JOURNAL OF WOMEN'S HEALTH
Volume 23, Number 11, 2014

DOI: 10.1089/jwh.2014.4910

Effects of Sex and Gender on Adaptation to Space: Musculoskeletal Health

Lori Ploutz-Snyder, PhD,[1] Susan Bloomfield, PhD,[2] Scott M. Smith, PhD,[3] Sandra K. Hunter, PhD,[4]
Kim Templeton, MD,[5] and Debra Bemben, PhD[6]

Abstract

There is considerable variability among individuals in musculoskeletal response to long-duration spaceflight. The specific origin of the individual variability is unknown but is almost certainly influenced by the details of other mission conditions such as individual differences in exercise countermeasures, particularly intensity of exercise, dietary intake, medication use, stress, sleep, psychological profiles, and actual mission task demands. In addition to variations in mission conditions, genetic differences may account for some aspect of individual variability. Generally, this individual variability exceeds the variability between sexes that adds to the complexity of understanding sex differences alone. Research specifically related to sex differences of the musculoskeletal system during unloading is presented and discussed.

Musculoskeletal Health in Space

It is well known that men and women differ in many aspects of the musculoskeletal system, with men generally having greater muscle and bone mass. Important questions for spaceflight application are whether the time course of loss with unloading is the same for men and women, whether the initial bone or muscle mass influences the rate of loss, whether that rate of loss is linear over an ~3-year period (the most likely duration of initial exploration-class missions), and whether loss of bone and/or muscle over this period of time has secondary effects on other musculoskeletal tissues such as articular cartilage. If there are large sex differences in the time course of loss, this would be a compelling argument for sex-specific countermeasure development for exploration-class space missions. However, to the best of the authors' knowledge, there are no published human studies that have directly assessed sex differences in either the time course of disuse-induced bone or muscle loss or the impact of starting values.

It is well established that the human musculoskeletal response to unloading is highly variable among individuals, with 10-fold differences in response among participants often observed. As an example, after 30 days of unilateral lower limb suspension, individual responses ranged from a 2.5% to a nearly 20% decline in plantarflexor cross-sectional area compared with before the suspension.[1] Similarly, with actual spaceflight the loss of cancellous bone in the distal tibia after 6 months aboard Mir ranged from 2% to 24%; such changes range from a negligible loss to deficits equal to those observed after spinal cord injury.[2] Understanding the factors that contribute to such large variability is an important step toward both selecting and protecting the first astronauts who undertake very long (2–3 year) exploration missions. The extent to which biological sex or sex-based hormones contribute to this variability is unknown.

While this review is focused on sex differences in the response of the musculoskeletal system to the unloading of microgravity, it is important to remember that the overriding uncertainty about which factors contribute to individual differences is a significant issue. The primary emphases of the literature review were to evaluate sex differences with respect to (1) the magnitude of response and time course of muscle/bone loss to unloading, (2) the influence of negative energy balance on muscle/bone loss, and (3) risk of joint injury and the impact on articular cartilage. This literature review evaluates sex differences in middle-aged, healthy adults and does not consider adolescent or early adult growth and development, menopause, osteoporosis, or old age. While these are all certainly important, there is very little, if any, literature related to spaceflight and these issues.

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[1] Exercise Physiology and Countermeasures, University Space Research Association and [3] Biomedical Research and Environmental Sciences Division, National Aeronautics and Space Administration (NASA) Johnson Space Center, Houston, Texas.
[2] Department of Kinesiology, Texas A&M University, College Station, Texas.
[4] Exercise Science, Marquette University, Milwaukee, Wisconsin.
[5] Department of Orthopedic Surgery, University of Kansas Medical Center Kansas City, Kansas.
[6] Department of Health and Exercise Science, University of Oklahoma, Norman, Oklahoma.

Time Course and Magnitude of Response: Muscle

There is considerable individual variability with respect to loss of muscle size and function as a result of unloading.[3] The precise extent to which sex differences contribute to this is unknown. There is limited evidence in the literature that sex differences related to muscle atrophy might exist. In the first 2 weeks of unloading, minimal sex differences are apparent in whole muscle atrophy (2%–4%) in side-by-side comparisons.[4,5] If unloading extends beyond 2 weeks, women may experience greater reductions in whole muscle volume[6] and fiber area, particularly in fast-type 2 fibers.[7,8] Slow-type 1 fibers in both men and women exhibit preferential atrophy with unloading. There is limited evidence that women experience greater loss of strength in the first 30 days of bed rest, but this sex difference in rate of loss may be reversed with long duration unloading (>4 months). Women demonstrate greater impairment in neural activation of muscle after short-term unloading;[4,5,9] future studies should determine if this leads to greater fatigue susceptibility in women in the first 2 weeks of unloading. There is one study suggesting that recovery of strength after unloading may be slower for women than men.[10] Taken together these data suggest that the time course of unloading-induced muscle loss may be sex specific.

There are also areas where sex differences appear quite unlikely. For both men and women, whole muscle and single muscle fiber atrophy does not fully account for the strength and power loss; the reduction in the force and cross-sectional area of type 1 fibers appears to be very similar in both genders.[8,11,12] A significant gap in knowledge is whether sex differences in strength loss/neural activation translate to differences in functional performance (e.g., mission-related tasks).

Time Course and Magnitude of Response: Bone

Sex differences in bone mineral density (BMD) are well documented; since bone mass scales to body mass, men on average have a larger skeletal mass. There is little evidence, however, on whether there is a sex difference in rates of bone loss with unloading or in the rate or magnitude of recovery therefrom. While the effects of bed rest on BMD and/or bone metabolism have been examined separately in men[13,14] and in women,[15,16,17] there have been no human studies that have been statistically powered to make direct sex comparisons. In one 17-week bed rest study that included both men ($n=13$) and women ($n=5$) at one of 10 sites measured (calcaneus), bone loss was markedly less in women than men.[6] However, the dual energy x-ray absorptiometry-assessed total hip BMD for women in a 60-day bed rest study[17] revealed a substantial loss at that site, whereas men in a similar study did not have a decrease in total hip bone mineral content.[13]

Volumetric BMD and bone geometry of tibial cancellous and cortical compartments have been evaluated after prolonged bed rest using peripheral quantitative computed tomography (pQCT) in men[13,15] and high-resolution pQCT in women.[16] The small gender differences observed in the bone loss rates at those tibial sites are within the reported precision for these pQCT variables. Side-by-side investigations using rodent hindlimb unloading (a commonly used surrogate for microgravity) reveal greater cancellous bone loss in skeletally mature female mice[18] and a distinct effect of starting values (mice with greater bone volume at the start lost less bone). However, in mature rats few differences between genders are apparent.[19]

There is little definitive evidence showing sex-specific differences in the rate of bone loss. Certainly, some of the individual differences may be related to sex-specific hormonal factors. As is the case with muscle, the individual variability within gender in response to unloading is large and should be better understood.

Negative Energy Balance

Some bed rest studies have restricted energy intake and allowed weight loss by design or allowed subjects to consume food at their discretion, so as to not coerce intake. The 60-day Women's International Simulation for Space Exploration study was one of these studies, and as a result, these female subjects did lose body weight (lean tissue more than fat) during bed rest at a rate of 0.06 kg/day.[20] In a similar 90-day study with male subjects conducted earlier at the same institution, men also lost weight at 0.04 kg/day (calculated from the published average weight loss).[21] Due to the many differences in study design, it cannot be concluded with any certainty if this slight difference in rate of weight loss between men and women is of any significance.

While ''weightlessness'' is a key aspect of space travel, an unexpected analog comes in the form of studies related to weight loss. Though there is a fair amount of literature on weight loss and effects on bone[22] similar to space-related research, few studies have examined the effects of negative energy balance on bone with regard to gender, and those that have attempted are plagued by many confounding factors (age, body size, diet- and/or exercise-induced weight loss, rate of weight loss, etc.), making drawing conclusions difficult.

Hence, there is a paucity of literature evaluating sex-related differences relative to the effects of energy deficit on bone and muscle metabolism. Making comparisons across separate studies evaluating male and female responses is fraught with confounding factors. If one were to speculate, there do not appear to be major sex differences in the bone or muscle responses to energy deficit between men and women.

Joint Injury

Sex-based differences have been identified in the incidence of osteoarthritis (OA), with OA of the knee, in particular, significantly more common in women. Sex-based risk factors explaining this include the loss of estrogen's anabolic effect on cartilage after menopause, a higher incidence of predisposing knee injuries–such as anterior cruciate ligament tears–in women, and increased joint laxity.[23] There is clear evidence from animal studies that regular mechanical loading is essential to cartilage health. In humans, 6 or more weeks of non-weight-bearing can produce changes in magnetic resonance imaging images of knee cartilage that resemble OA.[24] However, sex-based differences in the response to joint unloading have not been elucidated.

Because articular cartilage health is impacted by the quality of the underlying bone as well as the strength of muscles around the joint, assessment of the potential risk for articular cartilage injury imposed by unloading needs to include evaluation of all three tissues: bone, muscle, and cartilage. There is some evidence to suggest that osteopenia of subchondral bone underlying articular cartilage contributes to cartilage degeneration.[24,25,26] Conversely, damaged cartilage releases receptor activator of nuclear factor kappa-B ligand (RANKL) and other inflammatory components, which can lead to the loss of adjacent bone.[27] Since muscles serve to stabilize and dampen forces across joints,[28] loss of muscle mass and strength after a prolonged unloading can contribute to joint injury risk and early degenerative joint changes, especially in the knee. However, sex-based differences in the relative impact of bone and muscle loss on joint health have not been defined. Specific interventions to increase load-bearing or strengthening activities in space will be indicated. They may also identify the need for progressive strengthening and joint loading upon arrival on a planetary surface after extended microgravity exposure, after return from space or after prolonged period of non-weight-bearing on Earth.

Musculoskeletal injuries have been reported in-flight at a rate of 0.021 per flight day for men and 0.015 per flight day for women; hand injuries are the most common, with abrasions and small lacerations the most common manifestations.[29] There are few data on the recovery of the musculoskeletal system following spaceflight and even less data on sex differences in recovery rates. Generally, international space station crew have substantial recovery of muscle strength within a month following flight. The time course of recovery of bone mineral density has been evaluated but not specifically for sex differences. In general, half-lives for recovery of bone mineral density are ~150–200 days depending on site.[30]

Acknowledgments

The working group gratefully acknowledges Andrea Hanson, PhD, Wyle Science, Technology, and Engineering Group, National Aeronautics and Space Administration Johnson Space Center, for assistance in preparation of this manuscript.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Lori Ploutz-Snyder, PhD
Exercise Physiology and Countermeasures
University Space Research Associates
National Aeronautics and Space Administration Johnson Space Center
2101 NASA Parkway
Houston, Texas 77058

E-mail: lori.ploutz-snyder-1@nasa.gov