have undergone 4 to 6-month missions suggest astronauts experience a 1 to 1.5% decline in BMD per month in space for normal weight-bearing skeletal sites.³ Most theories attribute the rapid decrease in BMD to microgravity-induced alteration of bone metabolism, where removal of a normal physiologic loading stimulus disrupts homeostasis between osteoblasts and osteoclasts.⁴ However, emerging theories are beginning to show that bone loss in spaceflight might be propagated by the effects of microgravity on the vestibular system. Vestibular function is known to be altered during spaceflight.⁵ Animal studies have found that induction of bilateral vestibular lesions in rats produced notable bone loss at weight-bearing skeletal sites and was associated with reduced bone formation, just as is observed in rats under microgravity conditions.⁶ Evidence suggests that this is propagated by the sympathetic nervous system because rats given beta-blockers did not demonstrate BMD reductions.

DEXA scans to measure astronaut BMD currently are achievable only before and after spaceflight; however, analysis of urinary concentrations of bone metabolism biomarkers is available in flight. Such assays have demonstrated increased levels of bone resorption markers N-telopeptide and pyridinium crosslinks as early as during the first 2 weeks of spaceflight, suggesting a relatively rapid onset of microgravity-induced changes in BMD.⁷ Terrestrial studies in patients confined to prolonged bed rest on Earth found that BMD typically plateaus at 69% of its original value, after an initial period of decline.⁸

On returning from spaceflight, bone resorption biomarkers return to preflight levels at exponential rates, with more rapid returns to baseline after longer flights.⁹ Bone formation biomarkers on the other hand remain unchanged for the first month after landing and then

increase linearly for 3 to 5 months before plateauing.⁹ While bone formation increases after return to Earth from spaceflight, bone strength does not always return to preflight levels. Analysis of astronauts returning from space found that 12 months after flight, median tibia bone strength; total, cortical, and trabecular BMD; and trabecular bone volume fraction and thickness remained 0.9 to 2.1% reduced from preflight levels.¹⁰ Of note, while longer mission length is a predictor of speed of initial BMD recovery upon landing, it is also associated with a lower rate of return to preflight BMD levels in the 12 months after landing.¹⁰

Current countermeasures use a multipronged approach toward minimizing BMD reductions. Similar to osteoporosis prevention on Earth, weight-bearing exercise attenuates bone loss in space. However, creation of an artificial weight-bearing environment in spaceflight is challenging. To combat this problem, NASA developed the Advanced Resistive Exercise Device (ARED), which uses vacuum cylinders and inertial flywheels to generate weight-bearing force (Figure 1).¹¹ While no spaceflight exercise protocol to date has been able to completely prevent BMD loss, Comfort et al¹² demonstrated notable attenuation of bone loss with ARED protocols compared with control subjects. Additional interventions include use of anti-osteoporosis medications such as diphosphonates. These antiresorptive medications provide notable benefit when combined with ARED protocols as shown in a recent study, where diphosphonate plus ARED use reduced the expected decline in all indices of bone physiology during a 5.5-month spaceflight.¹³

Bone loss in spaceflight has been studied for decades, but ample opportunity for additional research remains. As human exploration to Mars is undertaken, understanding the effects of long-duration spaceflight missions beyond 6 months is vital. Furthermore, as vestibular system alterations have been implicated in potentially altering BMD, clinical research in human subjects should be conducted to determine the role of vestibular dysfunction in BMD reduction and pharmacotherapeutic ability to prevent it through use of beta-blockers. Finally, because of a substantially larger number of men compared with women who have participated in spaceflight, most human-based studies on BMD after spaceflight include a disproportionate number of men compared with women. BMD predictive models for missions to Mars account for these discrepancies and predict similarly decreased post-spaceflight T scores for men and women alike, regardless of ethnicity.⁸ Nonetheless, more specific research

Figure 1Images showing astronauts' demonstration of deadlifts and curls using the ARED¹¹

into the effect of spaceflight on female BMD would provide vital additional context.

Fractures

Fractures can pose notable health risks to astronauts depending on the characteristics of the fracture and treatment time line and availability. Furthermore, a fracture could render the astronaut unable to perform vital tasks that compromise the mission. Fracture healing in microgravity may not follow the same temporal pattern seen on Earth, and fracture management techniques used on Earth may not be available nor effective in a microgravity environment. As a result, it is vital to understand the effect of spaceflight on fracture risk and healing in astronauts during and after spaceflight.

Decreased BMD is a known risk factor of fracture on Earth.¹ Despite this, the risk of fracture from reduced BMD during or after spaceflight is thought to be minimal (<0.1%) for various reasons.³ This empiricism is supported by the low incidence of fracture in over 50 years of spaceflight.³ Risk of fracture while in low Earth orbit is decreased because the applied loads associated with falling are virtually nonexistent. Risk can increase while performing mission-related activities involving construction of habitats, jumping from platforms, etc. Fracture risk-identification models predict that during spaceflight, the reduction in BMD as-

tronauts experience put them at increased risk of fracture very similar to osteoporotic individuals on Earth.¹⁴ Anatomic locations at high risk of fracture include the femoral neck, lumbar spine, and distal radius.^{14,15} Owing to the increased use of hand-based propulsion, the distal radius has the highest risk of fracture in spaceflight compared with other skeletal locations.^{14,15}

Limitations in treatment and differences in bone healing in a microgravity environment may increase the severity of injury. In a microgravity environment, post-traumatic bone regeneration produces a smaller callus in the initial phases of healing and results in less fully bridged fracture gaps and lower strength of consolidated bone fragments.¹⁶ Spaceflight might also affect hemostasis, resulting in decreased blood cells and T cells recruited to the injury site, further impairing healing.¹⁶ Recent animal studies have found that after a closed femoral fracture, rats in a microgravity environment had markedly reduced levels of transcription factors associated with osteogenesis, chondrogenesis, and angiogenesis.¹⁷ As a result, prolonged exposure to microgravity may slow fracture healing or even prevent proper healing of fracture on long-duration spaceflights.

Splints are commonly included in spaceflight medical kits to immobilize extremity fractures and promote healing, but there is also emerging research regarding novel therapies to specifically enhance fracture healing in microgravity.¹⁶ Studies in rats exposed to spaceflight found systemic effects of thrombopoietin-enhanced

recovery of fractured bones by induction of increased trabecular thickness, reduced trabecular spacing, increased connectivity density, and decreased marrow area, although the exact mechanism remains unclear.¹⁸ There have also been indications that intermittent parathyroid hormone therapy and low-intensity pulsed ultrasonography may be efficacious in promoting tissue repair and exerting anabolic effects on fracture healing.¹⁶

What is currently understood about fracture risk in space mostly comes from human studies before and after spaceflights and from animal models. Little is known regarding the effect of either microgravity or spaceflight for a longer term. As a result, risk of fracture both during and after long-duration missions must be studied further. There is also a need to better understand and establish pharmacotherapies for fracture healing. Future studies should seek to determine the effect of therapies like thrombopoietin on human fracture healing.

Muscles, Tendons, and Entheses

On Earth, axial loading because of gravity allows humans to use bipedal ambulation to move between locations. In microgravity during spaceflight, astronauts rely more on their upper extremities for propulsion to move. Muscles and tendons like the rotator cuff are, therefore, recruited more frequently and in new ways to better navigate the environment. Moreover, for long-duration missions, such as missions to Mars, astronauts may be required to engage in physical labor immediately upon exposure to gravity environments that differ from Earth. Understanding how microgravity affects the muscle-tendon-enthesis unit is vital to maintain function and avoid injury both intra-spaceflight and post-spaceflight.

Upon microgravity exposure, muscle atrophy occurs at a very rapid rate. After a 5 to 11-day spaceflight, the muscle mass diminishes by up to 20%.¹⁹ While this decrease does not trend linearly as time in a microgravity environment increases, additional astronaut studies have recorded muscle mass decreases of 30% on 3 to 6-month missions.²⁰ Simulated microgravity studies on patients confined to bed rest seem to demonstrate that the loss in muscle mass plateaus after 4 months of gravitational unloading²¹; however, additional investigation is needed to confirm longer duration (>6 months) effects.

The macroscopic decreases in the muscle mass are accompanied by microscopic changes in muscle tissue that are associated with a decrease in size, not number, of

muscle fibers.¹⁹ In addition, spaceflight leads to a preferential decrease in class I slow-twitch myofibers *in vivo*, with class II fast-twitch fibers atrophying at a lower rate.²²

The tendon is similarly sensitive to mechanical loading.²³ As microgravity exposure unloads tendons, mechanical stimulation leads to tendon cellular response that results in changes to the extracellular matrix.²³ Lack of gravitational stimulus also alters tendon cell autocrine and paracrine pathways, reducing fibroblast activation and collagen synthesis while downregulating transcription factors essential for tendon strength.²⁴ These changes affect the stiffness of tendons in short and long terms. A recent study subjected 18 men to 90 days of bed rest, with half of the participants performing resistive exercise during the 90-day period.²⁵ In the bed rest-only group, Achilles tendon stiffness decreased by 58%, and in the bed rest plus exercise group, Achilles tendon stiffness decreased by 37%.²⁵ Another study unilaterally immobilized the knees of 16 men for 14 days and found patellar tendon stiffness markedly decreased on the immobilized side.²⁶ Additional research has found that in most cases, decrease in tensile strength of the tendon is not associated with corresponding atrophy.^{26,27}

Gravity affects the enthesis in addition to the tendon itself. Entheses have a fibrocartilaginous layer that serves as the transition point from the tendon to bone, which seems to be most sensitive to chronic reductions in mechanical loading.²⁸ During periods of unloading, there is a decrease in area of fibrocartilage and its proteoglycan content, a decrease in number and proliferation of chondrocytes, and disorganization and decreased expression of collagen II.^{27,29,30} Although limited animal model studies exist, murine studies in simulated microgravity environments have found unloading to cause decreased enthesis stiffness of the Achilles tendon.³¹ The effects on altered enthesis integrity seem to return to a preflight state shortly after return to a standard gravity environment.²⁷

As the muscle mass decreases and the tendon and enthesis become more lax from gravitational unloading, the function and strength of the muscle-tendon-enthesis unit diminishes. On analysis of knee extension, 12% loss of knee extension torque strength was noted after short spaceflights and 31% loss of knee extension torque strength after long spaceflight.^{19,20} The degree of loss of strength and function is often greater than the degree of muscle mass loss. After a 6-month mission, one astronaut experienced a 20% loss of calf muscle volume, but a corresponding 50% decrease in calf muscle explosive

force.³² It is likely that increased tendon laxity contributes to the disproportionate decrease in strength as the relaxed tendon reduces muscle-tendon unit force output and speed of contractile force.^{25,33} Additional mechanisms for the discrepancy are thought to be due to alterations of motor unit recruitment, the contractile apparatus, electromechanical efficiency, and muscle damage.¹⁹ This decrease in muscle strength correlates with muscle mass loss, similarly plateauing.³⁴

Studies show that the muscular atrophy experienced by astronauts during spaceflight is recoverable upon return to Earth, with literature demonstrating muscle mass returned to preflight values 1 to 4 years after return from spaceflight.³⁵ However, with aggressive rehabilitation and conditioning, muscle mass and function recovers as early as 1 to 2 months upon return.²⁰ No studies to date examine postflight tendon and enthesis health.

Exercise during spaceflight remains the primary means of muscle atrophy prevention. However, resistance exercise training only reduces the quantity of muscle volume and strength loss without completely preventing it.³⁶ While there has been discussion regarding optimization of testosterone, vitamin D, cortisol, growth hormone, and thyroid hormones to preserve the muscle mass, there is insufficient research to support their role in preventing muscle atrophy.²² Notably, no study to date has examined countermeasure efficacy in preserving tendon and enthesis health.

There are many knowledge gaps when it comes to understanding the effect of spaceflight on muscle, tendon, and enthesis health. Because astronauts rely upon upper extremity health for mobility in addition to task completion in a microgravity environment, specific attention should be paid to understanding the effect of microgravity on tendons of the upper extremity. Furthermore, after long-duration spaceflight to Mars, astronauts will rely on upper extremity health for habitat building. As a result, better understanding of how tendons and entheses respond to return to non-Earth gravitational environments after exposure to microgravity should be a priority. Finally, investigation into how vestibular changes affect muscle and tendon health should be explored.

Cartilage and Arthritis

Recently, research has emerged demonstrating the effect of spaceflight on cartilaginous health in spaceflight. While it remains true that spaceflight-related changes to cartilage may not immediately endanger mission suc-

cess, research on articular cartilage and development of osteoarthritis remains relevant for the post-spaceflight musculoskeletal health management.

Cartilage is sensitive to biomechanical signaling and adapts based on the articular load it is subjected to.³⁷ Disuse of joints causes mechanoadaptations that lead to notable loss of cartilaginous volume.³⁷ Loss of load-bearing stimuli creates metabolic changes that decrease sulfation of glycosaminoglycan terminal residues. As a result, less water is drawn into the cartilage, resulting in thinner, atrophied cartilage, similar to osteoarthritic phenotypes.^{38,39}

There are no imaging studies to evaluate cartilage thickness in humans intra-spaceflight or post-spaceflight to date, but studies have reported higher concentrations of a biomarker of cartilage degradation, urinary C-terminal crosslinked telopeptide of type II collagen (CTX II), during spaceflight.⁴⁰ Elevated CTX II levels are associated with incidence and radiographic severity of osteoarthritis as well as an independent risk factor of joint arthroplasty.^{41,42} This suggests that spaceflight may cause changes in cartilage physiology and increased susceptibility to arthritis. Additional murine studies have found decreased articular cartilage thickness and low glycosaminoglycan content in mice exposed to microgravity environments.⁴³

Cartilage may return to preflight health upon reloading with exercise.⁴³ In hind-limb unloaded mice, cartilage thickness only recovered to control levels in mice that exercised upon reloading—lack of exercise upon reloading was associated with lack of cartilage recovery.⁴⁴

Future confirmatory studies assessing cartilage health in humans subjected to microgravity conditions both for short-term and long-duration spaceflights are necessary. While cartilage injury does not acutely threaten mission success, spaceflight-induced cartilaginous changes could affect postflight quality of life. Future studies should be directed toward understanding how cartilage recovers after spaceflight and how spaceflight affects osteoarthritis risk upon return to gravitational environments.

Spine

During spaceflight, astronauts are subjected to prolonged periods of spinal decompression in microgravity and intermittent spinal compression from high-speed spacecraft acceleration. As a result, the spine is especially susceptible to spaceflight-related change. Spine injury has the potential to markedly hinder mission success. It is, therefore, necessary to understand how the

spine adapts to spaceflight to best preserve the musculoskeletal health of astronauts.

In microgravity environments, the spine elongates by 4 to 6 cm with associated flattening of lumbar lordosis, swelling of intervertebral disks, and loss of mass and tone of paravertebral muscles.^{45,46}

Unloading of the spine during weightlessness and supraphysiologic hydration of intervertebral disks causes disk swelling and increases the risk of herniation.⁴⁷ Analysis of over 300 astronauts found a 4.3 times greater risk of cervical or lumbar disk herniation after spaceflight compared with control subjects not involved in spaceflight.⁴⁸ These findings are especially pronounced in the first year returning from spaceflight, with up to a 35.9 times increased risk of cervical disk herniation in astronauts during this period.⁴⁸ Increased risk of herniation poses special concern for missions to Mars where astronauts may be required to perform immediate work in a partial gravity environment after long-duration spaceflight.

Currently, some strategies exist to mitigate back pathology in spaceflight and upon return to a gravitational environment. Interventions include wearing a penguin suit and sleeping in the fetal position to improve protection of lumbar IVD from herniation in spaceflight.⁴⁹ Furthermore, the highest priority prevention approach for the lumbar spine involves postflight care with limited spinal flexion, passive spinal loading in spaceflight, and exercises to reduce IVD hyperhydration after flight.⁵⁰

Most data on spinal injury and spaceflight come from before the 2006 implementation of NASA's ARED. Additional research is necessary to determine the effect of weight-bearing exercise on mitigating the effects of spaceflight on spinal health. ARED does not allow cervical spine weight-bearing, so future studies and protocols should be designed at protecting the more rostral aspects of the spine. Finally, because most risk of injury comes from return to a gravitational environment after spaceflight, better understanding how return to partial gravity environments affects injury risk is important to develop injury prevention strategies.

Summary

Virtually every component of the musculoskeletal system adapts upon exposure to a spaceflight environment. Existing research provides valuable insight for orthopaedic best practices in space medicine, but there is still much to be discovered that will inform countermeasure prescription and long-term management. Questions

remain concerning the details of these changes and the resulting phenotype, the long-term effect of these changes, how to mitigate the effects of microgravity on the musculoskeletal system, the effect of longer duration flights on health, the interplay between changes in each aspect of the musculoskeletal system, and the implications of these findings on terrestrial medicine, etc. This places increased emphasis on collecting pre, intra, and postflight data from current missions to best understand the true effect of spaceflight on musculoskeletal health. Future research should seek to determine the effect of novel countermeasures on bone, muscle, tendon, and spine adaptation to spaceflight, optimize diagnostic modalities in space and understand their limitations, and study novel methods of treating musculoskeletal injury in space.

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