Evaluating Bone Loss in ISS Astronauts

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INTRODUCTION: The measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is the Medical Assessment Test used at the NASA Johnson Space Center to evaluate whether prolonged exposure to spaceflight increases the risk for premature osteoporosis in International Space Station (ISS) astronauts. The DXA scans of crewmembers' BMD during the first decade of the ISS existence showed precipitous declines in BMD for the hip and spine after the typical 6-mo missions. However, a concern exists that skeletal integrity cannot be sufficiently assessed solely by DXA measurement of BMD. Consequently, use of relatively new research technologies is being proposed to NASA for risk surveillance and to enhance long-term management of skeletal health in long-duration astronauts.

KEYWORDS: densitometry, bone mineral density, trabecular bone, cortical bone.

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The possibility that space travel might have a detrimental effect on bone tissue due to mechanical unloading of the skeleton has been recognized since Project Mercury. Additionally, Skylab missions provided an opportunity to evaluate the effect of 28, 56, and 84 d of spaceflight on mineral metabolism (by quantifying bone mineral excretion) as well as bone density (by single-photon densitometry). The increased excretion of calcium in urine and the decline in bone mineral mass at the heel and wrist supported the concern that skeletal regions could atrophy with extended exposures to spaceflight. The understanding of skeletal adaptation was further enhanced in the 1990s through participation in long-duration missions aboard the Russian Mir space station and with the use of a newer imaging technology that could quantify changes across multiple skeletal sites by both whole-body and regional scans of the skeleton. Dual-energy X-ray absorptiometry (DXA) data from Mir crewmembers documented accelerated, site-specific losses in bone mass. These findings raised further concerns about potentially irreversible changes to bone and the impact on long-term health.

Current medical policy at the NASA Johnson Space Center (JSC) requires the assessment of skeletal health for active astronauts on a triennial basis through measurement of bone mineral density (BMD) by DXA. In addition, BMD measurements are conducted on astronauts before and after missions to the International Space Station (ISS), where mission durations exceed 30 d, but typically are 120 to 180 d. These serial measurements are used to characterize the skeletal effects of spaceflight and to monitor recovery from them.

As an X-ray based imaging technology, DXA provides an improved ability to monitor changes in bone mass with lower radiation exposure, better precision, shorter scan times, and measures over multiple sites, relative to what had been possible with earlier technologies such as dual- and single-photon absorptiometry. DXA scans were not conducted for crews on Space Shuttle missions because the total BMD loss or gain from preflight measurements typically did not exceed the measurement error. Since the time when the NASA Space Flight Human-System Standards for Crew Health (NASA-STD-3001) were developed, DXA has been shown—in a multitude of population studies worldwide—to be a clinically accepted surrogate for bone strength and remains the most widely applied predictor of osteoporotic fracture in terrestrial populations at risk for age-related bone loss.

BMD has historically been the key index for evaluating efficacy of in-flight countermeasures to bone loss, and exercise has been the cornerstone of countermeasures for U.S. astronauts. Two resistive exercise hardware systems were flown on the ISS during Expeditions 1–25: the interim resistive exercise device (iRED), which provided up to 136 kg (300 lb) of resistive force, and later the advanced resistive exercise device (ARED), which

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can provide up to 373 kg (600 lb) of resistive force while more closely simulating free weight lifts in the 1-G environment. Ground-based research suggested that mechanical loading of at least two to three times bodyweight would be required to maintain mass or to stimulate bone formation in the adult skeleton.[34] Hence, the DXA test was used to determine the efficacy of resistive exercise for protection of BMD in long-duration crewmembers before and after the on-orbit use of ARED for resistance exercise.

By the onset of ISS Expedition 1 in the year 2000, medical standards had been formulated to ensure that skeletal health risks, such as the early onset of osteoporosis or increased incidence of fracture, would not become an unintended consequence of participation in long-duration flights.[2,23] These standards were based on the BMD "cut-points" that comprised the available clinical practice guidelines used in terrestrial medicine to diagnose the osteoporosis syndrome.[14] Specifically, the minimum acceptable BMD outcome for ISS astronauts at the end of a mission is that BMD will be no greater than 2.5 SDs below the mean BMD of a population of young gender-matched individuals (i.e., a T-score of −2.5 for either the hip or lumbar spine). Hence, medical standards stipulate that in-flight mitigation strategies must not only be sufficient to maintain BMD above this minimum acceptable outcome, but also state that an astronaut is not qualified for an ISS mission if his/her preflight baseline BMD is not great enough to sustain the expected 1–1.5% monthly BMD loss seen in previous long-duration crewmembers.[20] Crew medical health standards also dictate that serial DXA scans be performed after return to Earth to assess and monitor the temporal recovery of bone lost during prolonged space exposures. This report summarizes information obtained by DXA scans in evaluating changes to BMD of astronauts serving on ISS expeditions as a means for assessing the risk for early-onset osteoporosis due to long-duration spaceflight.

METHODS

Subjects

Data from the bone Medical Assessment Test are reported herein for all U.S. and International Partner astronauts who were scanned at JSC before and after ISS Expeditions 1-25. Archival BMD data from cosmonauts who served on the Mir space station between 1990 and 1998 are also presented for comparison with ISS data. The demographic makeup of the ISS and Mir crewmembers is shown in **Table I**.

Table I. Demographics of ISS ($N = 33$) and Mir Crewmembers ($N = 35$).

	ISS		MIR	
	MEAN ± SD	**RANGE**	**MEAN ± SD**	**RANGE**
Flight Duration (d)	170 ± 29	90 – 215	179 ± 58	117 – 438
Age (yr)	46 ± 4	37 – 54	43 ± 5	32 – 54
Height (cm)	175 ± 6	163 – 185	174 ± 4	168 – 183
Weight (kg)	79 ± 12	59 – 101	75 ± 8	62 – 90
BMI	25 ± 3	20 – 31	25 ± 2	20 – 30

Densitometry

Data reported here are from ISS crewmembers who flew during the first 10-yr period of the ISS missions. This group consists of U.S. astronauts and International Partner astronauts (from the Japanese Aerospace Exploration Agency, Canadian Space Agency, or European Space Agency), all of whom were scanned at JSC on either a Hologic QDR 4500 (Expeditions 1-9) or Hologic Discovery (Expeditions 11–25). A comparison group consists of Mir cosmonauts ($N = 28$) and astronauts ($N = 7$) who flew on the Mir space station between 1990 and 1998. The Mir cosmonauts were scanned in Russia using a Hologic QDR 1000/W (pencil beam scans); these scans were subsequently reanalyzed by the JSC laboratory as part of a cooperative agreement.[31] The seven U.S. Mir astronauts were scanned in the U.S. using the pencil beam mode of a Hologic QDR 2000 densitometer. All DXA tests were obtained on the same densitometer with the same operator conducting preflight and postflight scans to reduce variability and improve precision.[*] The only exception was on ISS Expedition 10, where preflight BMD was measured on a Hologic QDR 4500 and postflight BMD was measured on a Hologic Discovery because the densitometer was upgraded during the 15-mo period between DXA scans performed before and after the ~6-mo mission.

Skeletal Sites

For ISS crewmembers, each DXA testing session included the following six scans: whole body, both proximal femora, lumbar spine, forearm, and heel. Scans performed on Mir cosmonauts and astronauts included the whole body, left proximal femur, lumbar spine, and heel. Although multiple skeletal regions can be obtained from a single whole-body scan (e.g., legs, arms, pelvis, head), the following sites have typically been reported to describe the effects of spaceflight: lumbar vertebrae 1–4, total hip, femoral neck, trochanter, pelvis, forearm, and calcaneus.[20] The hip, lumbar spine, and forearm are skeletal regions of clinical relevance for age-related fragility fractures,[9] whereas other skeletal sites (calcaneus, pelvis) have shown consistent declines in response to spaceflight[32] and, therefore, are evaluated to characterize effects of spaceflight and in-flight countermeasures to bone loss. No crewmember was scanned by DXA if the crewmember had participated in procedures using radioisotopes or radio-opaque contrast agents in the previous week. Negative pregnancy status was confirmed in all female crewmembers before DXA testing.

Medical Assessment Test

Baseline DXA values were defined as those from the most recent preflight DXA testing session (i.e., closest to launch). For Expeditions 1–16, the baseline DXA values consisted of data from a single measurement session (mean ± SD of 112 ± 101 d

[*] Hologic QDR 4500 and QDR 2000 were used for measurement of astronaut BMD. For QDR 4500, the least significant change (LSC) is 0.019 (trochanter), 0.035 (femoral neck), and 0.025 g · cm^{-2} (lumbar spine), and the LSC for the Hologic QDR 2000 was 0.024 (trochanter), 0.050 (femoral neck), and 0.035 (lumbar spine) g · cm^{-2}.

before launch). For Expeditions 17–25, two preflight scans were performed on the same test day and the values were averaged to establish the baseline values (mean ± SD of 140 ± 91 d before launch). Baseline data collection was generally repeated if the original launch date was delayed by more than 5 mo. Scans obtained on the Mir comparison group were obtained from a single preflight measurement session performed within 3 mo of launch.

The first postflight DXA scans for both ISS and Mir crewmembers were conducted within 1 wk to 30 d after landing. For ISS Expeditions 6–14, the Soyuz spacecraft landed in Russia and postflight DXA sessions occurred within 1 wk of return to JSC, which was typically 2 to 3 wk after return to Earth. DXA scans were then repeated up to four times after landing (at 6- to 12-mo intervals) over the next 3 yr until BMD was restored to within 2% of preflight baseline BMD, with stability confirmed at the next scheduled DXA scan. The generally accepted error in BMD measurements is 2%, although reproducibility studies performed by the JSC scanning laboratory have shown that its scans are well within this limit.

Test Results

The BMD clinical guidelines for diagnosing osteoporosis in peri- and postmenopausal women and in men older than 50 yr are based on T-scores.[14] As noted earlier, a T-score less than −2.5 for the hip or spine is the threshold for an osteoporosis diagnosis, where the T-score is defined as the number of standard deviations from the mean BMD of a gender-matched population of young persons (20 to 29 yr). In addition, the percentage change in BMD from preflight baseline measures was determined for every postflight DXA scan. A bone endocrinologist with a specialty in bone densitometry interpreted the BMD changes in terms of fracture risk and provided a clinical recommendation to the NASA Flight Medicine Clinic at JSC. Data were also pooled and analyzed to evaluate the relative efficacy of in-flight countermeasures.

Statistical Analysis

Data were analyzed using Student's *t*-test for the difference between group means. Although the data are reported as percentage change, all *t*-tests were based on the absolute change in BMD from before to after flight. Comparison of Mir vs. ISS mean BMD changes was performed using a two-tailed, unpaired Student's *t*-test. Mean BMD changes in crewmembers before the ARED was flown on-orbit and BMD changes for those who used the ARED were compared using a one-tailed, unpaired Student's *t*-test, with an a priori assumption that ARED use would have a protective effect (relative to no ARED use) on BMD. Probabilities less than 0.05 were considered statistically significant.

RESULTS

Fig. 1 displays the changes in BMD T-scores of individual astronauts from before flight to after flight for the lumbar spine, femoral neck, and trochanter—the sites commonly associated with osteoporotic fractures. BMDs for the forearm consistently show minimal changes during spaceflight and hence T-scores are not shown. Similarly, the calcaneus and pelvis are not evaluated terrestrially for clinical decision-making, and hence T-score reference data sets are not available. Fig. 1 shows that no ISS crewmember launched with a T-score less than or equal to −2.5. In the first 10 yr of the ISS era, no crewmember has returned from the ISS with a T-score less than −2.5. These observations meet JSC's medical standard requirements for bone health. **Fig. 2** displays the percentage change in DXA BMD of five skeletal sites for individual crewmembers after long-duration Mir and ISS missions. For the purpose of this figure, Mir astronaut ($N = 7$) and cosmonaut ($N = 28$) data were combined into a single group (Mir). Differences between Mir astronaut and Mir cosmonaut group means were not statistically significant, with the exception of the lumbar spine, where Mir cosmonauts had roughly twice the mean BMD decline measured in the Mir astronauts (~6% versus ~3%). The mean percentage changes in BMD in ISS crewmembers ($N = 33$, includes repeat missions) were significantly less than the percentage changes in Mir crewmembers ($N = 35$) except in the femoral neck, suggesting that the suite of ISS exercise hardware and protocols provided improved protection against bone loss in most areas.

Table II shows the individual changes in BMD ± SD for five skeletal sites of ISS crewmembers who flew before ARED was available ($N = 26$) and for ISS crewmembers who exercised on ARED for their entire mission ($N = 7$). Similar data, on a subset of crewmembers, have been reported by others.[33] Of the 11 ARED crewmembers, 4 participated in a bisphosphonate countermeasure study;[21] because of this confounder, their results are not included in Fig. 2 or Table II.

DISCUSSION

Assessment of the capability of in-flight exercise to mitigate bone loss is confounded by many factors, including the unexpected heterogeneity of BMD in the astronauts, the presence of multiple bone loss interventions (i.e., exercise, nutrition, and pharmaceuticals), the presence of multiple potential bone loss risk factors in flight (e.g., high dietary sodium, radiation, fluid shifts), and the limited capability of DXA technology to detect spaceflight effects on bone structure.

Extensive variability in the BMD responses existed among long-duration crewmembers, with BMD changes ranging from losses of 21% to gains of nearly 5% depending on the specific skeletal site. Possible sources of this variability include numerous differences in exercise hardware, exercise regimens, and individual levels of activity.[22] Exercise hardware flown on orbit also provided different levels of resistive forces. In contrast to the iRED, for example, the ARED more closely simulated lifting free weights in the 1-G environment and could provide up to 272 kg (600 lb) of resistive force. The iRED was limited to a maximum of 136 kg (300 lb) of resistive force. Furthermore,

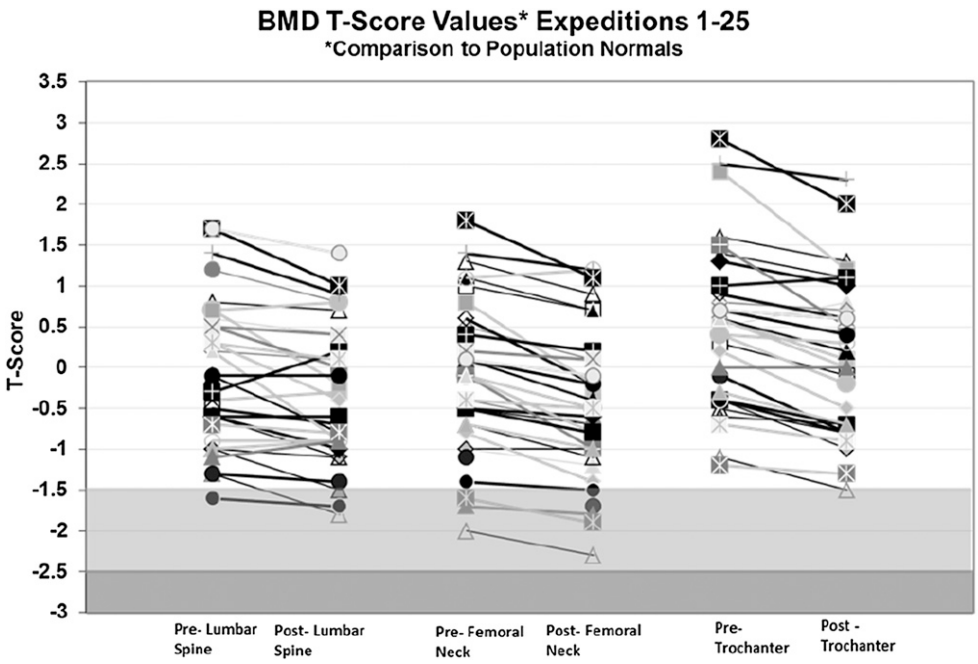

Fig. 1. Change in DXA BMD T-scores before and after ISS flights (Expeditions 1-25). T-scores, as referenced to the mean BMD of gender-specific young persons, were calculated from preflight and postflight measures of BMD in astronauts during an ISS mission. The unshaded region (T-score > -1.5) represents optimal bone health for long-duration astronauts according to medical standards for crew health.[20] The lighter shaded region (−1.5 > T-score > −2.5), represents a permissible outcome after an ISS mission, and the darker shaded region (T-score < −2.5), represents a nonpermissible outcome.

eccentric loading provided by the iRED was significantly less than concentric loading, and the ratio of concentric/eccentric loading in ARED was about 90%. Many researchers think that eccentric loading is the most critical component of heavy resistive exercise. The heterogeneity in BMD data from a crewmember cohort, which was expected to be more homogeneous than patient populations, also suggested that operationally induced risk factors (e.g., dietary constraints, radiation exposure, and exposure to hypercapnia) further complicate the interpretation of results.

The medical standards for crew bone health were derived from terrestrially based diagnostic guidelines for osteoporosis. Osteoporosis is the intermediate skeletal condition that serves as a hallmark for increased fracture risk and a trigger for possible clinical intervention. Thus, when clinical guidelines were formulated in 1994,[14] it was judicious to implement DXA measurement of BMD as the medical test for evaluating the potential detrimental effect of spaceflight on bone health and skeletal integrity. The fact that no diagnostic T-score for osteoporosis was observed in astronauts after missions on the ISS suggests that ~6 mo of space travel does not increase the risk for "fragility" fractures. In fact, the medical standards ensure that astronauts launch with minimal risk for fracture (most astronauts have T-scores > 0 before flight) and return with minimal risk in spite of the fact that some crewmembers have considerable percentage decreases in BMD (greater than 10% over one spaceflight mission). These data also suggest that NASA's standards for crew health have been successful. Thus, it may be inferred from these data that the current in-flight countermeasure approaches are sufficient to prevent unacceptable levels of bone loss during a 6-mo mission. However, no current fracture prediction calculators exist (e.g., Fracture Risk Assessment Tool) that can estimate fracture probability from a percentage change in BMD, especially in younger persons (<50 yr).

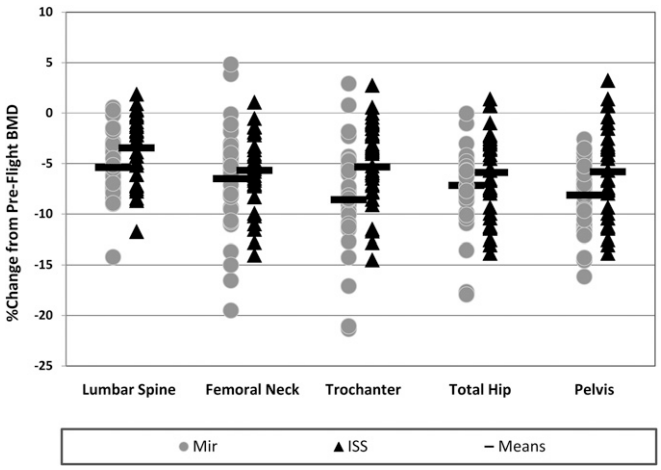

Fig. 2. The percentage change in BMD of crewmembers who served on long-duration missions of the Mir spacecraft ($N = 35$) and the ISS ($N = 33$, Expeditions 1-25) from preflight (baseline). None of the crewmembers were participants in the studies evaluating pharmaceutical therapies for bone loss. The following *P*-values are based on unpaired, two-tailed Student's *t*-tests for the difference between Mir and ISS group means: lumbar spine, $P = 0.015$; femoral neck, n.s.; trochanter, $P = 0.009$; total hip, $P = 0.020$; pelvis, $P = 0.034$.

Information obtained during the first 10 yr of long-duration ISS missions has led to an interest in expanding the medical requirements necessary for evaluating changes in bone mass (i.e., BMD) and in better understanding how spaceflight could contribute to fracture risk in the ISS astronaut. The BMD measured by DXA may account for only 50–70% of bone strength.[1] The utility of DXA is due in large part to the abundance of epidemiological data underlying BMD as a surrogate for fracture risk and not to its correlation with the mechanical strength of bones.[8] DXA guidelines were developed for a terrestrial population already known to be at high risk for fractures (i.e., postmenopausal women and the elderly) and the application of BMD-based diagnostic guidelines to young (age < 50 yr), physically fit ISS astronauts is not likely to be clinically meaningful. The sole use of T-scores for evaluating serial changes in BMD or for evaluating risk in premenopausal women or men

Table II. Mean Percentage Change from Preflight BMD ± SD for ISS Crewmembers Before ($N = 26$) and After ($N = 7$) ARED Exercise Hardware Became Available On Orbit for Resistance Exercise.

	IRED USE (PRE-ARED)		ARED USE		
SKELETAL SITE	% CHANGE	SD	% CHANGE	SD	*P**
Lumbar Spine	-3.7	3.5	-2.6	2.3	0.27
Femoral Neck	-6.1	3.7	-4.1	2.6	0.12
Trochanter	-6.1	3.7	-2.5	1.7	0.03
Total Hip	-5.8	2.6	-3.1	1.2	0.01
Pelvis	-6.6	4.4	-2.8	4.1	0.04

* *P*-values are the result of one-tailed, unpaired Student's *t*-tests for the difference between means.

less than 50 yr of age is being readdressed because of the lack of terrestrial evidence substantiating an increased risk of fragility fractures due to low BMDs (< -2.5 T-scores) for the age range of astronauts.[13,15]

In the past decade, clinical trials involving pharmaceutical interventions for osteoporosis (e.g., sodium fluoride and bisphosphonates as potential therapies) revealed a reduced sensitivity and specificity of DXA BMD to forecast the occurrence or mitigation of fractures.[3,28] These inconsistencies implied that other determinants of bone strength aside from BMD were not being detected by the DXA measurement of BMD. As a result of these observations, a consensus statement was made that a more complete assessment of skeletal integrity would require measures beyond BMD (i.e., indices of bone quality) that influence bone strength independent of BMD.[24]

This paradigm shift for assessing skeletal integrity has strong implications for the space program, both for the bone medical standards and for the way countermeasure efficacy is established for ISS astronauts. For example, the fact that DXA technology measures a 2-dimensional projection of bone limits its ability to assess bone size and structure, which are key determinants of bone strength.[5,30,32] Moreover, the ISS astronaut is exposed to a complex array of novel bone loss risk factors, such as adaptation to reduced mechanical loading, concurrent muscle atrophy, dietary issues, cardiovascular fluid shifts, and exposure of bone marrow cells to ionizing radiation. As the unique combination of established[10] and putative risk factors for bone loss, as previously mentioned, cannot be easily studied using spaceflight analogues on Earth, their interactive impact on bone remains poorly understood. The data obtained to date from research studies, albeit limited, indicate that the adaptation to prolonged microgravity and exposure to other novel risk factors of spaceflight induces changes in bone mass and structure that are unlike changes seen with terrestrial age-related bone loss.[25]

A new index has been proposed for assessing the risk for early-onset osteoporosis in ISS astronauts. This index requires scanning of astronauts' hips by quantitative computed tomography (QCT). This research bone imaging technology is capable of discerning the BMD in the trabecular bone compartment of the hip, in addition to quantifying an integral BMD of the hip, which combines the trabecular and cortical bone compartments.[17] The clinical evidence from QCT research is insufficient to support the development of clinical practice guidelines at this time;[11] however, QCT-specific measures of bone structure may enhance understanding of the underlying physiological response of the hip bone to spaceflight and to countermeasures.

The proposed application of QCT to ISS astronauts is based on data from a flight study that described changes to subregions of hip BMD (trabecular and integral) after spaceflight.[18] These changes had not returned to baseline status after 12 mo of reambulation on Earth.[19] An extension of the original flight investigation was approved to assess recovery with an additional QCT scan conducted between 2 and 4 yr after return from flight.[6]

Eight ISS crewmembers, who had previously received QCT scans before flight, after landing, and 1 yr after return as part of the original flight study, consented to the additional scan. Their hip trabecular BMD had not returned to preflight levels at the time of the final scan. An additional complicating factor is that BMD changes assessed by both DXA and QCT showed a discordant pattern of recovery after return to Earth.[6,25] The impact of these BMD differences on potential fracture or osteoporosis risks is not known.

NASA convened a panel of bone clinical experts in 2010 to review the biomedical data generated by both Medical Assessment Tests and research from long-duration astronauts.[25] Part of the charge to this panel was to identify a clinical trigger for the NASA Space and Clinical Operations Division to recommend post-mission surveillance for early-onset osteoporosis. The panel recommended that the clinical trigger should be the failure to detect recovery in QCT trabecular BMD of the hip within 2 yr postflight, in addition to using the DXA BMD standard for a nonacceptable outcome. The panel recommended that failure to recover hip trabecular BMD within 2 yr should be followed up by an endocrine evaluation.[25] Specifically, panel members were concerned that irreversible changes to this site of the hip might combine with age-related changes to result in premature osteoporotic fractures.[7,27,29]

Data from a prospective study of fracture risk in elderly men have validated trabecular BMD of the hip, among other QCT parameters, as an independent predictor (aside from DXA BMD) for hip fracture in aging men,[4] underscoring the potential clinical value of QCT for monitoring recovery of this skeletal site in ISS astronauts.[25] Densitometry manufacturers are offering methods to enhance the evaluation of hip structural parameters by DXA, such as hip structural analysis and femur strength index.[12,16,26] Some of the proposed DXA measures, however, have not shown increased capability to predict fractures relative to that of BMD itself.[12,16,26]

In summary, the ISS astronaut cohort represents an understudied "at risk" population exposed to a novel array of risk factors that induce unique changes in bone that may or may not increase the risk for fracture or for early-onset osteoporosis. Skeletal adaptation is similar to a rare disease that affects a small number of persons and about which knowledge is limited. Evaluating the effects of additional variables on bone will help

define the probability and severity of risk and will aid in developing, testing, and implementing countermeasures before, during, and after flight. The high level of uncertainty associated with using only the current Medical Assessment Test for bone may necessitate expanding astronaut medical standards for bone health to include multiple variables (e.g., DXA BMD, QCT BMD, bone geometry) to describe changes to the total hip in the long-duration astronaut; these additional indices will help to refine medical standards and guide the evaluation of in-flight countermeasures and postflight rehabilitation. To illustrate this point, the positive effect of ARED exercise on decreasing BMD loss is encouraging, but the currently available BMD and bone loss data do not necessarily demonstrate that spaceflight-induced bone loss is sufficiently mitigated. In addition, the identification of a clinical trigger (the failure to recover preflight hip trabecular BMD by 2 yr after return) increases the importance of evaluating the ability of exercise, or any other in-flight countermeasure for bone loss, to mitigate the occurrence of this trigger.

The variety of in-flight exercise programs performed on the ISS makes it difficult to determine the efficacy of in-flight countermeasures. The BMD data obtained from ISS astronauts who exercised on the ARED are encouraging, but whether the ARED capability can be adapted for exploration-class missions that will take astronauts beyond low-Earth orbit remains an open issue. The occurrence of bone loss in a small cohort of younger persons exposed to novel environmental factors and the complex nature of skeletal changes in long-duration astronauts necessitate the continued evolution of sensitive medical tests and research technologies to characterize the effects of spaceflight on bone morphology (mass and structure) and to assess the impact of these effects on bone quality.

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