

**Human Research Program  
Human Health Countermeasures Element**

**Evidence Book**

***Risk of Bone Fracture***

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## **I. PRD Risk Title: Risk of Bone Fracture**

**Description:** Bone mineral loss occurs in microgravity due to unloading of the skeletal system, with average loss rates of approximately 1% per month. It is unclear whether this bone mineral density will stabilize at a lower level, or continue to diminish. It is also unknown if fractional gravity, present on the moon and Mars would mitigate the loss. This level of bone loss does not create an unacceptable risk of fractures for ISS missions, but longer missions could create higher fracture risk. The risk of fracture during a mission cannot be estimated with any level of certainty until mechanisms and probabilities of bone overloading during the missions are understood. Mission-related bone loss cannot be corrected by post-mission rehabilitation; crewmembers could be at greater risk of osteoporosis-related fractures in later life. Greater understanding of the mechanisms of bone demineralization in microgravity is necessary to frame this risk, as well as to understand how current and future osteoporosis treatments may be employed.

*The risk, as quoted (above), is taken from the Program Requirements Document (PRD) and is not considered current with the paradigm shift from using areal BMD, measured by DXA technology, as a sole surrogate for bone strength. This paradigm shift will be discussed in the Introduction and Background sections of this report.*

## **II. Executive Summary**

Spaceflight-induce bone atrophy, due to the mechanical unloading of the skeletal system, is targeted to specific regions of the skeleton. These site-specific losses occur at normally weight-bearing skeletal areas (on Earth) suggesting that the regions that experience the larger deficits in mechanical loading undergo the greater adaptation. Collectively, the average decrement of *preflight areal bone mineral density (BMD)* per month is 1-1.5%, although there are considerable variations of loss between different skeletal sites and between different crewmembers. The time course of bone mineral loss, during a typical 6-month long-duration mission, has not been characterized nor for mission durations > 6 months. Consequently, it is not known at what level bone atrophy – that is, the loss of bone mineral – will eventually plateau; nor is it known if mineral loss can be mitigated by the partial gravity environments of the moon and of Mars. Moreover, the clinical ramifications of spaceflight-induced bone atrophy have not yet been defined. It is unclear whether whole bone strength is recovered on Earth after a spaceflight mission. To better understand the risk of increased fracture during a mission and later in life, the effects of spaceflight-induced changes need to be evaluated on an expanded scale. A hierarchy of skeletal measures can be assessed from systemic measures of bone turnover, to evaluations of compartment-specific bone mineral densities, to assessment of microarchitecture, to measures performed at the level of the basic multicellular unit. Acquisition of this body of knowledge is central to framing the risks and to outlining the prophylactic and treatment strategies that can be operationally implemented to best preserve the skeletal health of crews on exploration missions.

In addition, relative to population studies of fracture incidence, there is limited experience with humans in long-duration spaceflight. Thus, statistical modeling approaches are useful tools to understanding how physiological changes can influence the probability for incurring an adverse event, such as a bone fracture. Incorporating assumptions, based on the volume and accuracy of input data, is essential to the reliability of the model prediction. However, a balance

between a) increasing the accuracy and predictability of the model, and b) reducing the complexity and usefulness of the model is still being sought.

A component of Probability Risk Assessment models is the Factor of Risk index where the Factor of Risk for *fracture* evaluates applied loads as well as the failure load of bone. The risk for fracture is minimal during missions in low Earth orbit because applied loads associated with falling, or with other events, are non-existent in a weightless environment or are mitigated by operational procedures. Mechanical loads to bone, however, may increase in the fractional or 1G environment of planetary surfaces or with the performance of mission activities during exploration missions (for example, during construction of habitats, ambulation in extravehicular suits, jumping from ladders, conducting vehicle egresses). More importantly, the risk for increased bone fracture may exist with return to Earth's gravity and with the cumulative effects of ageing and of spaceflight on skeletal health.

There is a medical requirement to monitor the skeletal effects of long-duration spaceflight in crewmembers; these evaluations, however, are limited to measurements of areal BMD by DXA and of biomarkers for bone turnover. Longitudinal DXA measures over the lifetime of astronauts have only been recently implemented. Moreover, the occurrence of some types of fractures during or immediately after spaceflight (for example, stress and vertebral compression) is unknown because specific measurements (lateral spinal DXA scans, microfracture assessments) have not been systematically performed in crewmembers after return. Structural evaluations of bones using newer technologies have not been measured longitudinally in the majority of astronauts. For instance, the effect of spaceflight on the microarchitecture of trabecular bone or in the recovery of BMD in the trabecular bone compartment has not been completely determined. The timeframe of BMD loss is also unknown, particularly for durations of greater than 6 months and in partial gravity environments. The pattern of BMD loss and recovery needs to be evaluated further on a multifactorial, cross-discipline level. In order to understand, identify, and define the risk for increased bone fracture during and after spaceflight, bone needs to be fully evaluated with specific and expanded measures to reflect the so-called "bone quality" aspect. This is highlighted further by the most modern definition of osteoporosis: "... a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality." (JAMA, 2001)

To summarize:

1. Bone atrophy occurs due to space travel.
2. DXA-measured areal BMD has been shown to be an incomplete indicator of whole bone strength.
3. Knowledge regarding changes in bone geometry and microarchitecture is incomplete.
4. The relative contribution of microarchitecture and geometry to bone strength is not known but the literature indicates that it could be substantial.
5. Due to the multiple contributors to bone strength, the full impact of spaceflight on whole bone strength is unknown.
6. The state of bone loading for different mission scenarios is unknown.

### **III. Introduction**

After more than 40 years of space travel, it is assumed that fractures have not occurred during missions in low Earth orbit nor in the immediate postflight time frame. This outcome could be attributed to a number of issues.

- There is a lack of impact forces to the body in the weightless environment;
- Significant decrements in bone mineral density (BMD) have not been detected for missions of less than 90 days;
- Postflight rehabilitation programs on Earth promote skeletal recovery and reduce fracture risk; and
- No measurements looking specifically for fractures were obtained in returning astronauts with musculoskeletal pain.

Moreover, not all crewmembers incur significant losses at all weight-bearing sites although all crewmembers incur a significant deficit in bone mass in at least one site (LeBlanc, 2007).

However, because of the extreme environment and locations, and the remote level of medical care during exploration missions to planetary surfaces, the severity of the risk for fracture is very HIGH even if the probability of the risk would be considered LOW. The occurrence of a fracture in a crewmember not only jeopardizes performing mission objectives due to morbidity and loss in human performance, but could also lead to complications which can result in loss of life. Even if a fracture does not result in death, the documented effect of the weightless environment on bone cell activities could impair the healing process, increase the risk for non-union fractures, and expose the crewmember to additional complications such as sepsis or thromboembolytic clots. Therefore, it is of paramount importance to evaluate the propensity of a crewmember to fracture a bone under the conditions and effects of a spaceflight mission.

In this regard, evaluating the probability of a bone fracture during a spaceflight mission requires assessing the relationship between two measurable parameters: the loads experienced by bones of the skeleton (Applied Loads) and the structural integrity of the bone (Whole Bone Strength). This relationship determines the “Factor of Risk.” Estimating a Factor of Risk for bone fracture uses the engineering approach of calculating the “Factor of Safety” (in the design of structures) where structural failure likely occurs when the ratio of Resisting Force (strength) to Disturbing Force (stress) is  $<1$ . Factor of Risk is the *inverse ratio* of Factor of Safety (the ratio of Applied Force to Bone Strength) where fracture likely occurs when the ratio  $>1$ . Clearly, a simple and accurate approach to determining the Factor of Risk for a bone fracture is to quantify the maximal force to fracture a bone. Because this approach is neither practical nor ethical, whole bone strength is determined by measuring a surrogate, such as the mineral density of bone. In particular, the measurement of bone mineral density [BMD] by dual-energy x-ray absorptiometry [DXA], an x-ray based imaging technology, has been the gold standard surrogate for bone strength for ~ 15 years.

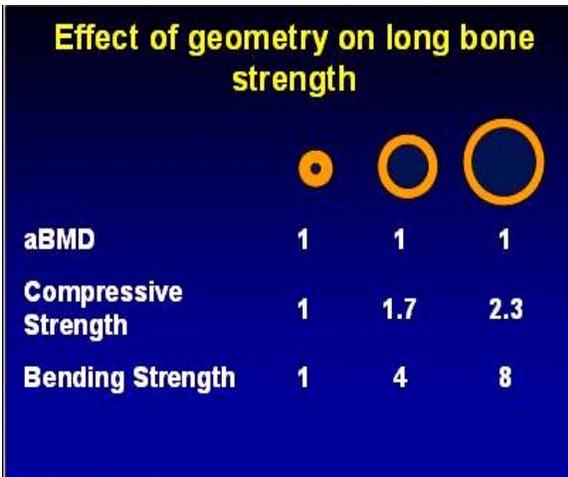
Moreover, the noteworthy value of DXA-measured BMD as a surrogate for whole bone strength is based upon the abundance of epidemiological data correlating areal BMD with the incidence of fractures in population-based studies. In a meta-analysis of fracture incidence in elderly white females, DXA measurement of areal BMD as a surrogate for whole bone strength had been validated by prospective studies covering 12 cohorts, representing 60,000 subjects, and monitoring over 250,000 person-years with 5,400 total fractures (Kanis, 1994). This meta-analysis provided the basis for the diagnosis of osteoporosis (and increased fracture

susceptibility) by the World Health Organization (WHO) guidelines. In this case, BMD is a good index for stratifying postmenopausal, Caucasian women according to fracture risk but it is not a good predictor of *who* will fracture (Cummings, 1995).

Consequently, it has become widely recognized that the assessment of fracture risk based *solely* on DXA areal BMD is inadequate and fails to provide a complete reflection of whole bone strength. Reports in the literature highlighted a disconnect between areal BMD and its ability to predict fracture (Riggs, 1990; Cummings, 1998; Gutteridge, 2002; Wainright, 2005). And greater reductions in fracture risk were associated with only modest improvements in areal BMD (Chesnut, 2005; Sornay-Rendu, 2007). The limitation of areal BMD as a surrogate had also been expressed in the previous evidence-based Bioastronautics Report reviewed by the Institute of Medicine (2005) (Bioastronautics Roadmap). Moreover, areal BMD data from women of all other ethnicities and from men did not factor into the WHO meta-analysis – which validated areal BMD as an index for fracture risk – thereby minimizing the application of the guidelines to the younger-aged, predominantly male astronaut population. Thus the Human Research Program appreciates the need to supplement the measurement of spaceflight effects on the skeleton with novel and emerging technology in order to measure indices of “bone quality” and obtain a complete reflection of skeletal integrity.

A limitation of the DXA application is in its measurement of *areal* BMD ( $\text{g}/\text{cm}^2$ ). This index fails to account for the depth and geometry of a bone. Figure 3-1 depicts how the bending and compressive strength of whole bone are dependent upon its size and geometry – which cannot be directly evaluated by DXA.\* There are emerging technologies for the non-invasive assessments of other skeletal indices besides areal BMD – the so called “Bone Quality” parameters which contribute to whole bone strength. For instance, measurements of volumetric BMD ( $\text{g}/\text{cm}^3$ ) of whole bone and of bone compartments can be obtained by quantitative computed tomography (QCT). Furthermore, there are novel MRI and high resolution QCT technologies for the measurement, at peripheral skeletal sites, of cancellous bone microarchitectural indices. Such measures are used to reflect the thickness, the linear concentration and the connectivity of trabeculae in the bone marrow compartment of bone. Changes to these indices can influence the mechanical properties and distributions of loads in cancellous bone (Van der Linden, 2001).

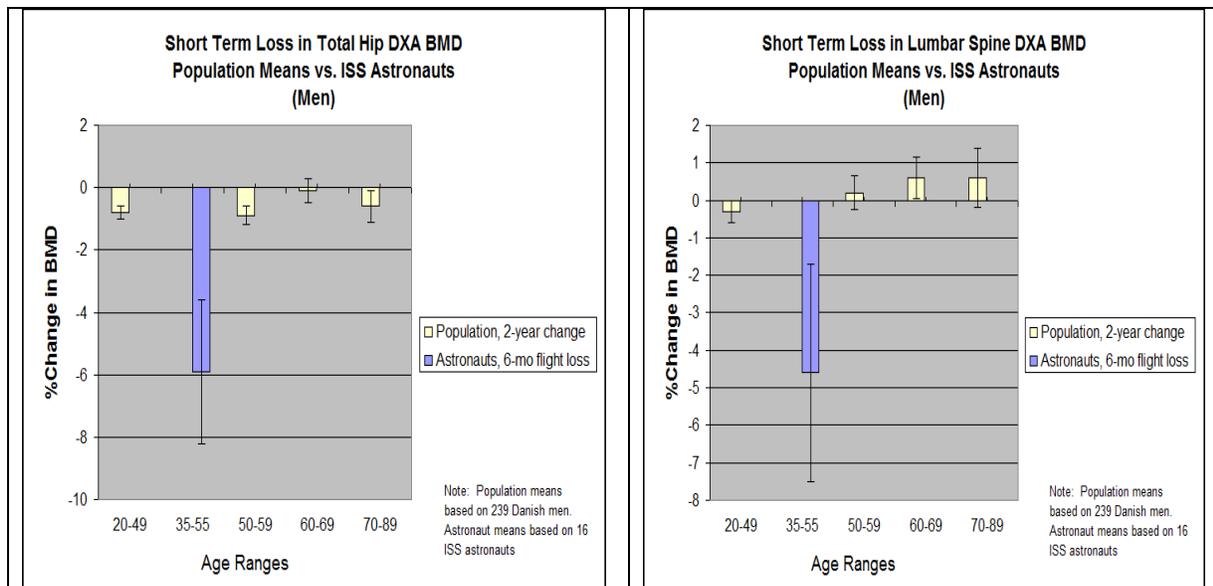
\***Note:** There have been recent modifications of the DXA technology for the purported assessment of volumetric BMD of scanned bone.



**Figure 3-1.** Mary Bouxsein, Ph.D., Bone Geometry and Skeletal Fragility. *May 2005 Bone Quality Meeting*

Until recently, the risk for increased fracture during spaceflight had only been evaluated by DXA measurements of areal BMD performed in crewmembers before and after the typical long-duration spaceflight mission of 6 months. Therefore, evaluation of “Bone quality” indices is required to substantiate this risk because spaceflight may impact more than areal BMD. While there are multiple indices that can influence the material properties of bone and whole bone strength (for example, degree of mineralization, microcrack accumulation, resorption cavities, activation frequency), NASA is focused on non-invasive measurements of its crewmembers, particularly if such measures can be supported by portable technology used during a spaceflight mission.

To date, the DXA measurements conducted pre- and postflight in long-duration crewmembers have characterized deficits in areal BMD for weight-bearing skeletal sites, with losses, averaged per month, that are greater than the losses detected in per year in women suffering from menopause-induced bone loss. In particular, Figure 3-2 demonstrates the greater percentage loss in areal BMD in male astronauts over a typical 6-month mission compared to the BMD loss over 2 years measured at the same skeletal site in similarly-aged Danish men. (Reference Chapter 2, Risk for Accelerated Osteoporosis). A comparison of female data is not shown because of the small number of female astronauts (n=3) in the database.



**Figure 3-2.** Comparison of BMD changes for hip and lumbar spine in male crewmembers vs. population mean. ISS: International Space Station. (Adapted from Warming, 2002, and Johnson Space Center Bone Mineral Lab).

Although the assessment of bone integrity is incomplete, there are data in the evidence base that extend skeletal evaluation beyond DXA areal BMD. While these additional measures are not surrogates for bone strength that have been validated in prospective studies of fracture incidence, these measures add to the characterization of spaceflight effects on bone. These measures are described in more detail in a Chapter 2, Risk of Accelerated Osteoporosis, but the significance of these data is summarized in the following:

- i) The application of QCT technology provides measurements of volumetric BMDs for whole bone and for separate bone compartments (cortical vs. cancellous bone, and combined) and three-dimensional geometry of whole bone – which can be used to assess the impact of spaceflight on whole bone strength by applying a finite element analysis (Keyak, 2005; Hernandez, 2006). The data from QCT scans conducted in long-duration crewmembers characterized how the separate compartments of the hip adapt to space differently and – described later in this report – were used to estimate a Factor of Risk for hip fracture on Mars, moon, and after return to Earth (Lang, 2006).
- ii) Monitoring the changes in bone turnover markers is reported to be predictive for changes in bone mass and fracture (Garnero, 1996; Bonnicksen, 2006). Biological specimens (urine and blood) collected before, during, and after flight were evaluated after sample return to Earth. The data suggested that bone adaptation in space is driven by a predominating catabolic process (Smith, 2005).
- iii) The human skeleton also serves as mineral reservoir for maintaining calcium balance, which could be a greater issue than fractures for exploration missions exceeding a year. Studies on calcium-regulating hormones demonstrated how the processes for calcium homeostasis are influenced by the bone atrophy that occurs in space (Smith 1999; 2005). (Data are described in detail in Chapter 2, Risk of Accelerated Osteoporosis.)

More importantly, because the risk for fracture is dependent upon the relationship between the structural integrity of bone and the loads that are applied to bone, the calculation of the Factor of Risk for fracture is only as accurate as the measurements of skeletal integrity and of applied loads.\* Likewise, the accuracy of models for fracture probability is also dependent upon the accuracy of the data used to create the model. Unfortunately, estimations of applied load to bone are based upon large uncertainties. For instance, some reported algorithms to calculate loads incurred by the hip on Earth are based upon body weight, height of fall, velocity of fall and dampening of force by fat padding (Robinovitch, 1991; Riggs, 2006). QCT data strengthens the estimation because it can provide measurements of hip padding (Riggs, 2006). Estimations of applied loads in the fractional gravity environment are required to calculate the factor of risk for exploration missions on a planetary surface. These predictions however are even more difficult since planetary surfaces provide unique scenarios that may:

- i) reduce the forces applied to the bone structures;
- ii) influence how the skeletal structures adapt to those reduced mechanical loads; and
- iii) introduce additional risk factors, such as repetitive loading in partial gravity (for example, loping), or multi-system deconditioning with prolonged exposure in space.

In addition, it would be of value to conduct ground-base studies to collect kinematic measures from motion analysis that could be used estimate fall velocity and fall orientation.

It is also important to note that age is an independent risk factor for fracture. The probability for fracture in the postmenopausal woman, for example, increases exponentially with every decade over 50 years for a given measurement of BMD (Figure 3-3). Younger persons do not have the metabolic bone diseases or the nutrition issues that induce bone loss in the elderly populations. Younger individuals also do not have the muscle loss, the postural instability, the impaired neuromuscular control and poor visual acuity that increase the risk for falling in aged persons. It is the integration of these clinical risk factors that accounts for the increased probability for fracture since these latter risk factors increase the propensity for falls and accordingly, the applied loads to bone (DeLaet, 2005). Panel members of WHO have reported an improved ability of areal BMD to predict fractures when considered concurrently with clinical risk factors that will predispose persons to osteoporosis (Kanis, 2007).

Incidentally, clinical risk factors associated with terrestrial osteoporosis (see Table 3-1, Espallargues, 2001), are rarely observed in younger-aged, physically healthy persons of the Astronaut Corps (<55 years of age) *prior to launch*. However, there are risk factors for osteoporosis, as identified by Cummings (also Table 3-1), that are more relevant to crewmembers after the typical 6-month, long-duration mission in space; many of these factors are evident in crewmembers during flight and during readaptation to a gravitational environment. This includes the astronaut returning to their “normal” high physical activity level soon after

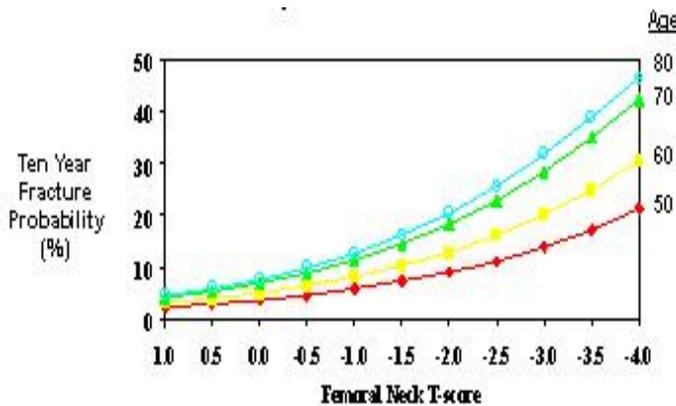
\***Note:** The orientation by which loads are applied is also a critical factor in the Factor of Risk (Carpenter, 2005; Keyak, 2007).

return to Earth as well as the presence of gait instability or postural imbalance that may increase the fracture risk soon after landing. Vitamin D deficiencies, also evident in crewmembers due to insufficient supplementation, have been associated with an increased risk for falling due to vitamin D's benefit to neuromuscular coordination (Bischoff HA, 2003; Bischoff-Ferrari HA 2004). Given the severity of the risk (loss of human performance to loss of life), development of these probability risk assessments, based upon the skeletal adaptations to space, should also consider the presence of the observed risk factors that influence the risk for falling.

**Table 3-1.** Clinical Risk Factors observed in osteoporosis patient population and proposed risk factors relevant to long duration crewmembers

Clinical Risk Factors for Osteoporosis (Espallargues, 2001)	Proposed and identified Risk Factors relevant to Long-duration and Exploration Crewmembers (Cummings 1995)
Aging (>70 years)	On Feet ≤ 4 hours per Day (reduced ground reaction forces)
Low body weight	Can't Rise From Chair Without Using Arms
Weight loss	Lowest Quartile Depth Perception
Physical inactivity	Lowest Quartile Contrast Sensitivity
Corticosteroids	Fair, Poor or Very Poor Health
Anticonvulsant drugs	Vitamin D deficiency
Primary hyperparathyroidism	Weight Loss to BW at Age 25
Diabetes mellitus (Type I)	Balance instability
Anorexia nervosa	Gait impairments
Gastrectomy	Sarcopenia
Pernicious anemia	Low sunlight exposure
Prior osteoporotic fracture	Low calcium absorption

Thus this evidence base report asserts that an increased risk for fracture will be substantiated when more data are collected and the uncertainty is reduced. This report will summarize the evidence from measurements of risk factors that influence “bone strength” and will highlight the knowledge requirements (gaps in knowledge base) in order to calculate and assess the risk for fracture during exploration missions.



**Figure 3-3.** Age as an Independent Risk Factor for Osteoporotic Fractures. Probability of first fracture of hip, distal forearm, proximal humerus, and symptomatic vertebral fracture in women of Malmö, Sweden. While the relative risk for fractures may be the same based upon BMD, the probability of fracture in the 50 year old is less than the probability for fracture in the 80 year old. Adapted from Kanis JA et al. Osteoporosis Int. 2001. Slide courtesy of S. Petak, M.D.

## **IV. Evidence**

A large portion of the evidence for fracture risk has been presented in a separate Evidence Base Report on Accelerated Osteoporosis since osteoporosis is characterized by an increased risk for fracture – specifically, fractures under the mechanical loading of normal activities. Astronaut risk for the fractures is primarily due to the deterioration of skeletal integrity with no diminution of their “normal” activity. In contrast to the Osteoporosis Report, this report will highlight computer modeling that is used to assess the probability that crewmembers, who will undergo skeletal atrophy in space, will encounter loading during the length of an exploration mission that is sufficient to induce a bone fracture.

A summary of risk factors for fracture in crewmembers after spaceflight is provided in the following:

1. Reduced BMD at weight-bearing sites, increased bone turnover in the whole body, geometrical changes in the proximal femur, and a rapid rate of bone loss collectively suggest a decline in whole bone strength by reducing bone mass, reducing cross-sectional moment of inertia and increasing the birth rate of bone remodeling units (LeBlanc, 2000a; Lang, 2004; Smith, 2005).
2. Cortical thinning and compartment-specific reductions in volumetric BMD in cortical and cancellous bone of hip are associated with reductions in compressive and bending strength (Lang, 2004).
3. Finite element analysis [FEA] of hip strength, applied from pre- and postflight QCT hip scans of crewmembers, estimates significant reductions in bone failure loads associated with one-legged stance and posterolateral falls (Keyak, 2007)
4. Preferential losses in volumetric BMD of cancellous bone may be a reflection of disrupted trabecular struts or of reduced trabecular thickness, which could affect biomechanical strength of bone (Van der Linden, 2001; Hernandez, 2006).
5. Deficiencies in vitamin D observed in long duration crewmembers after long-duration missions may induce similar impairments in neuromuscular coordination and increased risk for falling as documented in the elderly (Bischoff, 2003; 2006) if in-flight supplementation efforts cannot be achieved.

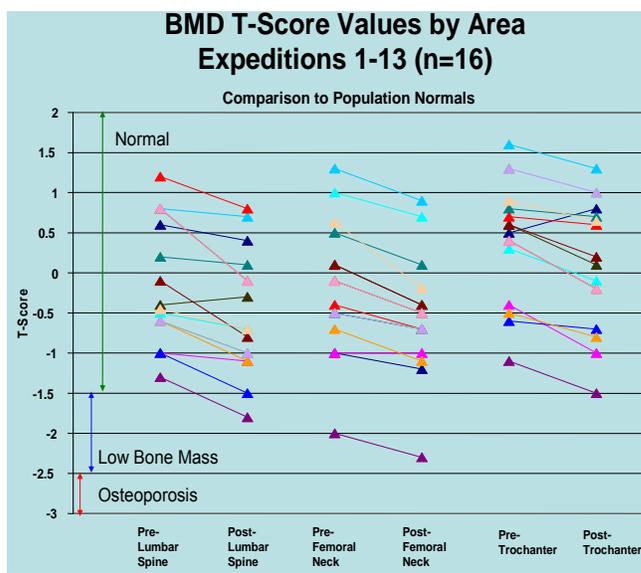
### **A. Spaceflight Evidence from Long-duration Missions (Mir and ISS)**

#### **1. Fracture Risk Factor: Loss in bone mass**

There is a medical requirement to perform DXA measurements of areal BMD in the hip, lumbar spine, whole body, forearm, and calcaneus in long-duration crewmembers to evaluate the effects of spaceflight. DXA scans were performed within 45 days prior to launch and within approximately 5 days of landing. Recovery of bone mass, as indexed by BMD, takes considerably longer than the time to incur the loss (Vico, 2000; Sibonga, 2007). Recovery can be influenced by multiple factors such as age and postflight activity which may account for the restoration of BMD to preflight status as early as 6 months after return, but there is large variability in the response between skeletal sites and between crewmembers. Bone turnover

markers are performed in long duration crewmembers at similar time points. Biomarkers for bone resorption are reported to increase early in flight where they remain elevated until their restoration to preflight levels soon after return (Smith, 2005). Biomarkers for bone formation, on the other hand, are not impacted during spaceflight but circulating levels are increased approximately 1 month after landing (Smith, 2005).

Based upon these DXA measurement of areal BMD and the WHO Guidelines for Osteoporosis Diagnosis (c. 1994), there are no data to indicate a diagnosis in astronauts after a long-duration mission (Figure 3-4), that is, no long-duration astronaut has returned with a T-score of  $\leq -2.5$  for the femoral neck, trochanter, and spine. However, these guidelines were developed for diagnosis in the postmenopausal, Caucasian female population and are based solely upon areal BMD as a surrogate of bone strength.



**Figure 3-4.** T-scores based upon preflight and postflight measurements of BMD and references back to young white sex-matched population. *No long duration crewmember has returned from the typical 6-month mission in low Earth orbit with a diagnosis of osteoporosis according to 1994 World Health organization guidelines.*

More importantly, as reported in the Evidence Base Report for Accelerated Osteoporosis, the average monthly BMD loss (LeBlanc, 2000a) in the crewmember is almost equivalent to the annual loss of areal BMD loss measured in women soon after the onset of menopause, which is the most rapid phase of involutional bone loss (Riggs, 1998). This comparison of bone loss rates was also demonstrated in Figure 3-2 which compared the loss in BMD induced in male crewmembers over 6 months in space to the loss in BMD measured over 2 years in similarly aged men in a Danish population (Warming, 2002). The rate of BMD loss in crewmembers suggests aggressive bone resorption by osteoclasts; the targeted location of resorption cavities on the surface of cancellous bone (aka trabecular bone) will influence cancellous bone strength and stiffness regardless of the changes in volumetric BMD in the cancellous bone compartment (Hernandez, 2006). The depth and location of resorption cavities, however, cannot be determined non-invasively, but can be inferred from combined in vitro analyses (histology, microCT) of bone samples.

## **2. Fracture Risk Factor: Falls**

In addition, clinical risk factors that influence the propensity for falling have been observed in crewmembers after return to Earth following long-duration missions. Losses in postural muscle mass are a contributing factor to postural instability while assessments of head-trunk coordination suggest instability during standing and ambulation (LeBlanc, 2000a,b; Courtine, 2004). Actual impairments in gait (Bloomberg, 2003), jumping (Newman, 1997) and decrements in dynamic visual acuity (Peters, 1996) are evident after long-duration missions in space.

## **3. Fracture Risk Factor: Absence of Vitamin Benefits**

Finally, the shielding for radiation will also prevent ultraviolet conversion of 7-dehydrocholesterol in the skin to vitamin D. Vitamin D is associated with improved neuromuscular coordination (Bischoff, 2003; Bischoff-Ferrari, 2006). In addition, a deficiency in vitamin D could lead to mal-absorption of calcium in the intestine and poor re-absorption by the proximal tubules of the kidney. The failure to conserve calcium because of vitamin D deficiency will limit the availability of calcium to support the anabolic effects of exercise and physical activity on bone and muscles.

### **B. Ground-based Evidence**

There are no ground-based experiments with human subjects that have evaluated Factor of Risk for bone fracture. There are numerous animal models (rodents, dogs, non-human primates) that immobilize or skeletally unload limbs or whole bodies as a means to induce “disuse osteoporosis.” These animal models are valuable resources with which to characterize the cellular and tissue effects of mechanical unloading under well controlled experimental conditions (Turner, 2000). These models can be further applied to evaluate the efficacy of pharmacological and mechanical countermeasures using mechanical strength testing (that is, fracturing bones under defined loads) to quantify bone strength directly. However, as previously discussed, there are multiple physiological and biological measures that influence whole bone strength in humans which might not be completely modeled and assessed by any single species model.

To this aim, Probability Risk Assessment (PRA) models, in development, are accessing data from the elderly patient population to test the utility of the computer modeling to predict risk in a crewmember. In essence, this modeling will be used to predict ability of an atrophied bone to resist loads incurred during performance of exploration mission objectives.

### **V. Computer-Based Simulation Information**

As previously discussed, the Factor of Risk for fracture is the ratio of Applied loads to Failure loads, where fracture is likely to occur when ratio > 1. The *probability* of fracture, on the other hand, is dependent upon multiple factors or variables. Two approaches have been used to calculate the Factor of Risk for Bone Fracture in crewmembers during and after long-duration missions. One calculation of Factor of Risk applies Finite Element Analysis to determine the Failure Load of bone (that is, “bone strength”) after long duration spaceflights (data obtained from 11 crewmembers scanned at the hip by QCT) (Keyak, 2005; Lang, 2006). This approach will be discussed in Section VI. Risk in Context of Exploration Mission Operational Scenarios

## Risk of Bone Fracture

The other approach is the Integrated Medical Model – Bone Fracture Risk Module (BFxRM) that was developed at the NASA Glenn Research Center (GRC) in Cleveland, OH (Nelson, 2009). This model is being used to estimate bone fracture probability and incidence rates of loading. To predict the probability of fracture for space missions and post-mission scenarios, the BFxRM takes into account specific crew data (for example, age, height, body mass, initial bone mass), the cumulative exposure to low-gravity at any given time during the mission, the capabilities of the extravehicular activity (EVA) suit to absorb the energy of impact, the protective strategies of the astronaut to protect themselves from injury during fall, and the specific mission profiles and tasks that would lead to high levels of skeletal loading. There are many factors contributing to the likelihood of bone fracture which may contribute to high variability and uncertainties; thus, the BFxRM is a statistically-based analysis implemented to estimate the probability of fracture.

The BFxRM estimates the incidence rate of loading and the likelihood that the bone can support the load once it is applied. Incidence rates of loading are derived from previous mission data. The ability of the bone to support the applied load is addressed by considering both intra-skeletal and extra-skeletal factors – such as the rate of bone mineral loss as measured by DXA, well-validated bone strength data, and biomechanical models of skeletal loading – adjusted for the variations in gravity and for the extenuating factors associated with astronaut performance within their protective equipment. This is accomplished by using random combinations of these factors, selected through a Monte Carlo methodology, to calculate a statistically significant number of probable outcomes for the loading scenario under consideration.

The probabilistic modeling approach allows a mean estimate of fracture probability – quantified for specific fracture scenarios – but, equally important, it provides a measure of the uncertainty associated with the estimate of risk. The model provides a familiar metric (probability of occurrence) which can be applied to decision making and for comparison to other risks in the Program Requirements Document. The BFxRM bounds the uncertainty associated with the probability of bone fracture in space by using the best available data and prevailing assumptions.

Two primary variables are calculated in the risk analysis: 1) the Factor of Risk for fracture and 2) the probability of fracture. As previously discussed, the Factor of Risk for fracture is the ratio of the applied skeletal loads to the bone failure load (that is, bone strength). The probability of fracture, on the other hand, is the combined probability of the occurrence of an event and the Factor of Risk for fracture *converted to a probability*. The probability of occurrence was derived using Apollo EVA films and documents of activities and using astronaut reports. The Factor of Fracture Risk was converted to a probability of fracture from a logistic regression of actual fractures and assumptions from the literature governing the factor of risk for fracture threshold.

The Factor of Risk levels for male astronauts during a specific EVA mission scenario are displayed in Table 3-2. The femoral neck fracture factor of risk is for a fall inside the space craft (IVA) and the 90° trunk flexion, while holding a load is also an IVA activity. The 45° trunk flexion, while holding a load and the falls from 1 and 2 m, landing on two feet occur during EVAs.

**Table 3-2.** Mission average Factor of Risk levels for several different mission scenarios for a male astronaut.

Activity or event	Mission location	Mission duration	Mean Factor of Risk	Std

## Risk of Bone Fracture

<b>Femoral Neck Fracture</b>				
Fall to side	Moon	Short	0.09	0.07
Fall to side	Moon	Long	0.10	0.08
Fall to side	Mars	Short	0.23	0.16
Fall to side	Mars	Long	0.28	0.20
<b>Lumbar Spine Fracture</b>				
45° trunk flexion, holding a load	Moon	Short	0.12	0.03
90° trunk flexion, holding a load	Moon	Short	0.08	0.03
Fall from 1m, landing on two feet	Moon	Short	0.30	0.05
Fall from 2m, landing on two feet	Moon	Short	0.46	0.10
45° trunk flexion, holding a load	Moon	Long	0.12	0.03
90° trunk flexion, holding a load	Moon	Long	0.08	0.03
Fall from 1m, landing on two feet	Moon	Long	0.31	0.06
Fall from 2m, landing on two feet	Moon	Long	0.48	0.10
45° trunk flexion, holding a load	Mars	Short	0.29	0.08
90° trunk flexion, holding a load	Mars	Short	0.20	0.06
Fall from 1m, landing on two feet	Mars	Short	0.56	0.12
Fall from 2m, landing on two feet	Mars	Short	0.77	0.16
45° trunk flexion, holding a load	Mars	Long	0.34	0.11
90° trunk flexion, holding a load	Mars	Long	0.23	0.08
Fall from 1m, landing on two feet	Mars	Long	0.64	0.17
Fall from 2m, landing on two feet	Mars	Long	0.88	0.24

While no Factor of Risk for fracture exceeds 1 for any single event (indicating fracture), the probability of fracture will increase as the frequency of an event increases. As previously mentioned, the utility of this model to predict risk will be tested with data access from the elderly osteoporosis patient population.

## VI. Risk in Context of Exploration Mission Operational Scenarios

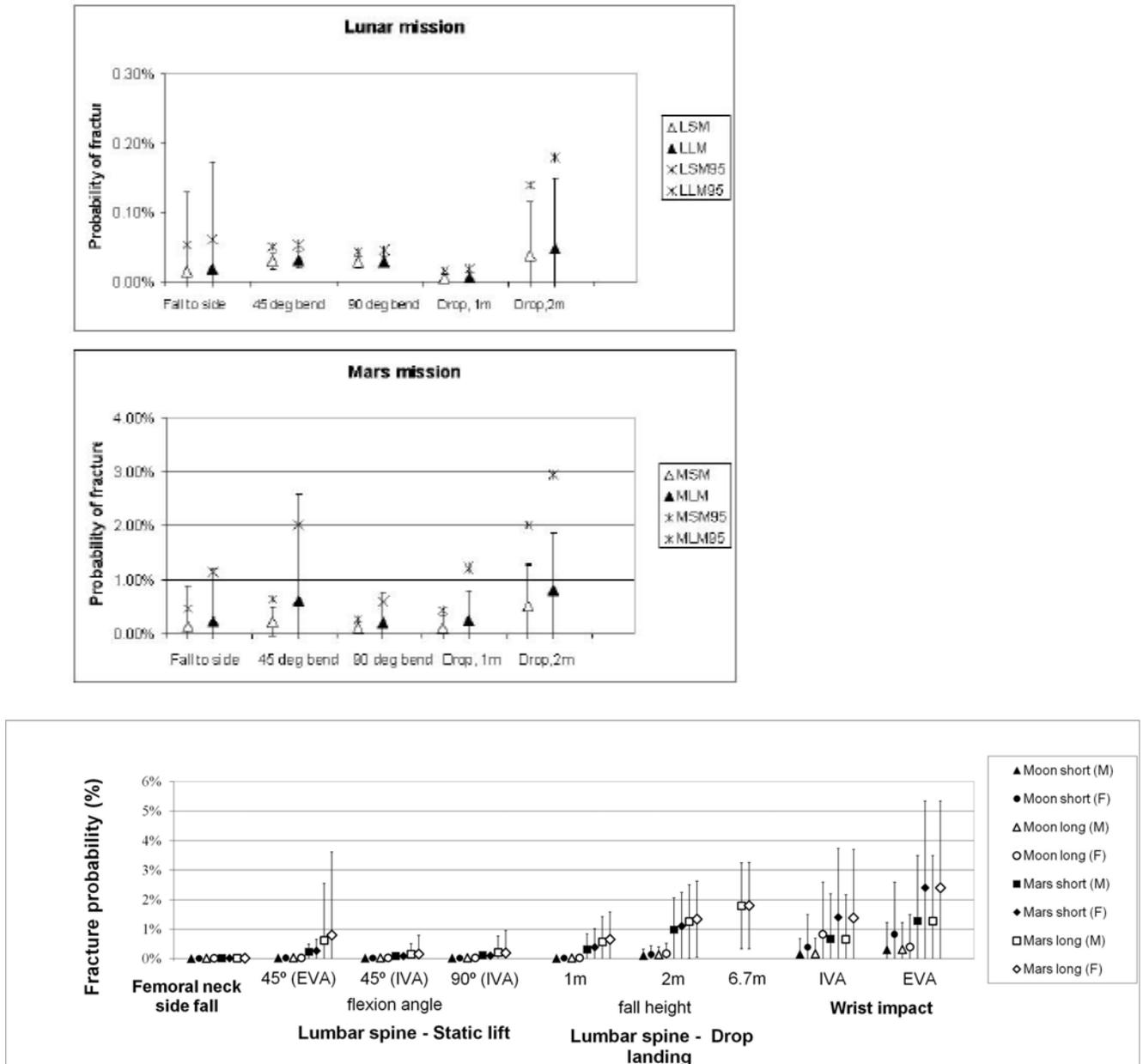
Specific exploration mission scenarios are defined according to the duration of the time in space (Table 3-3). The BFRM was applied to each of these mission scenarios to determine the probability of bone fracture during specific mission activities.

**Table 3-3.** Definition of Exploration Mission Scenarios by Duration

<b>Duration Length</b>	<b>Mission Location</b>	<b>Transit time to Location (days)</b>	<b>Length of Stay (days)</b>	<b>Transit time back To Earth (days)</b>
Short	Moon	3	8	3
Long	Moon	5	170	5
Short	Mars	162	40	162
Long	Mars	189	540	189

Figure 3-5 provides a graphical illustration of the probability of bone fracture resulting from various activities or events during a lunar or martian mission.

### Risk of Bone Fracture



**Figure 3-5.** Probability of bone fracture for male and female astronauts during mission activities on the moon and Mars. Mission scenarios are as defined in Table 3-3.

As expected, the risk of fracture was most pronounced during the Mars missions due to compromised bone integrity from longer duration in space and increased gravitational forces relative to the moon. No statistically significant differences in fracture probability by gender were found. For all of the modeled missions, the most likely location for fracture was at the wrist. Femoral fracture resulting from a fall to the side during an EVA was unlikely, even on the long-duration Mars mission, which suggests effective use of hip padding. While within a spacecraft, the risk of lumbar spine fracture due to lifting heavy objects was relatively low in

## Risk of Bone Fracture

most cases, but it approached a 1% probability during EVAs on Mars missions due to the added spacesuit mass and reduced bone integrity. Considering the catastrophic consequences to the crew and the mission, this may pose a considerable risk. For the EVA calculations, the spacesuit design was assumed to limit the astronaut's range of motion to 45°, so that the most punishing angle (90°) was not considered. The risk of spinal fracture due to up to 2m jumps or falls onto both feet was small for lunar missions, but similar 2m drops on Mars boosted the probability to above 1%. For a 6.7m drop (equivalent to falling from the top of the Lunar Lander ladder), the risk of fracture increased to about 2%.

As previously mentioned, a Factor of Risk had been calculated to address the impact of a Mars mission for fracture risk after return to Earth (for further detail, see Chapter 2, Risk of Accelerated Osteoporosis). This estimation was based upon the QCT scans of the hip performed in ISS crewmembers (Lang, 2006). The pre- and postflight QCT data from the 11 ISS subjects were analyzed by FEA to determine Hip Fracture Loads before and after spaceflight (Keyak, 2007). These data were used to calculate a Factor of Risk for fracture at the time of launch (preflight), after return to Earth (postflight Mars Long mission), as provided below in Table 3-4. These estimations indicated that crewmembers that returned back to Earth from a Mars mission would have a comparable risk of fracture on Earth to an elderly postmenopausal female particularly for a loading condition associated with a posterolateral fall but not for forces associated with postural stance (See discussion in Chapter 2, Risk of Accelerated Osteoporosis).

**Table 3-4.** Estimated Factor of Risks based upon Finite Element Analysis of Fracture Load

	Factor of Risk: Estimated Applied Load/Fracture Load Ratio*
Astronaut preflight	0.89±0.21
Astronaut on Earth after Mars mission	1.07±0.30
Women, 70-80 years of age	1.04±0.37
Astronauts on Mars (0.38 G)	0.66±0.15

\*a ratio larger than 1 indicates that the applied load exceeds the fracture load (strength of the bone) and the fracture will occur.

The following assumptions were made in these calculations of Factor of Risk:

1. The only applied forces were from gravity fields. Not only does this assumption underestimate fracture risk, but it also does not address a potential protective effect of an exoskeleton (EVA suit). The applied loads on skeleton due to suit design, EVA activities or tasks performed on planetary surfaces are not known.
2. There was a consistent loss in bone mass during space travel (to and back from Mars) based upon an estimated monthly loss of BMD, which presumes a constant loss, for weight-bearing sites. The actual time course of bone mineral loss is not known.
3. No further bone loss occurred during exposure to 1/6 (lunar) or 1/3 G (martian). Do not know the extent, if any, that these partial gravity fields will mitigate bone atrophy.

Similar calculations of Factor of Risk can be performed for other mission scenarios (Table 3-3). Calculations will have less uncertainty as more data become available.

Another operationally relevant area of concern for fracture risk occurs during the landing of the Orion (Crew Exploration Vehicle (CEV) - next generation crewed space vehicle) capsule following long duration orbital and planetary surface missions. The Human Systems Integration Group for Constellation and the Health and Medical Technical Authority have developed requirements to limit landing loads to the crew, to reduce the risk of crew injury, especially to lower bone fracture rate. A bone de-conditioning factor was applied to those limits, for crewmembers returning from long duration microgravity missions. The deconditioning factor was derived from models of fracture risk developed by the team in 2008; progress on this fracture risk model will be provided in future updates of the Evidence Book for HRP Risks.

## **VII. Gaps**

The following listed gaps reflect (a) the uncertainty about the effects of space on bone strength (because of the need to assess more than areal BMD and to know the time course of bone loss etc.); and (b) the uncertainty about surface activities that load bones and *how* those bones are loaded (that is, orientation, the energy of impact). Some of the knowledge gaps highlighted in the text of this report are repeated in this section. Additionally, the gaps that are outlined in the Evidence Base Report for the Risk of Accelerated Osteoporosis are relevant to this Risk for Bone Fracture.

1. The impact of spaceflight on whole bone strength is not fully known. Crewmember deficits in areal BMD as measured by DXA do not reflect changes in bone geometry, bone thickness or microarchitecture – indices which could influence whole bone strength. There is a need to supplement DXA BMD with non-invasive technologies to provide a more complete assessment of bone strength.
  - Assess microarchitecture of peripheral and central skeletal sites (new technology);
  - Measure volumetric BMD in bone compartments (cortical and cancellous bone) of weight-bearing skeletal regions.
  - Evaluate the incidence and prevalence of stress fractures and microcracks (additional factors, independent of mechanical unloading, for increased bone remodeling in space).
  - Evaluate the influence of reduced muscle forces on site-specific bone atrophy.
  - Collect measures of morphological changes to vertebral bodies (for diagnosis of asymptomatic compression fractures) in crews after long-duration spaceflight; characterize morphological changes to vertebral bodies with longitudinal measures in Astronaut population to characterize changes over time.
2. Impact of spaceflight on balance, coupling and rate of remodeling has not been quantified at the level of the bone remodeling unit.
3. Need to integrate how the deconditioning of other physiological systems poses a risk factor for fracture by addressing the following issues: How is the risk for falling impacted by the loss of postural stability, loss of muscle mass and forces, and re-adaptations in gait and locomotion? Do the unique conditions of the EVA suit and of lunar environment (light exposure) and surface (lunar topography) influence visual acuity and contrast sensitivity such that the risk for falling is increased? How does

- the loss of muscle forces and changes in stretch reflex affect the ability to mitigate the energy of applied forces?
4. Which kind of tasks (climbing, descending, bending, and walking) are associated with a greater propensity for falling in the crewmember de-conditioned by ~6 months in space? In which direction are these crewmembers likely to fall? What skeletal sites are more likely to be impacted by these falls? Can the impact force of falls be well estimated?
  5. Is the low vitamin D level a cause or an adaptive response to increased bone atrophy (increased bone turnover, some increase in blood calcium with decreased levels of parathyroid hormone and 1,25 di-hydroxylated vitamin D<sub>3</sub>)? Does the 1-hydroxylase activity (the enzyme responsible for generating the active vitamin D metabolite – 25(OH)D<sub>3</sub> to 1,25 di-hydroxylated vitamin D<sub>3</sub>) in the kidney need to be stimulated or replaced in the presence of suppressed parathyroid hormone? (Smith,1999)
  6. What role do countermeasures to terrestrial bone osteoporosis play in reducing the fracture risk from extended stays in reduced gravity environments during EVA and landing events?

### **VIII. Conclusion**

A high risk for fracture is a characteristic of osteoporosis, which is a consequence of the losses in bone mass and in structural deterioration. The distinction between the increased bone fracture risk in persons with osteoporosis and the increased risk for fractures during a spaceflight mission is based upon the Factor of Risk. Osteoporotic persons fracture under atraumatic conditions, that is, under the loading of normal activities or with falls from a standing height because the whole bone strength of a severely osteoporotic person is extremely low. Osteoporosis is diagnosed when the areal BMD, as a surrogate measure for bone strength, is more than 2.5 standard deviations *below* the average BMD of a young, gender-based reference population (T-score of -2.5 or less).

However, there is no evidence to suggest that crewmembers, who have met the medical standards for spaceflight, would experience this bone status during 6-months in space. Equally unlikely is the occurrence of an atraumatic fracture during and following 6-12 months in space. Still, there is more uncertainty related to whether crewmembers, with bone loss or morphological changes in one or more skeletal sites, would experience enough mechanical loads to bone, in a 0 to 1/3 G environment, to exceed the failure load of the altered bone during an extended period in space.

This evidence base report summarizes flight data with a subsequent assertion that the increased risk for fracture may or may not be substantiated when more data are acquired. These data would include the time course of bone loss in space and the morphological changes that accompany skeletal adaptation to space (including partial gravity environments). Documented reductions in bone mass and structural changes suggest declines in whole bone strength such that a deconditioned-person with atrophied bones are susceptible to fracture at smaller failure loads. A multi-factorial analysis of cross-disciplinary risk factors for fracture is also warranted. Hence, the Factor of Risk for fracture during a spaceflight mission requires a full understanding of the i)

changes in bone mineral density and in bone quality at specific sites and ii) how these sites will be mechanically loaded by activities during a spaceflight mission.

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**XI. List of Acronyms**

BFxRM	Bone Fracture Risk Module
BMD	Bone mineral density
DXA	Dual-energy x-ray absorptiometry
EVA	Extravehicular activity
FEA	Finite Element Analysis
GRC	Glenn Research Center
ISS	International Space Station
LLM	Lunar long mission
LLM95	Lunar long mission 95 <sup>th</sup> percentile
LSM	Lunar short mission
LSM95	Lunar short mission 95 <sup>th</sup> percentile
MLM	Martian long mission
MLM95	Martian long mission 95 <sup>th</sup> percentile
MSM	Martian short mission
MSM95	Martian short mission 95 <sup>th</sup> percentile
NASA	National Aeronautics and Space Administration
PRA	Probabilistic Risk Assessment
QCT	Quantitative computerized tomography
WHO	World Health Organization