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Osteoporosis in Spaceflight

Satoshi Iwase, Naoki Nishimura and Tadaaki Mano

Additional information is available at the end of the chapter

1. Introduction

1.1. Renal stones during spaceflight

No major medical diffiulties were experienced during spaceflight in the era of Russian Vostok/ Voshot or spaceflight programs of Mercury and Gemini, however, when prolonged stays in space stations began in the 1980's, astronauts or Russian cosmonauts had an increased risk of suffering from renal stones, and resultant bone loss. The detailed mechanism behind this phenomenon is still unknown, but one explanation is that unloading of the skeleton that would normally bear the bodyweight led to calcium (Ca) leaving the bones for the bloodstream. The Ca entered the kidneys, filtered into the urine, causing hypercalciuria, and increased the risk of kidney stone formation. Such stones formed in the kidney break down and travel into the ureter, causing flank pain. Thus astronauts continually subjected to risks of bone and Ca loss while in microgravity [Buckey, 2006].

Factors that seem to affect the bone and Ca loss while in microgravity are as follows; low light levels, high environmental CO_2 levels, and minimal skeletal loading. It is reported that urinary Ca excretion increases by 60-70 % within a few days of entering the microgravity. Data from the Skylab program in 1973-74, when nine astronauts stayed in the space station for 28 to 84 days, showed that the estimated rate of Ca loss from the bone per month was 0.3% of the total body Ca [Whedon et al. 1974].Data from the Mir program indicated that the bone losing the most Ca losing bone is the coxal bone estimated to lose 1.5% of the total body Ca per month [Le Blanc et al. 2000]. Skylab was a space station launched and operated by NASA (National Aeronautics and Space Administration of the USA) and was the America's first space station, which orbited the Earth from 1973 to 79, and included a workshop, a solar observatory, and other systems with the weight of 77 tons. Mir (мир, peace/world) was a space station that operated in low Earth orbit from 1986 to 2001, at first by Soviet Union and then by Russia. Assembled in orbit from 1986 to 96, Mir was the first modular space station and had a greater

mass than that of any previous spacecraft until its deorbit on March 21, 2001. Many experiments including biomedical sciences.

In spite of rapid bone loss under conditions of weightlessness, a slow recovery rate is reported. Data from the Mir program showed that approximately 12% of bone was lost during 4.5 months in space while only 6% recovered in a year on the Earth [Linenger 2000]. Follow-up study of the Skylab crew members after 28-84 days of the microgravity exposure suggested that not all the bone lost on the station had been recovered [Tilton et al. 1980]. These findings indicate the seriousness of bone loss under conditions of microgravity, which could present significant problems, and may progress to osteoporosis, in long-duration spaceflight. Bone loss under conditions of weightlessness should be strictly monitored and controlled.

2. Calcium metabolism during spaceflight

During spaceflight, several factors influence the Ca metabolism, including alterations in diet intake, low lighting, increased ambient CO_2, and the most important factor is unloading of the bodyweight when considering the long duration spaceflight.

The recommended Ca^{2+} intake is 1,000 mg/day, and nutritionists prepare the space food to satisfy this criterion.

In spacecraft, where no sunlight or ultraviolet light exposure is occurs, vitamin D deficiency may develop without sufficient Ca intake, which causes poor mineralization of bone, diminished intestinal Ca absorption, decreased serum Ca^{2+} levels. These situations may cause an increase in parathormone, but actually, sufficient Ca intake protects the bone loss, and serum Ca^{2+} level has been proved to be increased, and parathormone level is suppressed..

Compared with the low CO_2 level on the Earth, which is 0.03% of the atmosphere, confined and isolated circumstances such as in spacecraft or a space station have increased CO_2 levels of 0.7-1%, which affects the acid-base balance, and consequently the bone metabolism. Increased CO_2 levels in inhaled air cause acidosis, and carbonates and phosphates in the bone play important roles in neutralizing the acidosis, which leads to bone resorption [Bushinsky et al., 1997]. Although CO_2 levels >1% were reported to have some effects on urinary bone absorption markers [Drummer et al. 1998], respiratory acidosis may decrease the urinary pH, and increase the risk of kidney stone formation [Coe et al. 1992].

Bone remodeling and the remodeling changes during spaceflight are profoundly dependent on genetic factors in terms of the baseline level [Boyden et al. 2002, Judex et al. 2002]

3. Bone formation factors

3.1. Mechanical loading

The mechanism by which bone senses and responds to loading has yet to be fully clarified yet. Frost [1987] postulated that bone has a mechanostat that senses strain and maintains bone mass

at an appropriate level to keep the strain within an appropriate range, showing that exceeding the setpoint of bone strain bone modeling intiates reduction of the strain back to the setpoint had been carried out. Surveys on athletes indicated that high weight bearing, which is observed in weightlifters and significant impact loading in gymnasts resulted in significantly high bone mass [Nilsson & Westlin, 1971, Uusi-Rasi et al. 1971, Taaffe et al. 1997, Huddleston et al., 1980].

As for the gravity-induced high bone mass density, evidence has shown that heavy-weight people exhibited higher bone density, and spinal injury patients with a wheelchair lose significantly bone mass at lower extremity while not in the lumbar spine [Biering-Sorensen et al., 1988, 1990]. The impact of contact with the ground on the bones of the coxa and the lower extremities is an important factor to maintain the bone mass density [Kreb et al., 1998].

Not only impacts or weight bearing on the bone, but also muscular contractions also play a role in strain bearing on the bone at 1 G [Kreb et al., 1998, Schulthesis et al., 1991]. However, 0 G conditions may influence the skeletal loading both through a loss of ground reaction forces and through marked reduction in the forces needed to move the weightless limbs.
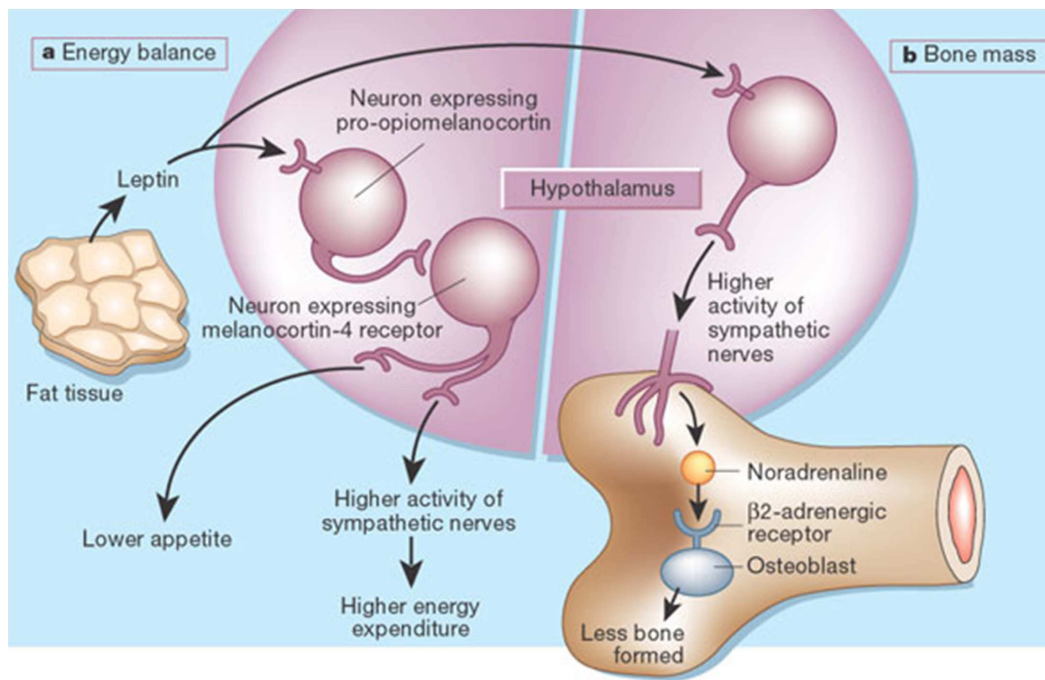
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Figure 1. Regulation of energy balance and bone mass Leptin suppresses appetite and enhances sympathetic nerve activity through the hypothalamus elevating energy expenditure. At the same time higher activity of the sympathetic nervous system inhibits bone formation of osteoblasts, inducing bone loss.

3.2. Hormones

Sex hormones, estrogens and androgens are associated with bone mass density; however, there seems to be no significant changes in sex hormones during spaceflight. Growth hormone increases the bone mass, but it does not seem to have a relationship with spaceflight. Insulin-

like growth factor (IGF-1) has also been shown to be an agent that can increase bone mass, and in animal experiments performed during the Space Shuttle experiment, administration of IGF-1 to rats during the 10 days of the Shuttle flight increased bone formation in the humerus.

Parathormone has a complex effect on the bone. Its ultimate goal is to increase the serum Ca^{2+} level, so that without enough Ca^{2+} intake or vitamin D deficiency, it acts on bone resorption and reduces the bone mass. The action sites of parathormone are the bone, the kidney, and the intestine.

The mechanism of parathormone action on the bone is indirect since osteoclasts have no receptor of parathormone, rather parathormone binds to osteoblasts to increase their expression of RANKL (receptor activator of nuclear factor kappa-B ligand, osteoclast differentiation factor) and inhibits their expression of osteoprotegrin. Osteoprotegerin binds to RANKL and inhibits it from interacting with RANK (receptor activator of nuclear factor kappa-B, receptor of osteoclast differentiation factor). The binding of RANKL to RANK is facilitated by the decreased amount of osteoprotegerin, and stimulates osteoclast precursors to fuse. It resulted to form new osteoclasts, which ultimately enhances bone resorption.

Parathormone also acts on the kidney to enhance the active reabsorption of Ca^{2+} and Mg^{2+} from the distal tubules and the thick ascending limb, and maintains or increases the serum Ca^{2+} levels.

It also enhances the absorption of Ca^{2+} from the intestine indirectly, by increasing the production of activated vitamin D, which is activated in the kidney. The activated vitamin D increases the absorption of Ca^{2+} by the intestine.

Calcitonin is secreted from the thyroid gland by an increase in serum Ca^{2+} levels, and acts to lower the Ca^{2+} levels, which counteracts parathormone. Calcitonin lowers Ca^{2+} levels by 1) inhibiting Ca^{2+} absorption by the intestines, 2) inhibiting osteoclast activity in bones, 3) inhibiting renal tubular cell reabsorption of Ca^{2+} by allowing Ca^{2+} to be secreted in the urine. Therefore, calcitonin protects bone from Ca^{2+} loss, however, it has not proved to be effective in preventing bone loss in immobilization in either animals [Thomas et al., 1995] or humans [Hantman et al., 1973].

3.3. Dietary factors

Ca, vitamin D, and vitamin K are the essential factors for bone formation, and their oral intake is recommended during spaceflight.

3.4. Electric fields and vibration

Studies have shown exposure of marrow culture to low-frequency, low-intensity electric fields inhibited the recruitment of osteoclasts [Rubin et al., 1996]. Low magnitude (0.25 G) and high frequency (30-90 Hz) vibration has been proved to be effective in inhibiting bone loss and increasing bone formation in humans [Bosco et al., 1999, Rubin et al. 2004]. This vibration constitues a promising countermeasure against bone loss in spaceflight, and studies are now being conducted to clarify the optimal magnitude and frequency.

4. Bone resorption factors

4.1. Immobilization

The unloading of weight bearing on bone on Earth is associated with prolonged bed rest, immobilization, or paralysis. Studies of patients with spinal cord injury have demonstrated that approximately 30–50% of lower extremity bone mass can be lost before reaching a plateau, which occurs an average of approximately 16 months after admission [Biering-Sorensen et al. 1990, Garland et al. 1992].

4.2. Hormones

Chronic increase in parathormone levels enhances resorption, which causes osteoporosis. This increase in parathormone is sometimes produced by lower serum Ca^{2+} and vitamin D; however, intermittent administration of parathormone with enough Ca^{2+} levels with vitamin D can also be anabolic. Thyroid hormones and glucocorticoid can be a cause of osteoporosis, but it is unlikely to occur in space.

4.3. Dietary factors

High Na^+ intake enhances Na^+ excretion as well as urinary Ca^{2+} excretion. A high level of dietary protein also provides an acid load, which causes bone loss mediated by skeletal buffering. Therefore, it is favorable for space food to contain low salt as well as low protein.

5. Bone loss and osteoporosis in spaceflight

Skylab missions were the first opportunity to study the Ca metabolism in space [Whendon et al., 1974]. These included the unmanned Skylab 1, Skylab 2 with 3 crew members staying 29 days of stay, Skylab 3 also with 3 crew members staying 59 days, and Skylab 4 again with 3 crew members staying 84 days. Thereafter, various Space Shuttle Programs have been conducted to examine the effects of space flights on Ca metabolism in humans.

Urinary excretion of Ca^{2+} is enhanced promptly just after microgravity exposure, and remains elevated for several months throughout weightlessness exposure or eventually returns to normal depending on individual. The mechanism behind individual differences has not benn well clarified. Data from two Russian cosmonauts demonstrated no Ca^{2+} excretion increases were observed after 218 days of microgravity exposure [Grigoriev et al., 1994]. The reason for this lack of an increase in Ca^{2+} might be the effectiveness of countermeasure program.

5.1. Bone loss markers during spaceflight

Frozen urine samples from the Skylab mission were subsequently examined; the data showed that N-telopeptide was increased throughout the flight [Smith et al., 1998], and C-telopeptide also remained elevated throughout on a-180 day Mir flight [Caillot-Augusseau et al., 1998].

Elevation of these two markers demonstrated that the increased urinary Ca^{2+} was due to an increase in bone resorption. Osteocalcin, a bone formation marker, measured during a 180-day Mir flight showed a decrease.

5.2. Bone loss location

Bone mineral density was measured before and after flights on the Mir program. The changes per month were as follows; +0.6% in the skull, +0.1% in the arm, −1.07% in the spine, −1.35% in the pelvis, −1.16% in the femoral neck, −1.58% in the trochanter major, −1.25% in the tibia, and −1.50% in the calcaneus, all per month, with comparable results obtained from the International Space Station [Lang et al., 2004].

The bones that are most affected during spaceflight seems to be weight bearing bones, such as the pelvis (os coxae), the trochanter major of the femur, the femoral neck, the tibia, and the calcaneus.

5.3. Parathormone and Vitamin D

Data from the Skylab program exhibited a slight increase in serum Ca^{2+} levels and decrease in parathormone. Spacelab Life Sciences 1 (9 days), and 2(14 days) flights and a 180-day Mir flight showed decreased serum parathormone levels in crew members, and active vitamin D levels were also decreased, which in turn reduced Ca absorption [Caillot-Augusseau et al., 1998].

5.4. Summary

In summary, bone resorption is increased, bone formation is decreased, bone loss occurs in weight-bearing areas, and parathormone is suppressed during space flight, which are comparable to the data from immobilization under conditions of bedrest or spinal cord injury.

6. Sympathetic modulation of bone metabolism during spaceflight

It has been reported that sympathetic neural traffic to bone inhibits the function of osteoblasts and enhances that of osteoclasts thus facilitating bone loss. Possible roles of the sympathetic nervous system in the mechanisms of bone loss in humans exposed to long-term space flight will be discussed [Mano et al., 2010].

6.1. Alterations in sympathetic neural traffic under microgravity

Sympathetic neural traffic indirectly measured by plasma noradrenaline level has been reported to increase during spaceflight compared with the pre-flight control level [Christensen & Norsk, 1998, Ertl et al., 2002], and vagal activity estimated by power spectral analysis of heart rate variability has been shown to be reduced after long-term spaceflight [Cooke et al., 2000, Mano, 2005].

Microneurographically, on the other hand, recorded neural traffic in humans is known to reflect muscle and skin sympathetic nerve activity (MSNA and SSNA), and MSNA controls the vasomotor function of the muscular bed, responding to blood pressure changes against gravitational stress [Iwase et al., 1987, Mano 1990, Mano et al., 2009]. MSNA was found to be suppressed during an exposure to short-term microgravity induced by parabolic flight [Iwase et al., 1999], to mild lower body positive pressure (10-20 mmHg LBPP) [Fu et al., 1998], and to thermoneutral head-out water immersion [Miwa et al., 1996] responding to the loading or unloading of cardiopulmonary receptor stimulated by cephalad fluid shift. Contrarily, MSNA was enhanced after an exposure to long-term microgravity in spaceflight and its simulation induced by dry immersion (Iwase et al., 2000), and 6°head-down bed rest (Kamiya et al., 2000), caused by various mechanisms including plasma volume loss, changes in baroreflex, and vascular compliance after the human body has acclimated to microgravity situation..

As for the sympathetic influence on bone metabolism, sympathetic stimulation facilitated bone resorption, while it inhibited ossification by osteoblasts mediated by hypothalamus and leptin in mouse. Loading of weak chronic stress in mouse reduced the osteoblastic activity with elevated noradrenaline, which was prevented by β-blocker [Kondo et al., 2005]. The beneficial effects of β-adrenergic blocker on bone mass and metabolism were reported in mice and rats [Minkowitz et al., 1991, Pierroz, et al., 2006]. Other studies were controversial, however, recent studies have indicated that there are two systems that regulate bone metabolism; one through β_2 receptors in bone which facilitates osteolysis and inhibits osteogenesis, and the other that facililtates osteogenesis through a kind of neuropeptide called CART (cocaine amphetamine regulated transcript) [Elefteriou et al., 2005].

From human studies, there have been reports that administration of β-blockers may reduce the risk of bone fracture as well as higher bone density (Graham et al., 2008, Levasseur et al., 2005, Pasco et al., 2004, 2005, Reid et al., 2005a, b, Reinmark et al., 2004, 2006, Schlienger et al., 2004, Turker et al., 2006)

6.2. Space flight-related changes in sympathetic regulation on bone metabolism

Prolonged exposure to microgravity in space for 14 days enhanced the sympathetic neural traffic in humans as evidenced by the Neurolab mission[Cox et al., 2002, Fu et al., 2002, Levine et al., 2002, Ertl et al., 2002], with comparable results in elevated noradrenaline spillover and clearance in space [Ertl et al., 2002]. Corresponding results were obtained from simulated microgravity including dry immersion [Iwase et al., 2000] or head-down bed rest [Kamiya et al., 2000]. Elderly people generally have low bone mass and density and high sympathetic neural traffic to muscles although response to gravitational stress becomes lowered (Iwase et al. 1991). Our preliminary data show that changes in sympathetic neural traffic to muscles after long-term bedrest of 20 days had a significant correlation with changes in the urinary secretion level of deoxypyridinoline (Mano et al., 2009, Nishimura et al., 2010) (Fig.2), which a specific marker for bone resorption (Robbins et al., 1994). On the basis of these findings, it is postulated that an exposure to prolonged microgravity enhances the sympathetic neural traffic to bone, which increases the noradrenaline level, inhibits osteogenesis and facilitates osteolysis through β-receptors to induce bone mineral loss; however, it is no better than hypothesis.

$$y = 0.2107x + 99.143$$
$$r=0.63 \ (n=11)$$
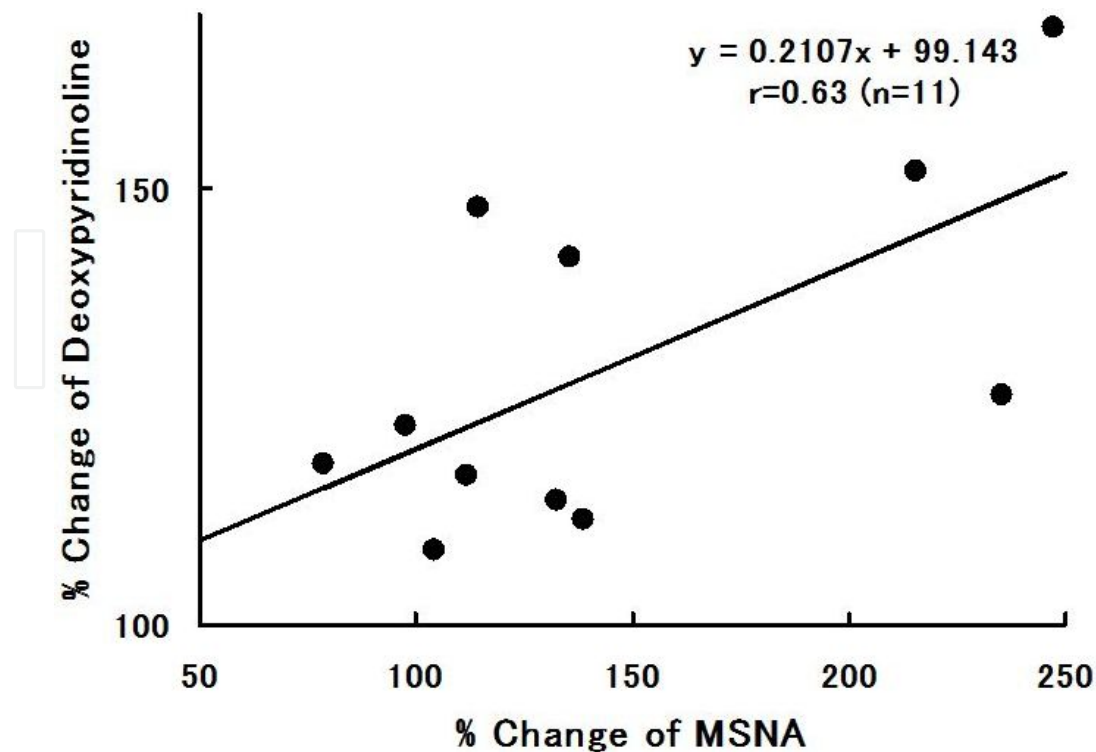
Adapted with permission from Nishimura N et al: Space Utiliz Res. 26: 122-124 (2010)

Figure 2. Correlation between muscle sympathetic nerve activity (MSNA) and urinary secretion of deoxypyridinoline in healthy humans exposed to long-term bed rest. A significant correlation was found between percent changes in burst numbers per minute of MSNA recorded microneurographically from the tibial nerve (abscissa) and percent changes in urinary secretion of deoxypyridinoline (ordinate) in 11 young healthy male subjects (24±5 years old) exposed to long-term head-down bed rest (20 days).

7. Countermeasures for space-related osteoporosis

The bone has difficulty regaining its density and once it is lost, as shown by the studies of bed rest and spinal cord injury patients. Data from spaceflight suggest that this slow recovery is also exhibited by astronauts as well [Linenger, 2000, Tilton et al., 1980]. Bone can be recovered, but it takes a longer time to recover it than to lose it. This means that the prevention of bone loss is a more preferable than its recovery by aggressive rehabilitation. The strategy of "less loss to regain fast" might be an effective way to minimize the necessary amount of postflight rehabilitation needed and to extend the time people can remain in microgravity.

7.1. Vitamin D and calcium intake

The low light levels in the spacecraft necessitate sufficient oral intake of vitamin D and Ca since parathormone levels are suppressed during spaceflight. Oral intake of 600–800 IU/day vitamin D is recommended in the absence of sunlight although 400 IU/day is usually adequate to maintain bone mass density [Holick, 1996].

The Ca intake necessary to minimize a negative Ca balance is approximately 1,000 mg of elemental Ca (~40% of $CaCO_3$), which is currently recommended for space station flights up to 360 days [Weaver, 2000]. Howver, excessive oral intake of Ca is associated with a risk of hypercalciuria due to skeletal unloading, which may lead to high risk of kidney stones. However, kidney stones may not develop because orally administered Ca may bind to oxalate in the intestine and reduce the oxalate absorption [Heller 1999]. Therefore, Ca intake during spaceflight should be taken orally [Martini & Wood, 2000].

7.2. Physical factors

Exercise upon exposure to weightlessness has been incorporated into some countermeasure programs, however, exercise alone cannot prevent the bone loss. The current exercise program for the ISS is a combination of aerobic and resistive exercises for 2.5 hrs, 6 days/week. Data from the space flight demonstrate that bone loss occurs mainly in the femur, tibia, calcaneus, and vertebrae. Therefore, exercise should be concentrated on these bones, and impact loading should primarily be provided rather than static loading [Taaffe et al., 1997].

Hip joint: Some of the larger bone losses observed in the space program have been concentrated in the hips (os coxae mainly) [Le Blanc et al., 1999]. A study using hip joint pressure sensors has demonstrated that peak joint forces can range from 3–4 times when walking, 5.5 times with jogging, and as high as 8.7 times bodyweight with stumbling [Hall, 1995], which are do not seem to be generated during the exercise in microgravity. The peak pressure in the articulatio coxae (hip joint) during supine isometric abduction was 3.78 mPa, which was as high as those during walking of 3.64 mPa [Strickland et al., 1992], and that during rising from a seated position, was 7.14 mPa [Hodge et al., 1986]. These data suggest that running on a treadmill generates an insufficient load to generate enough loads, but short periods of high loading using abduction, adduction and squatting would be necessary to load sufficient pressures on the hip joint.

Lumbar spine: The bodyweight is loaded on the L_3 vertebra when standing under conditions of 1 G state, but unloaded vertebrae would lose their bone mass density under microgravity. The concern is the minimum period of standing position required to maintain the bone mass, which has not been clarified. Moreover, the even if this duration is clarified; weight loading under weightlessness is difficult. Whether a shorter duration of a higher load can provide the same bone protection as a longer duration of a lower load has also yet to be solved.

Femur: The femoral neck and the trochanter major are the principal sites of weight bearing under the condition of 1 G, and are site at which significant bone mass is lost during the spaceflight. The femoral shaft mainly consists of cortical bone and the loss of bone mass from the femoral shaft were −1.6% on average after 4–6 months of spaceflight [Oganov, 1996]. The kind of exercise that be most effective to prevent bone loss from the femur is not known.

Tibia: The proximal tibia consists of trabecular and cortical bone, and its loss of bone mass was reported to be −1.25% per month. The most effective exercise to prevent the bone loss from this area seemed to be squatting exercise.

Calcaneus: The calcaneus receives a reaction force from the ground of 2–3 times of body weight to the foot while running under 1 G. The fact that the calcaneus of gymnasts exhibits increased bone density suggests that not only the number of loading cycles but also peak loading is significant in increasing bone mass density in the calcaneus [Taaffe et al., 1999].

7.3. Pharmacological factors

Since bone mass is adequate at the onset of spaceflight, the optimal strategy for pharmaco-therapy against bone loss is the prevention of bone loss, not the acceleration of bone formation, when the loading is removed during spaceflight. Several drugs have been proposed for the prevention of bone loss under microgravity.

7.3.1. Bisphosphonates

Bisphosphonates have two phosphonate (PO_3) groups and have a similar structure to pyro-phosphate. They bind to hydroxyapatite in the bone matrix, and prevent the bone loss by inhibiting the osteoclastic bone resorption. Bisphosphonates have been demonstrated to be effective in preventing bone loss during bed rest studies [Grigoriev et al., 1992, Rodan & Fleisch, 1996, Thompson et al., 1990, LeBlanc et al., 1998]. Among several kinds of bisphosph-onate, pamidronate has been proved to suppress bone mineral loss and to prevent the formation of renal stones during bedrest study (Watanabe et al., 2004).

In 2010, LeBlanc and Matsumoto proposed an experiment on the effectiveness of bisphosph-onate as a countermeasure to spaceflight-induced bone loss. The astronauts chose either oral administration of alendronate at 70 mg once per week or intravenous administration of zoledronate at 4 mg before flight, and were examined their bone density by DEXA (dual energy x-ray absorptiometry), QCT (quantitative computed tomography), and pQCT (peripheral qualitative computed tomography), bone metabolism markers including bone formation and resorption markers, and renal stone formation. One of the co-investigators, Ohshima reported successful results in suppressing the space flight-induced bone loss and renal stone formation [Ohshima, personal communication].

The disadvantages of bisphosphonates are local irritation of the upper gastrointestinal (GI) tract, and poor absorption from the GI tract. Therefore, the oral administration of bisphosph-onates requires the intake with 200 mL of water and for the subject to remain upright posture for at least 30 min, and until after consumption of the first food of the day to facilitate delivery to the stomach. The problem is that an upright posture cannot be achieved in space under conditions of microgravity. Another problem is the possibility of osteonecrosis of the maxilla and the mandible occurring although the incidence of this is low [Durie et al., 2005]. Since these osteonecroric or osteolytic phenomena are always accompanied by physiological stress (mastication), iatrogenic trauma (tooth extraction/denture injury), or tooth infection [Ruggiero et al. 2004, 2008], it is preferable to prevent such phenomena.

Bisphosphonates are hardly metabolized, and high concentrations of them are maintained in the bones for long periods. Because bone formation is closely coupled to bone turnover, long-term use of these compounds with the resultant suppression of bone turnover can compromise

the healing of even physiological microinjuries within bone. Osteonecrosis of the maxilla and the mandible likely results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling because several kinds of manipulation are associated with this necrosis.

7.3.2. Thiazide diuretics and potassium citrate

Thiazide diuretics and potassium citrate are not usually considered drugs for bone loss prevention, but are usually used for kidney stone prevention; they act by markedly reducing the urinary Ca level.

7.3.3. Selective estrogen receptor modulators

Estrogen is effective for bone mass preservation in both men and women, but it has a side effect of thrombophlebitis, which would be a very significant for bedrest subjects or astronauts in the space.

7.3.4. Statins

There is some evidence suggesting that statins might be effective to increase bone mass, in addition to their main role; however, no data from bedrest or immobilization studies have shown the effectiveness of their use. Therefore it might be too early to apply it to astronauts in spaceflight.

7.3.5. Parathormone

Parathormone has anabolic effects on bone, and also acts on the kidney to stimulate the resorption of Ca^{2+} and enhance the synthesis of vitamin D. In this sense, parathormone may stimulate the bone formation, increase vitamin D synthesis, and stimulate Ca^{2+} resorption. Since the suppression of bone resorption is favorable for stimulating bone formation during spaceflight, the administration of parathormone appears strategically unfavorable.

7.4. Artificial gravity

For human space voyages of several years duration, such as those envisioned for the exploration of Mars, astronauts would be at risk of catastrophic consequences should any of the systems that provide adequate air, water, food, or thermal protection fail. Beyond that, astronauts will face serious health and/or safety risks resulting from severe physiologic deconditioning associated with prolonged weightlessness [Buckey 1999]. The principal physiologic deconditioning risks are related to physical and functional deterioration of the loss of regulation of several systems including blood circulation, decreased aerobic capacity, musculo-skeletal systems, and altered sensory-motor system performance. These physiologic effects of weightlessness are generally adaptive to spaceflight and present a hazard only following G-transitions upon return to Earth or landing on another planet [Young 1999]. Among them, bone mineral metabolism would be greatly affected during prolonged spaceflight.

7.4.1. Why artificial gravity?

Space biomedical researchers have been working for many years to develop "countermeasures" to reduce or eliminate the deconditioning associated with prolonged weightlessness. Intensive and sustained aerobic exercise on a treadmill, bicycle, or rowing machine coupled with intensive resistive exercise has been used on U.S. and Russian spacecraft to minimize these problems. The procedures were uncomfortable and excessively time-consuming for many astronauts, and their effectiveness for maintaining bone, muscle, and aerobic fitness has not been demonstrated, owing, at least in part to the low reliability of the devices used to date. Furthermore, they have had inconsistent effects on postflight orthostatic hypotension or sensory-motor adaptive changes. With the exception of fluid loading before reentry, other kinds of countermeasures (e.g., diet, lower body negative pressure, or wearing a "penguin suit" to force joint extension against a resistive force) have been either marginally effective or present an inconvenience or hazard.

To succeed in the near-term goal of a human mission to Mars during the second quarter of this century, the human risks associated with prolonged weightlessness must be mitigated well beyond our current capabilities. Indeed, during nearly 45 years of human spaceflight experience, including numerous long-duration missions, research has not produced any single countermeasure or combination of countermeasures that is completely effective. Current operational countermeasures have not been rigorously validated and have not fully protected any long-duration (>3 months) astronauts in low-Earth orbit. Thus, it seems unlikely that they will adequately protect astronauts journeying to Mars and back over a three-year period.

Although improvements in exercise protocols, changes in diet, or pharmaceutical treatments of individual systems may be of value, they are unlikely to eliminate the full range of physiologic deconditioning. Therefore, a complete research and development program aimed at substituting for the missing gravitational cues and loading in space is warranted.

The urgency for exploration-class countermeasures is compounded by the limited availability of flight resources for vallidating a large number of system-specific countermeasure approaches. Furthermore, recent evidence of rapid degradation of pharmaceuticals flown aboard long-duration missions, putatively because of radiation effects, raises concerns regarding the viability of some promising countermeasure development research. Although the rotation of a Mars-bound spacecraft will not be a panacea for all the human risks of spaceflight (artificial gravity cannot solve the critical problems associated with radiation exposure, isolation, confinement, and environmental homeostasis), artificial gravity does offer significant promise as an effective, efficient, multi-system countermeasure against the physiologic deconditioning associated with prolonged weightlessness. Virtually all of the identified risks associated with cardiovascular deconditioning, myatrophy, bone loss, and neurovestibular disturbances, space anemia, immune compromise, neurovegetative might be alleviated by the appropriate application of artificial gravity.

7.4.2. Why artificial gravity with exercise?

While short radius centrifuge has been proposed several times, only the loading of artificial gravity has not so effective to prevent spaceflight deconditioning. Also human-powered short-arm centrifuge is effective to load exercise to the astronaut. Considering the size of the International Space Station, it is appropriate to employ the short-radius centrifuge

In 1999, Iwase proposed the manufacture of the facility of artificial gravity with ergometric exercise, and it was subsequently installed at Nagoya University [Iwase 2005]. Several studies were performed using this short-radius centrifuge with an ergometer. In 2002, bedrest study was carried out to validate the effectiveness of artificial gravity with ergometric exercise. In 2005, the facility was moved to Aichi Medical University, and bedrest studies were performed to finalize the protocol. In 2006, this daily AG-EX step-up protocol (1.4 G of artificial gravity load with 60W of ergometric exercise, and the load was stepped up by 0.2 G and 15 W respectively) has been shown to be effective to prevent cardiovascular, musculoskeletal, and bone metabolism deconditioning, while an alternate-day protocol failed to prevent this. In this experiment, bone metabolism was moderately ameliorated by this protocol, but not completely.

The authors proposed installing a short-radius centrifuge facility at the International Space Station, and using it to prevent this spaceflight deconditioning including bone loss. This project, Artificial GRavity with Ergometric Exercise (AGREE project) is promising for the prevention of bone loss in spaceflight (Fig. 3).

8. Bone loss monitoring in space

Most of the space medicine studies on bone metabolism have utilized the blood/urine samples collected before, during, and after spaceflight, and analyzed them in laboratories on Earth. However, during prolonged spaceflight now and in the future, the astronauts or spaceflight surgeons will necessitate to collect samples by themselves and to analyze them in the space station or spacecraft to assess the effects of any countermeasures. Although dual X-ray absorptiometry (DEXA) is effective to measure the bone mass, it cannot detect small changes in bone metabolism so may not provide timely information on the effects of countermeasures..

At least, serum/urinary Ca levels and blood/urinary markers of bone resorption should be determined and monitored, and additional information on bone mass (and/or density) and bone formation/resorption markers in blood and urine is desirable.

Guidelines for bed rest standardization [2012] suggest the use of osteocalcin, bone-specific alkaline phosphatase (BSAP), N-terminal propeptide of type I procollagen (P1NP) as bone formation markers, and N-telopeptide, C-telopeptide, and deoxypyridinoline as bone resorption markers.

Further measurements for bone loss using miniature mass spectrometers and ultrasound may be possible. In particular, ultrasound echography of the bone would be helpful to measure the
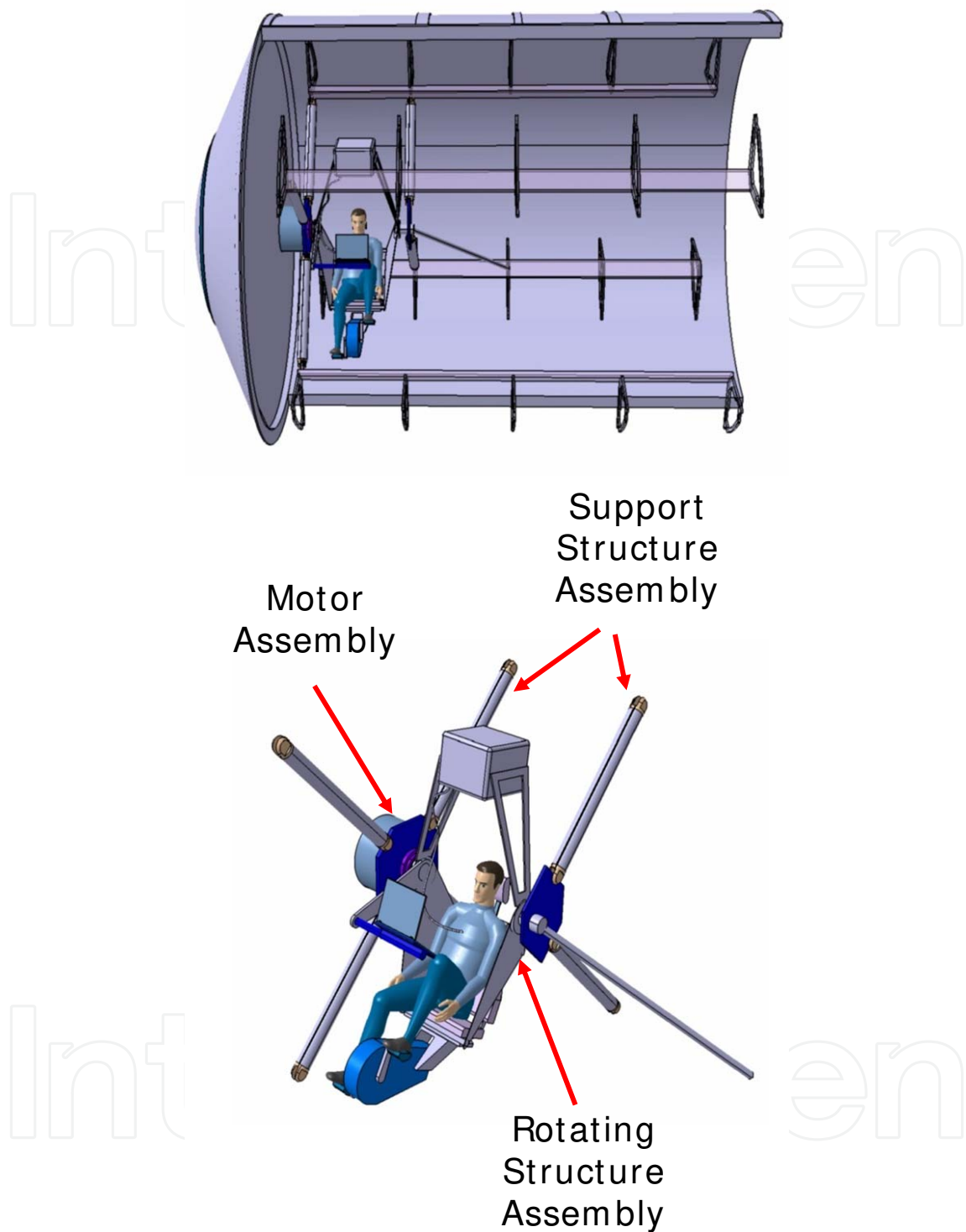
Motor Assembly

Support Structure Assembly

Rotating Structure Assembly

Figure 3. Short arm centrifuge to be installed in the International Space Station.

bone mass/density. Determination of bone mass/density at the hip joint or the calcaneus is helpful to assess the bone status and to validate the countermeasure programs in space [National Osteoporosis Society].

9. Conclusion and summary

In conclusion, it is favorable to administer bisphosphonate orally with artificial gravity with exercise in order to prevent the osteoporosis in space. Monitoring of the blood and urine samples in a space station or spacecraft by a simple method is necessary to assess the effectiveness of any countermeasure program against bone loss..

Author details

Satoshi Iwase[1*], Naoki Nishimura[1] and Tadaaki Mano[2]

*Address all correspondence to: s_iwase@nifty.com

1 Department of Physiology, Aichi Medical University, Yazako-Karimata, Nagakute, Japan

2 Gifu University of Medical Sciences, Seki, Gifu, Japan

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