NASA-STD-3001 Medical Technical Brief

Bone Loss

OCHMO-MTB-013
Rev D

Executive Summary

Bone density loss in microgravity has been a well documented crew health concern since the Skylab missions when calcaneal mineral bone density loss was detected using single photon absorptiometry (1974-1985), and later when cosmonauts showed bone mineral loss via DXA scanning (1986-2000) (Leblanc 2000). Since that time, much research both terrestrially and on ISS has occurred to address this risk. Thus far, there have been no spaceflight in-mission bone fractures, but NASA has identified the risk as "given the skeletal changes that occur during space missions there is a possibility that crew bones during and after spaceflight are not as strong as they were before the mission and fracture may occur for activities otherwise unlikely to induce fracture prior to space missions". This medical technical brief details bone physiology, spaceflight effects on bone, countermeasures that minimize bone loss, and requirements which provide limits and countermeasures to bone loss, including exercise, nutrition, and monitoring that are designed to protect crew health in-flight, post-flight, and throughout crew lifetime, as well as protect mission success. *NASA HSRB Risk*

Relevant Technical Requirements

NASA-STD-3001 Volume 1, Rev C
[V1 3002] Pre-Mission Preventive Health Care
[V1 3003] In-Mission Preventive Health Care
[V1 3016] Post-Mission Health Care
[V1 3017] Post-Mission Reconditioning
[V1 3018] Post-Mission Long-Term Monitoring
[V1 4020] In-Mission Nutrient Intake
[V1 4026] Pre-Mission Bone Mineral Density
[V1 4027] Pre-mission Bone Countermeasures
[V1 4028] Post-Mission Bone Reconditioning

NASA-STD-3001 Volume 2, Rev E
[V2 7038] Physiological Countermeasures Capability
[V2 7043] Medical Capability
[V2 7100] Food Nutrient Composition

Crewmembers participating in microgravity training aboard a NASA KC-135 aircraft. *Source: NASA*

Physiology

Spaceflight effects on bone health

Bone mineral loss has been monitored as a scientific experiment in Gemini, Apollo, and Skylab programs since 1965. The spaceflight environment of microgravity reduces the loading on muscles and bones. This reduction in the weightbearing function of muscles/bones in space may cause the tissue to atrophy – changing its form in response to not needing to be as strong to resist forces. The decrease in mechanical forces (i.e., the reduction in bone's weightbearing function) alters the balance in the bone remodeling cycle, ultimately resulting in decreased bone density and possible increased risk of fracture.

Spaceflight conditions that increase risk of bone loss

Microgravity reduces loading on muscles and bones, decreasing the weightbearing function of muscles/bones contributing to decreased bone density.

Longer duration missions (>90-100 days) including Lunar and Mars increase exposure to bone degrading conditions.

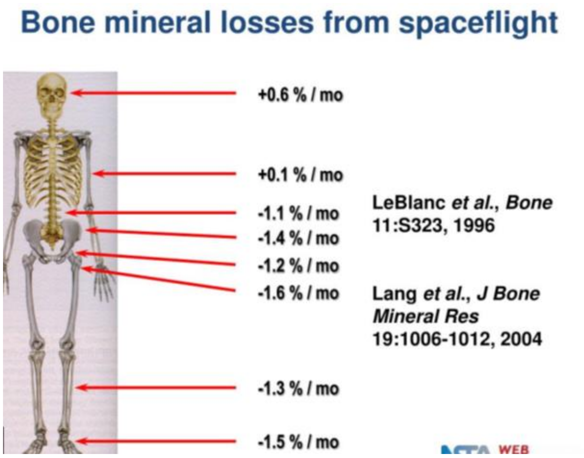
Bone formation markers microgravity alters bone osteoblast process resulting in loss of bone health.

Changes in bone structure cortical bone recover well after spaceflight, but trabecular bone may fail to recover leading to reduction in bone strength. Cortical vs. trabecular bone recovery is also influenced by the location of osteoblasts and osteoclasts and purposes of the cortical (for resistance to bending and torsional forces) and trabecular bone (for remodeling of bone to release calcium and maintain mineral balance without jeopardizing bone strength). Trabecular bone is metabolically active to release calcium without compromising the strength of the whole bone, which cortical bone is a major contributor.

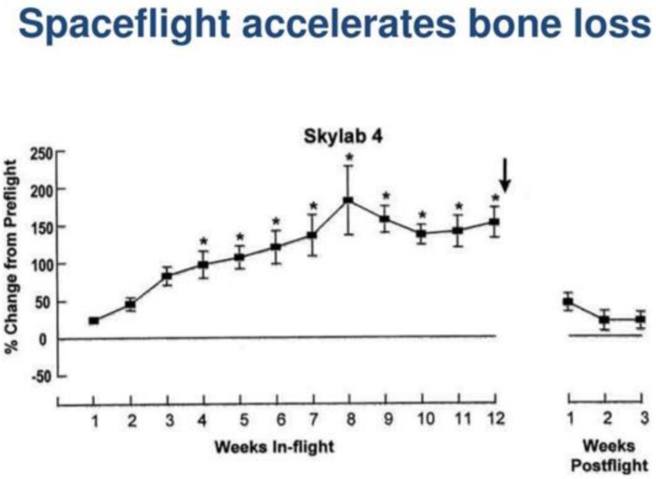
Mechanical-loaded events or physical activities during extravehicular activities (EVAs), an increase fracture risk in deconditioned astronaut, depending on expected applied loads and degree of skeletal fragility.

Radiation exposure may contribute to bone compromise.

Limited exercise equipment optimal hardware for bone growth stimulation may not be available.



Source: Scott et al. (1998) Collagen Cross-Link Excretion during Space Flight and Bed Rest



Source: Zwart & Smith (2005) The impact of space flight on the human skeletal system and potential nutritional countermeasures: review article

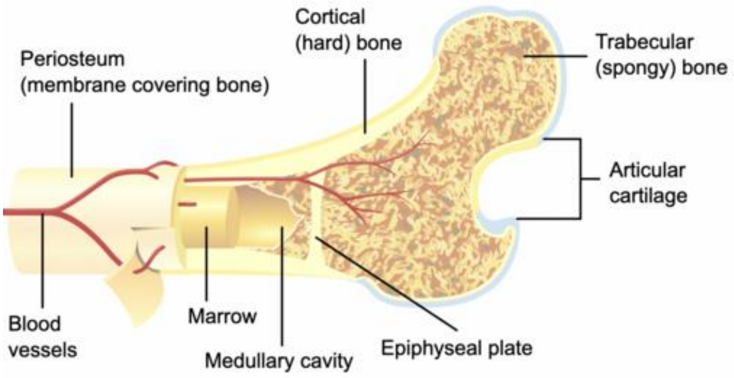
Mission risks due to spaceflight bone loss:

1. Bone density decrements leading to in-flight bone fracture.
2. Compromise to mission objectives due to crew bone/health decrements.
3. Post-flight bone fragility and increased long term risk of osteoporosis/bone fracture.
4. Bone loss leading to excess calcium loss to urine and increased risk of calcium renal stones

Physiology

There have not been any bone fractures during spaceflight but measured bone loss has occurred, and NASA is concerned with how that loss occurs in order to best prevent bone loss risk, especially during long duration/Mars missions. Human bone consists of cortical bone, which is the smooth hard outer layer of bone and trabecular bone, the spongy inner structure.

Cortical bone forms shafts of long bones and accounts for 75-80% of all bone mass in the skeleton. Cortical bone growth is stimulated by mechanical or load bearing, which can be compromised by microgravity conditions of spaceflight. Cortical bone loss has been detected during past and current missions and increases during long duration flights. Cortical bone loss is best mitigated by providing load bearing exercise during spaceflight which substitutes for the normal forces supplied by terrestrial gravity.

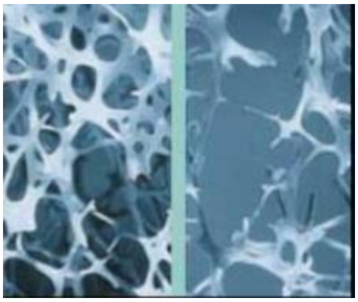


Source: Phsyiopedia

Trabecular bone is the spongy or cancellous bone located beneath cortical bone layer. It is a highly porous structure that makes up approximately 25% of bone that helps with bone strength, flexibility, and shock absorption, and contains bone marrow that circulates nutrients to bone and the human body. Trabecular bone quality can be measured by Quantitative Computed Tomography (QCT). Trabecular bone loss can be mitigated through nutrition and bisphosphonates, a medication that binds to the bone surface and inhibits bone resorption or breakdown. Currently QCT monitoring is not required but is being considered as research is suggesting additional benefits from addressing both types of bone loss.

Osteoporosis is a skeletal condition that has multiple etiologies. Primary or age-related osteoporosis has 2 types: menopause-induced and senile-induced (occurs at older ages). Secondary osteoporosis includes any osteoporotic condition not related to aging, including glucocorticoid-induced osteoporosis. NASA is assessing if disuse osteoporosis is evident following spaceflight. Spaceflight induced bone loss targets weightbearing bones and is locally regulated, bone resorption is increased while bone formation is suppressed or stable resulting in bone loss. Skeletal fragility, a hallmark of osteoporosis, results from reductions in bone mass, increased porosity in cortical bone, and microarchitectural changes in trabecular bone. NASA is considering additional factors that affect spaceflight related bone loss including age, altered loading environment, hormonal status, nutritional deficiencies, and genetic predisposition that may affect bone loss. *Rosenthal Case for Bisphosphonate Use in Astronauts Flying LD Missions 2024*

Measurement of cortical bone density with DXA was the only consideration of spaceflight bone loss. Currently trabecular bone measurement (bone quality) is also considered as the bone interior is evolving as being important to bone strength and fracture prevention, especially in vertebral and hip bones.



Microscopic views of healthy bone tissue compared to bone affected by osteoporosis. *Source: Medscape*

Physiology

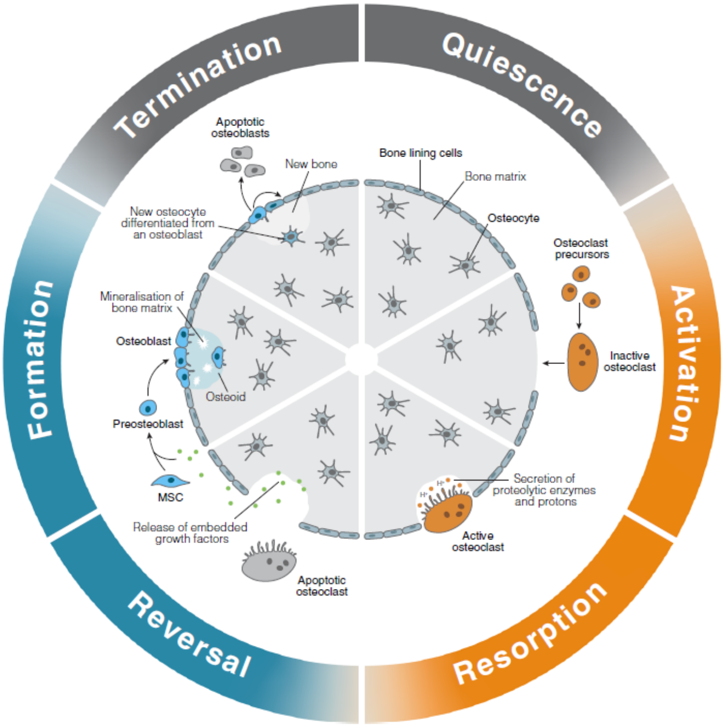
Bone Cellular Signals

On Earth, gravity is a constant force that imparts mechanical resistance to the body’s activities. This resistance is perceived by osteocytes (cells that regulate bone remodeling) and translated into cellular signals that regulate the balance between tissue formation (growth) and tissue resorption (breakdown), termed bone remodeling. *ISS National Laboratory.*

Osteoblasts are bone cells triggered by hormones or bone stimulation that strengthen existing bones by growing new bones, reshaping bones through remodeling, and healing damaged/broken bones. During spaceflight, the stimulation force is removed and bones, if untreated, can become vulnerable and fragile, especially during long duration flight. Currently, load bearing exercise provided on ISS can substitute for terrestrial gravity forces and can stimulate the osteoblasts to maintain bone health.

Osteocyte mature bone cell embedded within bone matrix, regulates bone remodeling by sensing, and translating mechanical stimuli into biochemical signals that affect other bone cell functions. In microgravity osteocytes become less functional and may not be as efficient to ensure osteoblast and osteoclast activity is properly balanced to ensure bone health.

Osteoclasts release enzymes creating chemical reaction that dissolve and break down old or damaged bone cells, making space for osteoblasts to create new bone tissue in areas needing repair. Osteoclasts are at risk of dysregulation in microgravity and can increase risk of more bone loss than rebuilding. Osteoclasts can be mitigated by bisphosphonate pharmaceuticals which adhere to bone surfaces and inhibit bone degradation. *Gena (2021) The Effect of Space Travel on Bone Metabolism: considerations on Today’s Major Challenges*



Source: Mann (2022) Effects of microgravity on bone structure and function

BioMed-ISS sponsored an experiment on ISS called the Osteocytes and Mechano-transduction experiment allowing crew to see inside the osteocyte cell as it responds to absence of mechanical force in microgravity at a cellular and molecular level. Experiments enable us to better understand the effects of spaceflight on bone loss. *ISS National Laboratory*

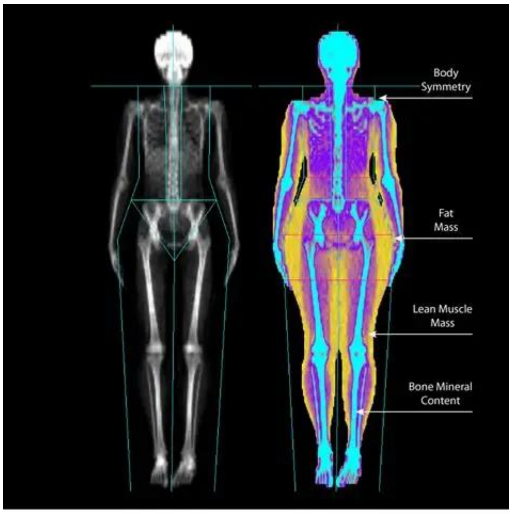
Application

Bone characterization Dual Energy X-ray Absorptiometry

Maintaining bone strength and quality during spaceflight is significant as bone loss can increase risk of fracture, compromising crew health and mission objectives. NASA bone mineral density (BMD) monitoring has evolved to be more protective for crew as knowledge is available:

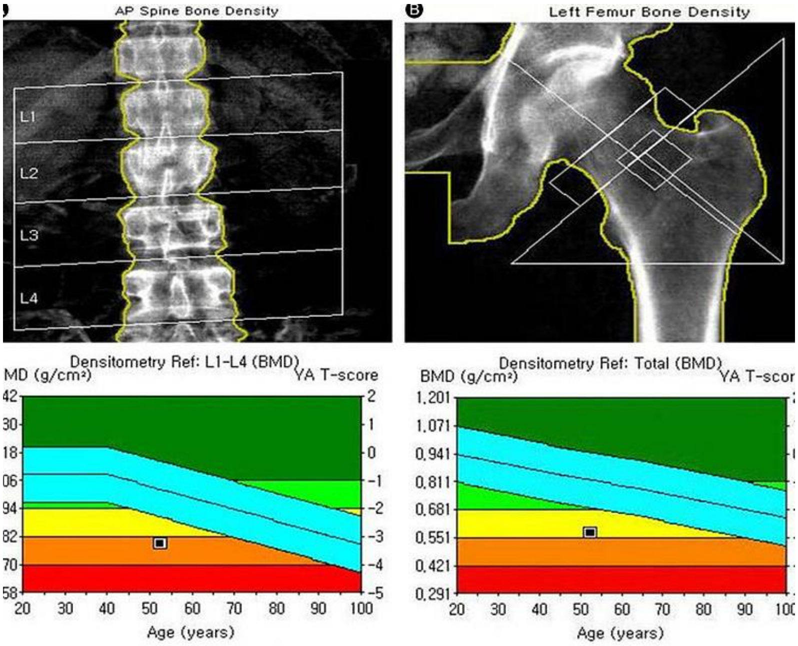
- Bone mineral density using the Dual Energy X-ray absorptiometry (DXA) pre- and post-flight became a medical requirement in 1997.
- Medical requirement for specific BMD for selection to long duration missions was addressed in 2001.

DXA uses two different X-ray energies that are differentially absorbed by bone and soft tissue, allowing separation of tissue into bone, lean, and fat tissues and eliminating the restriction of measurement to regions with minimal soft tissue presence. DXA scans were used initially as a research tool to assess BMD changes and now has become the primary tool for assessing skeletal health in astronauts, providing a minimum cut point for acceptable pre-flight skeletal fragility as well as monitoring post-flight and long-term BMD changes.



DEXA Scan Results

Source: Accurateimagingdiagnostics.com



Source: Prognosismri.com

DXA	QCT
Measures bone mineral density	Provides a 3D assessment of bone quality
Low radiation exposure	Greater radiation exposure
Standard osteoporosis screening	Specific clinical cases or/research
10-15 minutes	>15 min, depending on complexity
$100-300/scan	$300-6,000

*** the costs provided for comparison only; not specific to astronaut testing which may be affected by contracted pricing.*

DXA testing has been the accepted measure to monitor spaceflight BMD to date. There are concerns that while DXA is a reliable measure of bone density, it does not measure trabecular bone quality and may not give the full picture of spaceflight risk of bone loss.

Application

Quantitative Computed Tomography QCT BMD Testing

QCT distinguishes between cortical and trabecular bone compartments which can allow for improved assessment of fracture risk. QCT scans are conducted on the hip and spine to provide measurements of the whole bone (e.g., geometry, cross-sectional areas) and measurements for separate and combined bone compartments (cortical bone, cancellous or "trabecular" bone, and integral bone) *NASA Bone Fracture Evidence Report (2024)*. QCT data from astronauts may be used to assess impact of spaceflight on whole bone strength and estimate bone strength for specific loading orientations and help better determine long term astronaut risk of fracture. QCT may therefore be used as a supplemental tool.

Recent studies have shown the sensitivity of DXA measured BMD may not provide a full assessment of changes in bone strength. DXA technology has proven to be a good measure of cortical bone density but may not detect the full skeletal effects of spaceflight, as demonstrated on the hip bone, predisposed to age-related bone loss and skeletal fragility (Lang *et. al.,* 2004, 2006). "It is estimated that more than 50% of women and 70% of men who sustain a low trauma fragility fracture actually have a diagnosis of osteopenia rather than osteoporosis suggesting that other skeletal factors, such as the size (cross-sectional area), structure (macro- and micro-architecture) and intrinsic properties (porosity, matrix mineralization, collagen traits) of bone also play an important role in determining bone strength and fracture risk" *Beck 2017*.

QCT Scan. Source: Medco Blue

The updated *2024 NASA Fracture Evidence Report* has expanded the description of skeletal changes to capture the full effects of spaceflight on bone. This includes some Bone QCT testing information:

- Routine preflight-to-postflight surveillance by DXA does not provide the full detection of loss and recovery in the long-duration (LD) astronaut nor of hip trabecular bone.
- The inclusion of hip quantitative computed tomography (QCT) in flight studies delineates effects of spaceflight, countermeasures, and of post-flight recovery on cortical and trabecular bone parameters—some of which are verified predictors of hip fracture in the aged.
- QCT detects and compares the distinct countermeasure effects of the pharmaceutical alendronate and of resistive exercise (on the Advanced Resistive Exercise Device, ARED) in specific cortical and trabecular bone.
- A published comparison of QCT-determined loss rates of hip trabecular bone in LD astronauts compared to terrestrial cohorts suggest that accelerated loss rates in trabecular volumetric BMD during spaceflight might be analogous to skeletal effects of accelerated loss rates in females due to menopause, potentially leading to disruptions in trabecular microarchitecture.

Application

Measurement/Monitoring

In 1994, the World Health Organization (WHO) developed guidelines using DXA to diagnose menopause-related osteoporosis. T-score guidelines (below) are grounded in the epidemiology of fracture frequency and distribution based upon measurements of the hip and spine T-score results compare an individual's bone density to the group mean value of healthy young adults (30-year-old). Guidelines state that menopausal females with T-scores ≤ to −2.5 have a greater association with fragility fractures. NASA considers that this evidence-based test could help determine whether spaceflight induces a similar level of fragility and whether astronauts require protection against these changes during spaceflight. While the osteoporosis cut-point (T-score ≤ -2.5) may be diagnostic in younger humans, it does not predict fragility fractures in this age-group but serves as a somewhat arbitrary standard when assessing crew bone health. DXA testing is now used triennially on female and male astronauts to monitor for early onset osteoporosis.

WHO Classification	T-Score (SD from mean areal BMD of young Caucasian females)	NASA Bone Health Standard Classification	Adapted T-score (SD from mean areal BMD of young ethnic-based, sex-matched persons)
Normal	-1.0 to + 1.0	Preflight Certification for Long Duration Mission (4.2.9.1)	T-score = -1.0 or greater
Osteopenia	Between -1.0 and -2.5	Countermeasure Efficacy (4.2.9.2)	Maintain bone mass to T-score = -2.0 or greater
Osteoporosis	-2.5 or less	Post-flight End-of-Mission (4.2.9.3)	T-score = -2.0 or greater
Severe Osteoporosis	-2.5 or less and fragility fracture	Post-flight Rehabilitation	Return to baseline: T-score = -1.0 or greater

T-score based operating bands are used to:

1. Screen applicants for possible astronaut candidacy
2. Monitor skeletal health on a triennial basis in active astronauts
3. Affirm restoration of astronaut to pre-flight health and monitor skeletal health in retired astronauts
4. T-score are available for DXA measurements total hip and femoral neck, lumbar spine, and forearm

Z-score Another measurement used to measure BMD is z-score: a comparison of BMD and that of peer group age, sex, weight, ethnic origin (T-score compares to healthy 30-year-old). It is possible to have a z-score close to 0 but low BMD. Z-scores lower than -1.5 shows atypical BMD needing further investigation

	WM Z-Score	BM Z-score	HM Z-score	WF Z-score	BF Z-score	HF Z-score
Femoral Neck	-1.6	-1.9	-2.1	-1.2	-1.7	-1.3
Total Hip	-1.9	-2.2	-2.6	-1.5	-1.7	-1.3
Lumbar Spine	-2.1	-3.0	-2.1	-1.1	-1.9	-1.1

WM, BM, HM = white, black, and Hispanic male; WF, BF, HF = white, black, Hispanic female

Astronauts with a low z-score may require an intervention of diet, exercise, evaluation and/or intervention referral to the Astronaut Bone Health specialist.

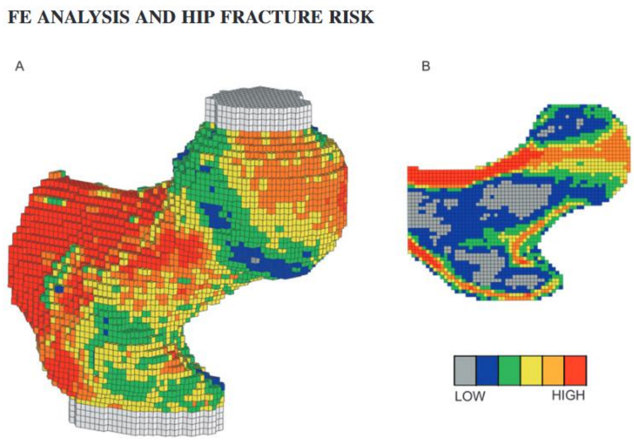
Application

Fracture Risk Assessment Tool (FRAX) is used to predict the risk of fractures within the next 10 years. FRAX is not applicable to individuals under the age of 50 except for special circumstances like premature menopause (<45 years) or spaceflight. A FRAX calculation is performed with each DXA scan session in addition to a T-score to help determine best treatment to mitigate bone loss. Any risk greater than 3% for a hip fracture or 20% for any major fracture is cause for referral to a bone specialist for possible management with bone anabolic agents or bone resorption inhibitors. For spaceflight, the first line of treatment is dietary and exercise interventions, with pharmaceuticals reserved for both failure to respond to diet and exercise and a risk of osteoporosis based on BMD value.

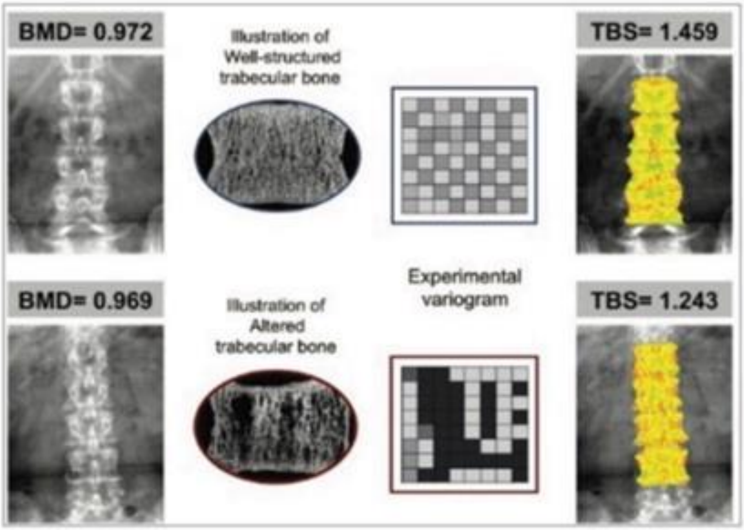
Presence of a fracture with no history of trauma and BMD lower than expected for age or low BMD may indicate an underlying skeletal fragility that requires medical management. Persons with this history should not perform any long duration missions until the disorder is corrected and fracture risk by FRAX has returned to less than 20% for major bones and less than 3% for the hip or until the total hip, lumbar spine, and femoral neck bone mineral densities are within the range expected for age (Z-score >-2).

Finite element (FE) analysis is a computational technique to simulate and assess the mechanical behavior of bones under various loading conditions to predict likelihood of fractures.

Two fracture categories:
Atraumatic (fragility) – low trauma fracture due to fragility of bones, osteoporosis.
Traumatic – fractures caused by applied mechanical load to bones exceeding bone strength.
These two types provide extremes, there is a continuum of conditions in between where applied mechanical loads are not necessarily excessive, and condition of bone is not necessarily fragile.



FE model of proximal femur, 3D and 2D sectional views. Color coding shows spatial variation of material strength assigned to individual finite elements. Source: Geusens et al. (2010) Can Hip Fracture Prediction in Women be Estimated beyond Bone Mineral Density Measurement Alone?



Source: Orwell et al. (2009) Finite element analysis of the proximal femur and hip fracture risk in older men

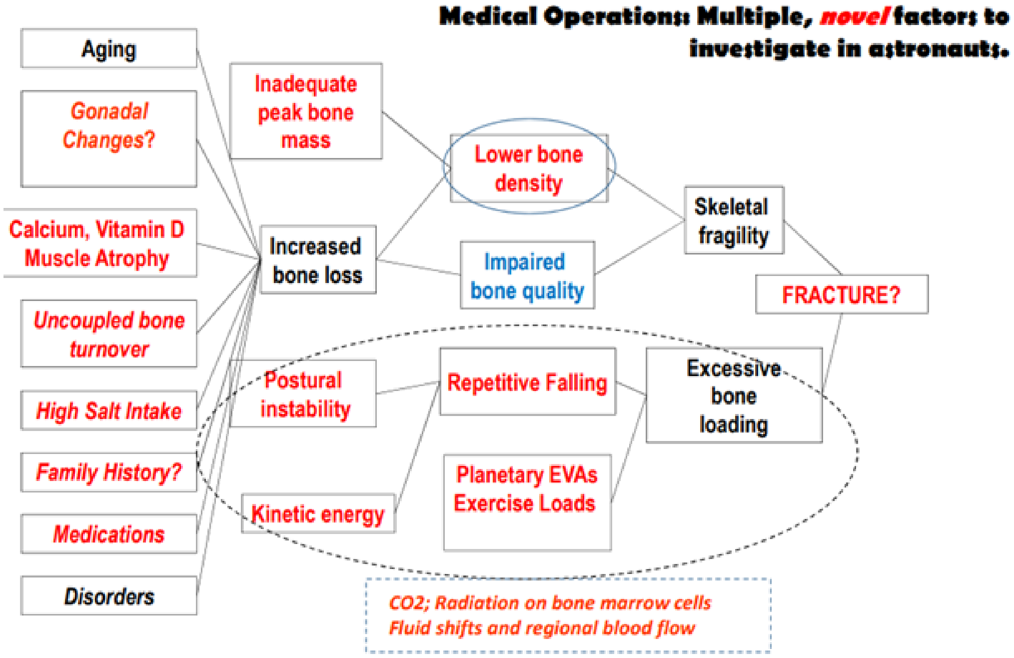
Trabecular bone score (TBS) is a recently developed and FDA approved software that measures bone structure for clinical use along with DXA to determine trabecular bone status in lumbar spine. TBS analysis has been reported beneficial in monitoring exercise countermeasure effects.

Physiology

Bone Loss Contributors & Disqualifying Conditions

Bone loss can be affected by many factors independent of the risks of spaceflight including family history, endocrine conditions, loading conditions, nutrition, biomarkers, and activity level. NASA screens astronaut candidates for conditions that can adversely affect bone density and would put crew at increased risk. Astronauts are screened for bone density (DXA), lab values, endocrine conditions, and bone conditions. Astronauts who have deficiencies at screening will be disqualified for flight. Astronauts who are selected, and encounter conditions may be able to waive conditions if they are treatable/modifiable.

Endocrine Factors affecting bone mineral density include thyroid, pituitary, diabetes, Cushing's Syndrome, and hormone alterations. The guideline for use by the individual managing the bone metabolic and endocrine evaluation are given in the decision flow diagram “Bone Metabolic and Endocrine Evaluation”. This overview is used in addition to any existing clinical practice guidelines used by NASA and the medical specialists to address the specific disorders that increase the rate of bone loss. Flight surgeons may institute therapy within their expertise or refer cases to the Astronaut Bone Health Specialist for evaluation and treatment to include consultation of the appropriate medical or surgical specialists.



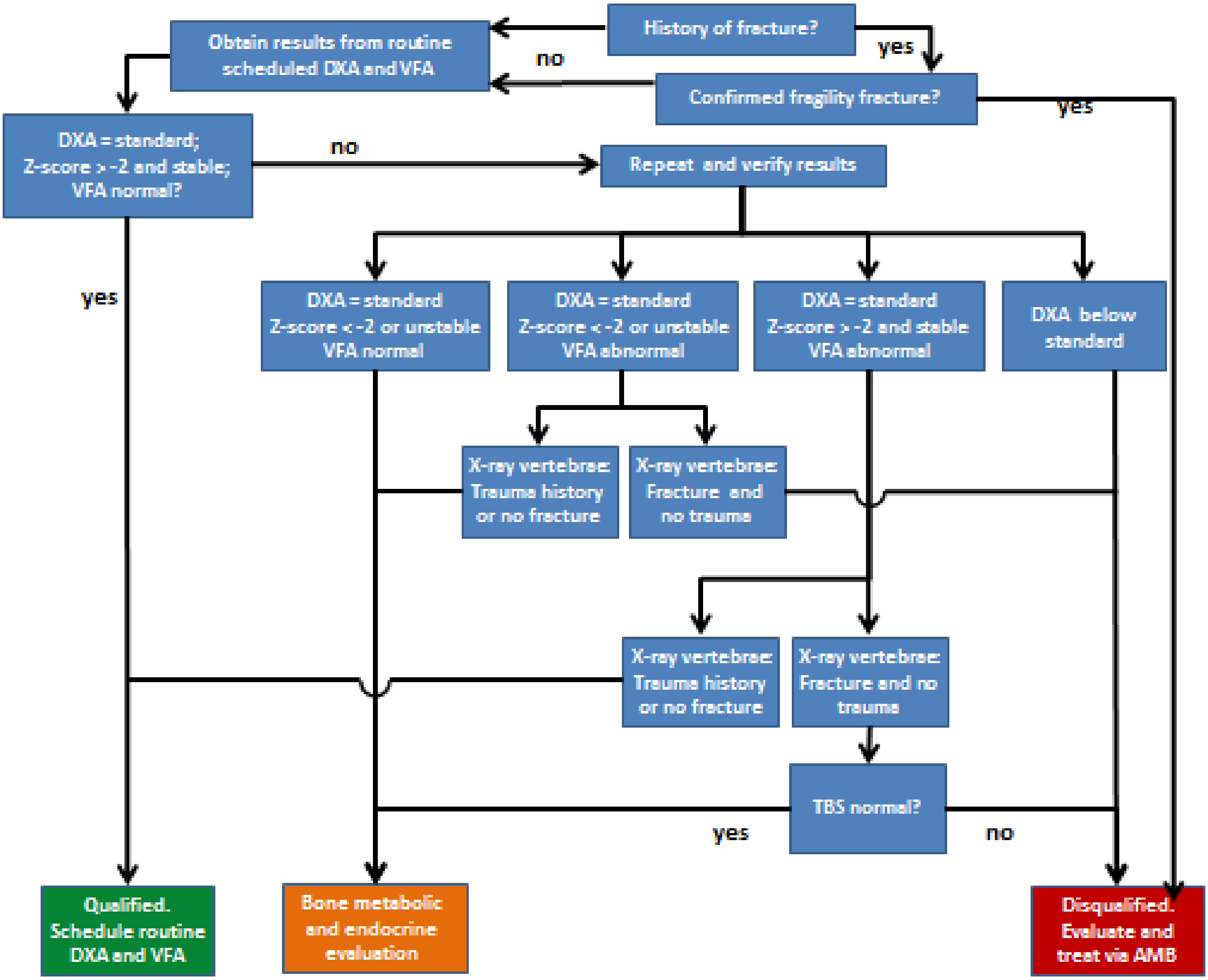
Source: Adapted from Pathogenesis of Osteoporosis-related fractures (NOF)
Cooper C & Melton LJ

Current disqualifying endocrine conditions at astronaut selection include:

1. Any endocrine disease or disorder affecting performance of duties
2. Presence of history of hypothalamus or pituitary gland, history of prolactin secreting pituitary adenoma
3. Diseases of thyroid gland
4. Disease of parathyroid gland
5. Diseases of adrenal medulla or cortex
6. Adrenal androgen excess
7. Metabolic disorders including diabetes, gout, familial hyperlipidemia, inborn metabolic errors, metabolic syndrome
8. Endocrine tumor, carcinoid syndrome, pancreatic endocrine tumors

Additional disqualifying information in NASA-OCHMO-100.1A

Sample of Medical Decision-Making Flow Diagram



History of fracture?

no

yes

Obtain results from routine scheduled DXA and VFA

Confirmed fragility fracture?

no

yes

DXA = standard; Z-score > -2 and stable; VFA normal?

no

Repeat and verify results

yes

DXA = standard Z-score < -2 or unstable VFA normal

DXA = standard Z-score < -2 or unstable VFA abnormal

DXA = standard Z-score > -2 and stable VFA abnormal

DXA below standard

X-ray vertebrae: Trauma history or no fracture

X-ray vertebrae: Fracture and no trauma

X-ray vertebrae: Trauma history or no fracture

X-ray vertebrae: Fracture and no trauma

TBS normal?

yes

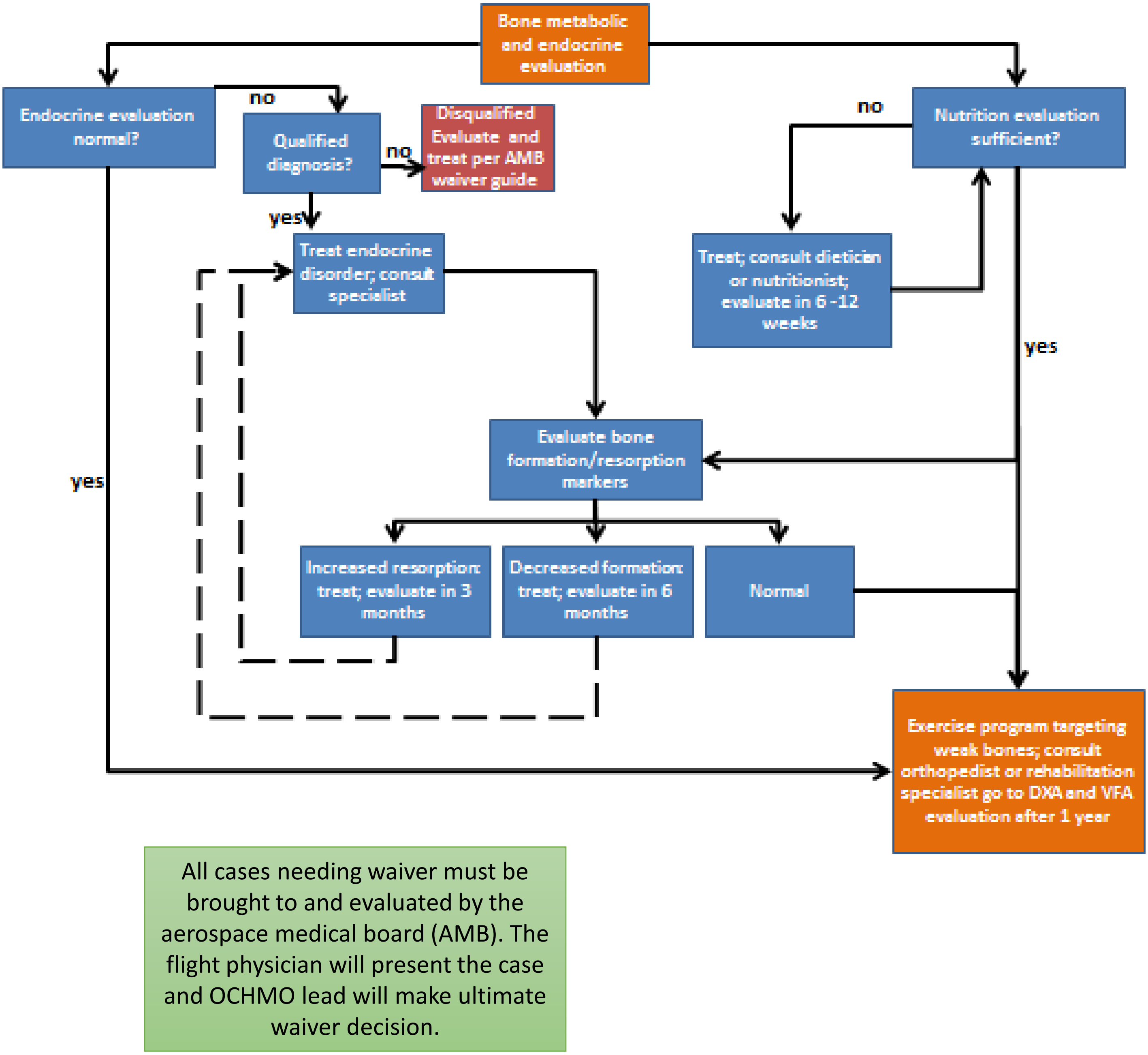
no

Qualified. Schedule routine DXA and VFA

Bone metabolic and endocrine evaluation

Disqualified. Evaluate and treat via AMB

Sample of Medical Decision-Making Flow Diagram (cont.)



Bone metabolic and endocrine evaluation

Endocrine evaluation normal?

Qualified diagnosis?

Disqualified Evaluate and treat per AMB waiver guide

Treat endocrine disorder; consult specialist

Nutrition evaluation sufficient?

Treat; consult dietician or nutritionist; evaluate in 6 -12 weeks

Evaluate bone formation/resorption markers

Increased resorption: treat; evaluate in 3 months

Decreased formation: treat; evaluate in 6 months

Normal

Exercise program targeting weak bones; consult orthopedist or rehabilitation specialist go to DXA and VFA evaluation after 1 year

All cases needing waiver must be brought to and evaluated by the aerospace medical board (AMB). The flight physician will present the case and OCHMO lead will make ultimate waiver decision.

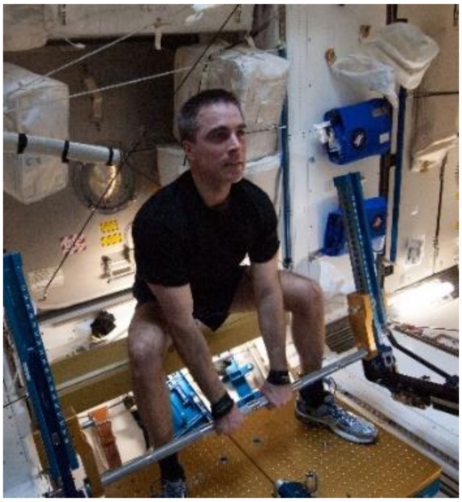
Reference Data

Countermeasures

Spaceflight associated bone health risks including bone fractures and early onset osteoporosis have resulted in NASA developing countermeasures to mitigate the risk of these conditions and associated mission compromise. Countermeasures such as exercise, adequate nutrition, and medications have been recommended and required to prevent bone demineralization, especially during long-duration missions such as planetary and deep-space exploration. Exercise as a countermeasure has generated the most data and may be sufficient to reduce postflight deficits in DXA-measured BMD. Exercise with axial loading has been most effective in terrestrial studies and in spaceflight for improving and maintaining bone health. NASA requirements ensure that crew are given sufficient space, time and hardware to complete exercises that enable them to meet NASA 3001 requirements. ISS currently uses the Advanced Resistive Exercise Device (ARED) for resistance and loading exercises. Load bearing exercise stimulates osteoblasts, leading to bone growth and bone density increase. Current ISS exercise equipment that assists with bone loss includes:

- **Advanced Resistive Exercise Device (ARED)** Capable of higher concentric resistance and eccentric-to-concentric ratio close to that recommended by expert panels and confirmed effective by exercise scientists. The ARED also collects data regarding the parameters associated with crew exercise and transmits it to the ground.
- **Treadmill 2 (COLBERT)** An exercise treadmill that can also be used to collect data such as body loading, duration of session, and speed for each crewmember.

Left: ESA astronaut Luca Parmitano exercising on the COLBERT, harness assists with bone loading.
Right: NASA astronaut Chris Cassidy using the ARED device
Source: NASA

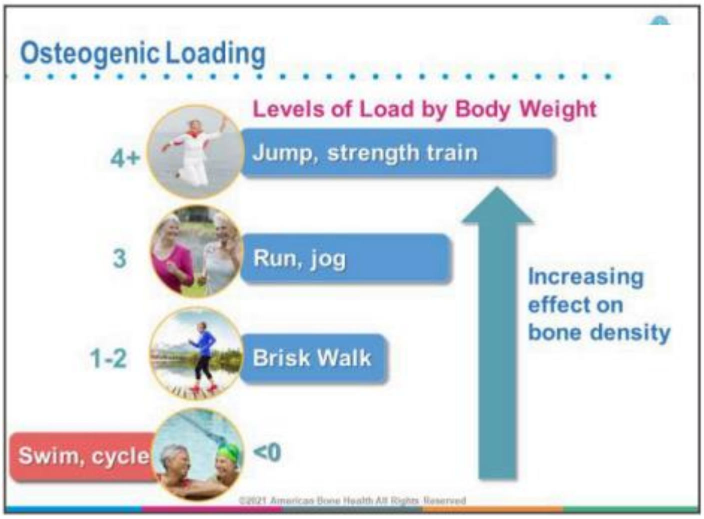


Since 2009, ARED exercise countermeasure on the ISS have provided new spaceflight BMD data. The ARED provides weight-bearing exercises with up to 600 pound-force resistance which more closely simulates the lifting of free weights on Earth. This capability provides the 2x–3x body weight resistance typically required to maintain bone mass (Kohrt et. al., 2004). Before ARED, only 300 pound-force was provided by the Interim Resistive Exercise Device (IRED), which was found to be insufficient to maintain ISS astronauts at their pre-flight skeletal BMD measurements (Lang et. al., 2004). Reference OCHMO-TB-031 Exercise Overview for additional information.

Reference Data

Activity Effects on BMD

Weight bearing activity is critical for bone health. The stress on the bones that results from weight bearing activities like running, jumping, and weightlifting, stimulates bone building. Weight slightly compresses the bone matrix and triggers the cells to assimilate more calcium and other minerals, and ultimately to increase bone density. The amount of weight that causes this response from the bone is called "osteogenic loading" because it takes a certain "load" to stimulate the bone building cells. In contrast, "unloading" the bones from prolonged bed rest or space travel can result in loss of bone density. While normal daily activities are sufficient to prevent the harmful effects of unloading, significant "loading" appears to be required to increase bone mineral density. *Bone Health and Osteoporosis foundation 2023*



Source: Osteogenic Loading (americanbonehealth.org)

"While there are some reports that brisk walking or walking combined with other impact loading activities may help postmenopausal women offset age-related bone loss, a meta-analysis of intervention studies reveals minimal or no effect of regular walking and other low intensity activities on bone in peri- and post-menopausal women." (Wu 2013, Beck 2017)

*"*Exercise training involving certain forms of weight-bearing impact exercise, such as hopping and jumping, and/or progressive resistance training (PRT), can improve bone health." (Beck 2017)

Beck 2015 reports the relevance of exercise quality in bone loss prevention and that bone responds most positively to impact activities and high intensity progressive resistance training.

Beck describes that exercise can be beneficial to bone but must be characterized by adequate loading.

- Be dynamic not static (i.e., cyclic not continuous) induce relatively high bone strains.
- Be applied rapidly with relatively few loading cycles, short bouts separated by periods of rest are more effective than the same number of loads performed all at once.
- Diversification of loading (e.g., multidirectional movements) is required to stimulate an adaptive skeletal response.

Greatest benefits to spine and hip shown when resistance (weight) increased over time, magnitude of loading high, training min of 2x/week, and target hip and spine large muscles.

Exercise prescription should take account BMD and risk factors for falls and fracture including: age, frailty, sarcopenia, loss of height, history of osteoporosis, back pain or osteoarthritis, history of fractures and falls, diseases known to affect bone metabolism, early or surgically-induced menopause, low testosterone (men), prolonged use of certain drugs (e.g., corticosteroids), inadequate dietary calcium, vitamin D deficiency, excessive alcohol intake, smoking, and previous physical activity (Beck 2017).

Application

Astronaut Strength, Conditioning, and Rehabilitation (ASCR) specialists are certified strength and conditioning professionals, licensed athletic trainers, and physical therapists who optimize the performance, durability, and sustainability of the astronaut corps. ASCRs are assigned to each astronaut and develop personalized exercise prescriptions to ensure crew safely maintains bone and muscle strength health prior to, throughout the mission, and rehabilitate the crew post-flight to ensure they safely reintegrate to their daily life activities. ASCRs receive data through exercise machines, flight surgeons, and in-flight virtual meetings to monitor and adjust exercise as needed.

Crew is required to exercise a minimum of time per day, dependent on the program mission as dictated by the medical team. Previous requirements have been 2 hours per workday with a strict exercise program.

Exercise frequency Two to three sessions per week **maintains** bone in terrestrial ambulatory persons, and four to six sessions per week **induces bone formation**. During bed rest and spaceflight, 6 to 7 sessions per week has been effective to maintain bone. Six days a week exercise of the hip abductors and of the gastro soleus in single leg stance has been found effective in increasing greater trochanter BMD and calcaneus BMD, respectively, in 17 weeks bed rest.

Examples of bone subregions and specific exercises Single leg squats load the greater trochanter, shallow squats generate greater loads than full squats. Single leg deep short arc squats with high sustained eccentric overload load the superior lateral femoral neck. Squats load the inferior femoral neck, particularly when near upright dead lifts load the lumbar spine, but loads may be limited by grip strength. Barbell good mornings load the lumbar spine. Sprinting and jumping load the inferior femoral neck. Finger pushups load the distal radius and ulna, wrist and flexor weakness may necessitate initial strengthening in a more upright position, leaning against a wall or tabletop to distribute more of the body weight onto the legs.

Artemis exercise Artemis 2 is an upcoming 10-day mission with very limited space, so rather than a treadmill, bike, or ARED exercise machine, Artemis will have a flywheel machine that can offer resistive exercise and aerobic workout in a limited space area. NASA is not as concerned about adverse effects on bone for a short 10-day mission, but this will be a good opportunity to test the flywheel for operational success and knowledge for future, longer missions.

Artemis Flywheel Exercise Device (FWED). Source: NASA

Application

Challenges to pharmaceutical use in space:
- Limited storage conditions
- Volume and weight considerations
- Possible side effects
- Expiration dates for long duration flights

Pharmaceutical Countermeasures

Terrestrially, pharmaceuticals are a commonly used countermeasure to bone loss. NASA continues to study the application of pharmaceuticals as countermeasures to spaceflight related bone loss. To date, NASA has not used bisphosphonates, other than in research. Side effects including GI concerns and jaw necrosis have caused concerns and limited use, but NASA is considering how pharmaceuticals may have a role in BMD loss prevention for longer-duration flights.

Pharmacologic and Nutritional Countermeasures for Bone Loss in Spaceflight

Agent	Mechanism of Action	Pros	Cons
Bisphosphonates Alendronate Zolendric acid	Inhibit osteoclast-mediated bone resorption by binding to bone mineral matrix	Proven efficacy in astronauts and bed rest studies, long-lasting effects	GI side effects (oral), rare risk of jaw osteonecrosis, may impair remodeling
BP-NELL-PEG	Combines bisphosphonate targeting with NELL-1 to promote osteoblasts and inhibit osteoclasts	Promotes formation and inhibits resorption, increased BMD in mice	Experimental, not tested in humans, long-term safety unknown
Myostatin Inhibitors	Block myostatin to preserve muscle mass, indirectly supporting bone via muscle-bone interaction	Preserves muscle and bone dual countermeasure	Experimental, off-target effects possible, not approved for human use
Calcium	Essential mineral for bone matrix, supports bone mineralization	Readily available bone health with vitamin D	Excess may cause kidney stones
Vitamin D	Enhances calcium absorption, regulates bone remodeling via PTH	Prevents deficiency in space, supports Ca homeostasis	Requires supplementation, risk of hypercalcemia
Denosumab	Monoclonal antibody, inhibits resorption	Suppress bone resorption for 6-month period following injection under the skin	Refrigeration required
Teriparatide	Recombinant PTH stimulates bone formation	Analog of PTH that induces an anabolic effect in osteoblasts (stimulated bone formation) when administered intermittently	Refrigeration required
Hydrochlorothiazide	Stimulates calcium retention by kidneys, decreasing BMD loss	Easy volume, storage	Lower efficacy
Estrogen (HRT)	Suppresses osteoclast activity via RANK/OPG pathway, maintains BMD	Effective postmenopausal BMD loss prevention	Risk of clots, stroke, cancer, requires risk assessment

Application

Nutrition Countermeasures

Although microgravity unloading of bone largely contributes to BMD loss, other factors can influence calcium metabolism including nutrition. Bone is dependent on serum calcium levels kept in normal range by balance of parathyroid hormone (PTH), calcitonin, and vitamin D. PTH is produced by the parathyroid gland in response to low serum calcium. If the parathyroid gland senses low serum calcium, PTH is elevated which increases bone resorption, releasing calcium into the bloodstream. PTH will not stimulate osteoblasts unless administered in a pulsatile intermittently. Calcitonin is produced by thyroid gland in response to high serum calcium, it binds to osteoclasts inhibiting bone resorption. PTH also promotes the metabolism of vitamin D to its active metabolite, 1,25-dihydroxy vitamin D. In response to low blood calcium levels and PTH stimulation, vitamin D metabolite promotes calcium absorption in the gut, reabsorption in the kidneys, and release of calcium through bone resorption. The maintenance of healthy bone mass requires a balance of all these factors.

NASA monitors calcium, vitamin D, PTH, and other bone markers from selection throughout the astronaut lifetime to detect nutritional issues that can affect bone. Currently NASA supplements vitamin D and NASA food lab nutritionists develop appropriate nutritional foods to ensure the crew have enough micro- and macronutrients to promote bone health. See OCHMO-TB-013 Food & Nutrition for additional information.

NASA-STD-3001 and OCHMO-STD-100.1A *NASA Spaceflight Medical Selection, Recertification and Mission Evaluation Standards* manage how crew is monitored and alert if supplementation or evaluation is needed.

[6037] Vitamin D Testing and Treatment Protocol Crewmembers shall be evaluated and treated prior to a long-duration mission. The timing of the testing at the discretion of the Crew Surgeon. The optimal/desired range for 25-OH Vitamin D is 35-90 ng/ml. The recommended maintenance dose of Vitamin D3 is 1,000 I.U. daily or 5000 I.U. once a week.

[6038] Nutritional Status Assessments Crewmembers shall undergo nutritional assessment testing according to the specifications and schedule: On-orbit dietary assessments may help assure adequate nutrient intake during the mission. Assessment of nutritional patterns of crewmembers may help guide adjustments to nutrient and micronutrient dietary composition for future missions.

Bone demineralization in spaceflight increases urinary calcium excretion leading to calcium released into the urine for excretion, as urine processes through the kidneys there is an increased risk of calcium renal stones. See OCHMO-MTB-003 Urinary Health.

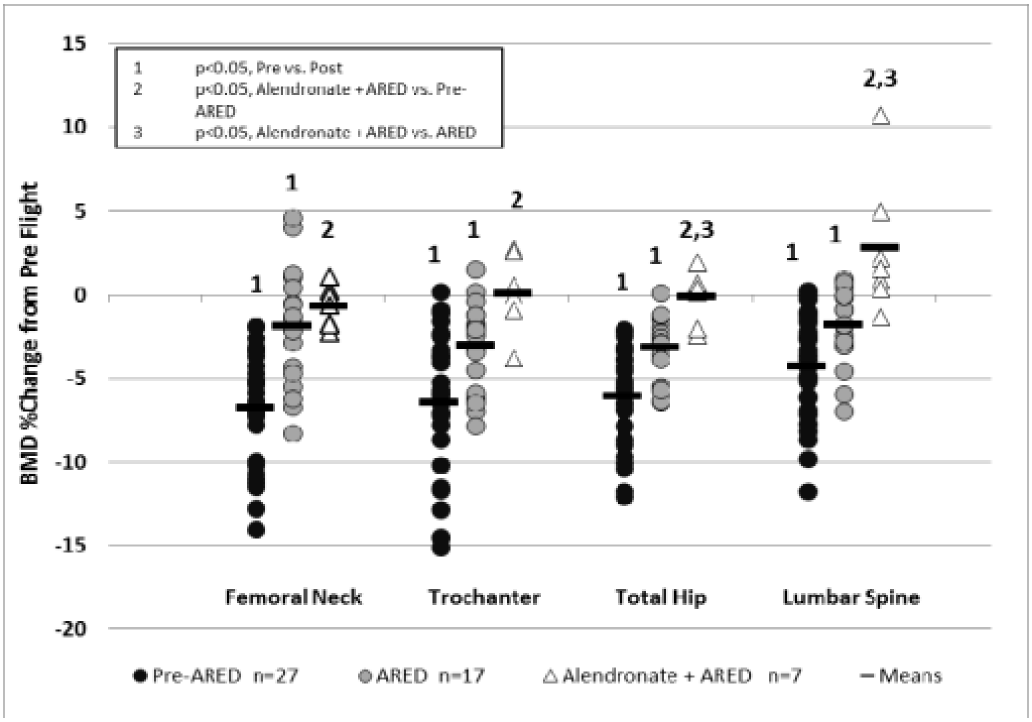
If 25-OH Vitamin D results are:	Vitamin D3 Treatment
35 ng/ml or higher	• Prescribe 1000 I.U. daily or 5,000 I.U. weekly (Maintenance dose)
20 to 34 ng/ml	• Prescribe 50,000 I.U. once a week or 5000 I.U. once a day for 4 weeks and then revert to maintenance dosing (1,000 I.U. daily or 5000 I.U. once a week). • May recheck 25-OH Vitamin D levels in 3 months.
Less than 20 ng/ml	• Prescribe 50,000 I.U. once a week or 5000 I.U. a day for 6 to 9 weeks and then revert to maintenance dosing (1,000 I.U. daily or 5000 I.U. once a week). • Recheck 25-OH Vitamin D levels in 3 months • Note: Rule out other causes such as celiac sprue or other malabsorption maladies.

Reference Data

Bisphosphonate Studies

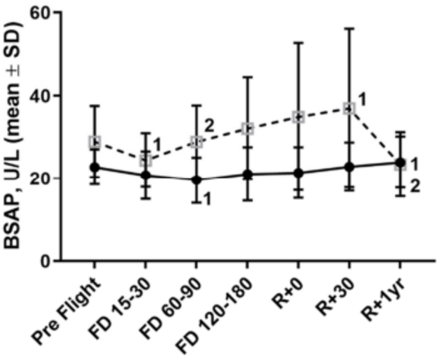
Bisphosphonates inhibit osteoclastic bone resorption by attaching to hydroxyapatite binding sites on bony surfaces, especially undergoing active resorption. When osteoclasts resorb bone treated with bisphosphonate, the bisphosphonate is taken up within the osteoclast cell where the drug impairs the adherence of osteoclasts to the bony surface and the production of protons for continued bone resorption. Bisphosphonates reduce cell-driven bone-resorption by decreasing osteoclast progenitor development and recruitment and by promoting osteoclast apoptosis. (UpToDate August 2025).

Leblanc (2009) study was done to determine if bisphosphonate antiresorptive drug would provide additional benefit to in-flight exercise to mitigate bone loss and hypercalciuria during long-duration spaceflight. Measurements included DXA, QCT, pQCT, urinary and blood biomarkers. Analysis completed immediately after flight (R+2 weeks) and R+1 year.



18 ISS astronauts on 5.5 m flight took Alendronate 70mg weekly starting 3 weeks pre-flight and continuing throughout mission. Crew used Treadmill, cycle ergometer and ARED for exercise. Results showed some BMD protection in ISS crewmembers using ARED, and increased protection using ARED and Alendronate.

Rosenthal (2024) study included how the cellular effects of bisphosphonates offer a prophylactic countermeasure for suppressing the elevated bone resorption observed during long-duration spaceflights. Results found differential effects of spaceflight and ARED changes on DXA and QCT. QCT showed additional bone vulnerabilities in trabecular bone treated with ARED alone. Bisphosphonate with ARED associated with no significant change between pre- and post-flight using DXA and QCT testing. Right image: Biomarkers NTX (marker of bone resorption), and BSAP (bone formation marker) show greater mitigation when bisphosphonate is added to ARED exercise.



Application

Bone mineral density T-scores between -1 and -2.5 undergo assessment for underlying pathology. Astronaut applicants (and existing astronauts for long duration missions) with T-scores lower than -2.5 will not be approved for selection. Femoral trochanter, one of the total hip subregions, is used along with femoral neck and lumbar spine BMD values to determine fitness for long duration spaceflight. One-third forearm density may be used to define osteoporosis if central DXA is not available.

Cases exist where individuals who meet the standards for long duration spaceflight have bone density lower than the expected range for age, gender, and ethnicity. Z-score evaluation is required to determine if the individual has a disqualifying condition or if exercise or nutritional intervention is needed. Disqualification is managed by NASA flight medicine procedures to include Astronaut Medical Board presentation for requested waivers. See OCHMO-MTB-002 Waivered Health Conditions for more information.

History of fragility fractures	Osteoporotic by definition and are disqualified
Astronauts with increased rate of bone loss relative to a similar normal population (decreasing Z-score) or with a BMD lower than expected for age, gender, and ethnicity (Z-score lower than -2.0) but whose bone density is high enough to meet the T-score based BMD selection standard	(1) Require further evaluation to determine if there is a disqualifying bone metabolic condition or diagnosis and initiate treatment (2) May require exercise and nutritional interventions to restore bone metabolism and bone density to the range expected for age, gender, and ethnicity
Astronauts requiring evaluation and/or intervention	May be referred to the Astronaut Bone Health specialist for diagnosis and management, or referral as needed.
Astronauts found to have disqualifying metabolic or endocrine disorders by NASA aeromedical standards	Disqualified separate from the issue of "bone density lower than expected for age and ethnicity". Preparation of waiver requests (as required for the specific diagnosis) to the AMB may be by the astronaut's primary flight medicine physician or the astronaut bone health specialist, whichever is preferred by the astronaut and Flight Medicine Clinic physician. (1) Waiver requests should follow the guidelines for the specific disorder. (2) Astronauts with a previously identified endocrine or nutritional disorder should continue management by and may be referred to the astronaut bone health specialist. The specialist will manage diet and exercise prescriptions and follow up bone diagnostic procedures to address the issues and assure bone density remains within acceptable standards for long duration spaceflight.
In the absence of a disqualifying disorder	If the astronaut meets the standards of bone density for long duration flight and has no fragility fracture history, the astronaut remains qualified regardless of Z-score or Z-score change. A qualified astronaut with BMD lower than expected for age, gender, and ethnicity or with increased bone loss is encouraged to but not required to participate in exercise and nutritional monitoring and modifications to restore bone densities and rate of bone loss to the expected range.

Application

BMD loss is a condition not usually detectable until a problem occurs. NASA monitors crew terrestrially pre- and post-flight but no system to date measures bone density in-flight. NASA addresses this challenge by ensuring practices are in place that protect bone through requirements.

NASA-STD-3001 bone related requirements:

[V1 4026] Pre-Mission Bone Mineral Density Crewmembers' pre-mission bone mineral density (BMD) T-scores for total hip and lumbar spine (L1-L4), as measured by mass dual energy X-ray absorptiometry (DXA) shall be consistent with an age, sex, gender, and ethnic-matched population.

- Bone density is screened at selection, any applicant who has low BMD (below -2.5 T score) will not be selected into the astronaut core.
- All selected astronauts are tested every 3 years to ensure they have appropriate BMD, and astronauts selected for flight will follow Med B schedule (below), to ensure they have bones strong enough for the rigors of spaceflight and will not be too vulnerable upon return.

All astronauts are monitored via DXA testing at selection and every 3 years. Astronauts assigned to flight will be tested as clinically indicated for short duration (30 day) flights, and more for longer duration. Example Schedule based on ISS 180-day mission: AME L- 21/18 m; L- 180/30 d (as close to launch as feasible), R+ < 30 days, at R+1 year, then as clinically indicated to assess BMD recovery.

[V1 4027] Pre-mission Bone Countermeasures Countermeasures shall maintain bone mineral density of the hip and spine at or above 95% of pre-mission values and at or above 90% for the femoral neck.

[V1 4020] In-Mission Nutrient Intake Programs shall provide each crewmember with 100% of their calculated nutrient and energy requirements, based on an individual's age, sex, body mass (kg), height (m), and appropriate activity factor.

[V1 4028] Post-Mission Bone Reconditioning Post-mission reconditioning shall be aimed at returning bone mineral density to pre-mission baseline values.

**** All NASA programs are required to meet the 3001 requirements unless a waiver is granted.**

NASA also monitors astronauts post-flight to ensure they are monitored and provided with reconditioning exercises to ensure they regain as much bone strength as possible.

[V1 3016] Post-Mission Health Care Post-mission health care shall be provided to minimize occurrence of deconditioning-related illness or injury.

[V1 3017] Post-Mission Reconditioning All programs shall provide the planning, coordination, and resources for an individualized post-mission reconditioning program, specific to each crewmember, mission type, and mission duration. The post-mission reconditioning starts with crew egress at landing and includes a guided, phased reconditioning protocol. The goals of the reconditioning program include the following:

a. To ensure the health and safety of returning crew.
b. To actively assist the crew's return to full functional abilities and return-to-flight status.
c. To actively assist in the crew's return to pre-mission fitness

[V1 3018] Post-Mission Long-Term Monitoring Crewmembers returning from spaceflight shall be monitored longitudinally for health, behavioral health, and well-being parameters in a standardized manner.

Application

Post-flight Monitoring and Testing

Based on historical losses due to spaceflight, the bone areas required for post-flight testing are lumbar spine, total hip, femoral neck, femoral trochanter, pelvis, calcaneus (used primarily to compare with historical database), and ultra-distal radius. Post-flight DXA scans are performed at 6 months, one year, two years, and 3 years post-flight or until recovered within least significant change of pre-flight.

During bone recovery exercise programs, hip MRI with fat suppression techniques to diagnose stress reactions and occult stress fracture should be performed if astronaut develops hip, knee pain, or soreness during or immediately after exercise. Suspected stress fractures in other bones should also be imaged and activity adjusted according to results. Post-flight activities to recover BMD must be designed with consideration of bone's nutritional and loading/strain experience. The first step in initiating a bone exercise program is to assure the endocrine and nutritional status of the astronaut will support bone formation in response to increased strain. Increasing strain with inadequate anabolic capability of bone tissue places the bone tissue at risk for microfracture and delayed or inadequate repair. Microfractures may propagate and result in stress fractures.

Post-flight Reconditioning Timeline

- Re-adaption to gravity begins upon re-entry and landing (R+0)
- Reconditioning program lasts 45 days starting R+1
- Reconditioning is scheduled for 2 hours per day/7 days a week
- Crewmember, Flight Surgeon and ACSR can request additional time past 45 days if needed
- Data is used to determine conditioning status compared to pre-flight levels
- Post-flight performed at R+7 and R+30
- Crewmembers are reassessed across the span of their lifetime

Reconditioning is a dynamic program using functional movement patterns, multiple planes/joints, and is tailored to individual deficits

ACTIVITY	DURATION	SCHEDULE	FLEXIBILITY	PERSONNEL REQUIRED
Post-flight Reconditioning	120 minutes	R+0 – R+45	Schedules should make every effort to schedule activities in the morning prior to any other meetings/debriefs. Schedule and activities may change at discretion of Crew Surgeon/ASCR staff.	ASCR, Crewmember and Crew Surgeon

CONSTRAINTS

- Duty days will include 2 hours of reconditioning for the first 45 days.
- Weekends and one-day within R+0+R+1 will include only reconditioning and medical status checks.
- The ASCR will make recommendations to the crew surgeon regarding certification of the crewmember for maximal muscle strength testing.
- Upon review of physical progress the crewmember, crew surgeon, and ASCR will determine if the crewmember will need to extend formal reconditioning past the required 45 days.

Back-Up

Major Changes Between Revisions

Rev C → Rev D

- Updated content throughout to include information from the NASA Clinical Practice Guideline.

Rev B → Rev C

- Updated information to reflect the revisions to language throughout both volumes of NASA-STD-3001.
- Updated/added website links due to new NASA website launch

Rev A → Rev B

- Updated information to be consistent with NASA-STD-3001 Volume 1 Rev B and Volume 2 Rev C.

Original → Rev A

- Overview
    - Added executive summary
    - Updated standards to Volume 2 Rev B
- Background
    - Added subcategory "Exercise as a countermeasure" after description in order to have more separation in the information
    - Added picture to support subcategory for more visual interest
- Application
    - Added diagrams of exercise equipment for more visual interest
- Other
    - Added revision page
    - Added referenced standards page

Referenced Technical Requirements

View the current versions of NASA-STD-3001 Volume 1 & Volume 2 on the OCHMO Standards website

NASA-STD-3001 Volume 1 Revision C

[V1 3002] Pre-Mission Preventive Health Care Pre-mission preventive strategies shall be used to reduce in-mission and long-term health medical risks, including, but not limited to: (see NASA-STD-3001, Volume 1 Rev C for full technical requirement).

[V1 3003] In-Mission Preventive Health Care All programs shall provide training, in-mission capabilities, and resources to monitor physiological and psychosocial well-being and enable delivery of in-mission preventive health care, based on epidemiological evidence-based probabilistic risk assessment (PRA), individual crewmember needs, clinical practice guidelines, flight surgeon expertise, historical review, mission parameters, and vehicle-derived limitations. These analyses consider the needs and limitations of each specific vehicle and design reference mission (DRM) with particular attention to parameters such as mission duration, expected return time to Earth, mission route and destination, expected radiation profile, concept of operations, and more. In-mission preventive care includes, but is not limited to: (see NASA-STD-3001, Volume 1 Rev C for full technical requirement).

[V1 3016] Post-Mission Health Care Post-mission health care shall be provided to minimize occurrence of deconditioning-related illness or injury, including but not limited to: (see NASA-STD-3001, Volume 1 Rev C for full technical requirement).

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Referenced Technical Requirements

View the current versions of NASA-STD-3001 Volume 1 & Volume 2 on the [OCHMO Standards website]

NASA-STD-3001 Volume 2 Revision E
[V2 7038] Physiological Countermeasures Capability The system shall provide countermeasures to meet crew bone, muscle, sensorimotor, thermoregulation, and aerobic/cardiovascular requirements defined in NASA-STD-3001, Volume 1.
[V2 7043] Medical Capability A medical system shall be provided to the crew to meet the medical requirements of NASA-STD-3001, Volume 1.
[V2 7100] Food Nutrient Composition The system shall provide a food system with a diet including the nutrient composition that is indicated in the Dietary Reference Intake (DRI) values as recommended by the National Institutes of Health, with the exception of those adjusted for spaceflight as noted in Table 7.1-2—Nutrient Guidelines for Spaceflight.

All referenced tables and figures are available in NASA-STD-3001 Volume 2.

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