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REVIEW

Adaptation to microgravity, deconditioning, and countermeasures

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Abstract Humans are generally in standing or sitting positions on Earth during the day. The musculoskeletal system supports these positions and also allows motion. Gravity acting in the longitudinal direction of the body generates a hydrostatic pressure difference and induces footward fluid shift. The vestibular system senses the gravity of the body and reflexively controls the organs. During spaceflight or exposure to microgravity, the load on the musculoskeletal system and hydrostatic pressure difference is diminished. Thus, the skeletal muscle, particularly in the lower limbs, is atrophied, and bone minerals are lost via urinary excretion. In addition, the heart is atrophied, and the plasma volume is decreased, which may induce orthostatic intolerance. Vestibular-related control also declines; in particular, the otolith organs are more susceptible to exposure to microgravity than the semicircular canals. Using an advanced resistive exercise device with administration of bisphosphonate is an effective countermeasure against bone deconditioning. However, atrophy of skeletal muscle and the heart has not been completely prevented. Further ingenuity is needed in designing countermeasures for muscular, cardiovascular, and vestibular dysfunctions.

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Introduction

Land-living vertebrates are believed to have evolved from fish [1]. During the process of evolution, the paired fins were modified into the limbs of early tetrapods or amphibia. The limbs came to be used to raise the animal body from the ground, and in combination with lateral trunk flexions, to propel the body forward. Reptiles are also descended from early tetrapods. When the mammals evolved, the trunk was also used to achieve an upright position. In humans, the trunk musculature has come to be used for balancing the body on the lower limbs and for movements of the head and trunk. In the lower limbs, the soleus is essential for bipedal standing and walking. In most mammals or quadrupeds, the center of gravity lies between the forelimbs and hind limbs, and the load on the hind limbs is thus smaller in quadrupeds than that on the lower limbs in humans. Thus, they do not require a large soleus mass. The soleus muscle, which acts on the ankle joint, is small in quadrupeds, but is relatively large in humans. In contrast, the gastrocnemius in the same triceps surae muscle is larger than the soleus in quadrupeds [2, 3]. The vestibular system senses the direction of gravity or posture and plays important roles in controlling posture via the motor neurons [4].

Standing, sitting, and walking exercise occupy about 16 h per day, and are the most common positions in the daily lives of humans. The gravity is loaded in the longitudinal direction of the body and has a major effect on the cardiovascular system [5, 6]. During recumbent posture, the body fluid, especially blood, is distributed uniformly

along the body, and arterial pressure (AP) is uniform from head to foot because the gravitational force and gradient along the longitudinal direction of the body is almost zero. However, changes in posture to either sitting or standing result in generation of a hydrostatic pressure gradient due to the force of gravity. The hydrostatic pressure on the head is low, whereas that on the feet is high. The high hydrostatic pressure on the feet causes high arterial and venous pressure. With this high venous pressure, the veins in the lower body are dilated, since their walls are highly compliant or extremely soft. With this pooling, the venous return and cardiac output are decreased, and AP should be decreased because it is the product of cardiac output and total peripheral resistance of the blood vessels. During postural change or standing, baroreflex control is considered important [7, 8].

Recently, humans have begun expanding their habitat into space. During human spaceflight and exposure to a microgravity environment, the effects of gravity on the body are diminished. The body and tissue structures adapt to the new environment, but the adaptation makes daily living difficult following return to Earth or a 1-*g* environment. To prevent adverse effects or deconditioning, various techniques or countermeasures have been considered and adopted. Multiple studies using Earth-based analogs and simulation of microgravity have been successfully performed in humans and animals, and are significant for their contribution to the study of adaptation and deconditioning [9–11]; however, the results are sometimes intermixed with data from spaceflights. Thus, this paper focuses on and summarizes general changes and deconditioning in the musculoskeletal, cardiovascular, and vestibular systems during human spaceflight, as well as reviewing the effects of the countermeasures.

Adaptation to microgravity and deconditioning

Skeletal muscles

Based on the myosin heavy chain isoform pattern, the skeletal muscles of the adult mammalian limb generally contain one slow fiber (type I) and two types of fast fibers (type IIa and IIb) [12]. In the triceps surae of the lower limb, the soleus is the slow muscle and contains primarily the type I slow-twitch oxidative fibers. The gastrocnemius is the type II fast-twitch glycolytic muscle [13–17]. Postural or antigravity muscles possess many slow-twitch myofibers, whereas propulsive or locomotor muscles have numerous fast-twitch myofibers [18–23].

Muscles are needed for movement and to counteract gravity, and they must be used in order to maintain the structure and the function. During spaceflight or in a microgravity environment, humans do not need to support their bodies; thus the antigravity muscles become atrophied. The volume of quadriceps and triceps surae decreased by −6.0 and −6.3%, respectively, after 8 days, and −5.5 to −15.4 and −8.8 to −15.9%, respectively, after 9–16 days of spaceflight [24, 25]. Fitts et al. reported that the slow-twitch and antigravity soleus shows greater atrophy than the fast-twitch gastrocnemius [26]. However, after 17 days of spaceflight, the gastrocnemius (−12%) tended to atrophy more than the soleus (−10%). Over longer spaceflight durations of 112–196 days, crew members showed further decreases in gastrocnemius (−24%) and soleus (−20%) volume, and the decrease was smaller in the soleus [27] (Fig. 1). In any of these cases, type II fibers are more atrophied than the type I (Fig. 2). In the atrophied vastus lateralis of the quadriceps muscle, the decline of cross-sectional area in the type II and I fibers were −21 and −11%, respectively, after 5 days of spaceflight, and −21 to −36 and −16 to −17%, respectively, after 11 days of spaceflight [28]. In the soleus muscle, type IIa fibers declined by −26% and type I fibers declined by −15% after 17 days of spaceflight [29]. Type IIb fibers are the most susceptible to a microgravity environment and the most atrophied. However, type I fibers also exhibit atrophy, and the percentage distribution of type II fibers becomes larger in the atrophied muscle (Fig. 2). These observations are opposite to those in rats. Type I and type II fibers declined by −30 and −15%, respectively, after 14 days of spaceflight, and hind limb suspension [30]. Thus, consideration of species difference is also necessary for discussion of the muscle atrophy mechanism during spaceflight. In the hind limb unloading rat model, electromyography is diminished at the onset of unloading. The amplitude recovers within a week, but the atrophy progresses [31–33]. Thus, species difference should be considered, but muscle atrophy is not induced by unloading only. After landing, following a 9- to 16-day spaceflight, the atrophy of the plantar flexor progresses for 4 days [25]. Muscle damage with weight bearing after spaceflight may be induced [27, 34]. Along with atrophy of the lower leg muscle, maximal voluntary contraction of the calf during plantar flexion is also reduced from −0.1 to −37.6% during 1, 3, and 6 months of spaceflight [35]. No correlation was found between the decrease and flight duration. As observed in the decrease in muscle volume, peak force decreased by −21 and −25% for type I and type IIa fibers, respectively [29].

Skeletal system

Bone has mainly two functions. One is a rigid structure to support and move the body on the ground, to protect organs. The other is a reservoir of calcium in the body [1]. In a microgravity environment, the function of support has less meaning, as in fish in water.

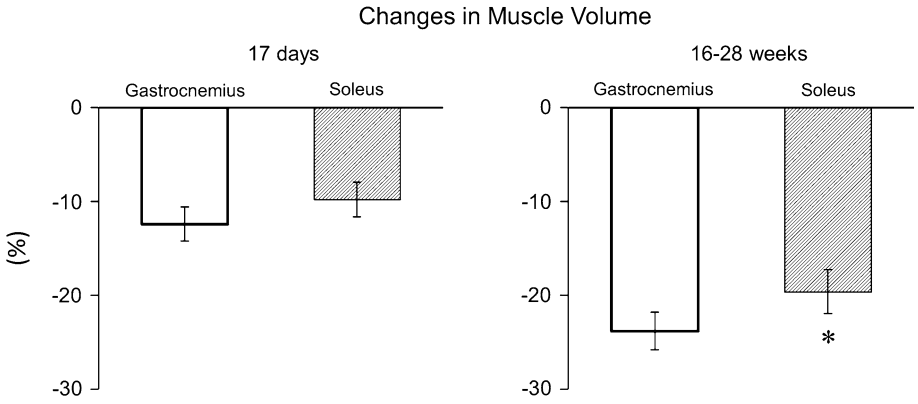

Fig. 1 Changes in muscle volume of triceps surae in astronauts after short (17 days) and long (16–28 weeks) spaceflights (drawn from data in Ref. [27]). $*p < 0.05$ vs gastrocnemius

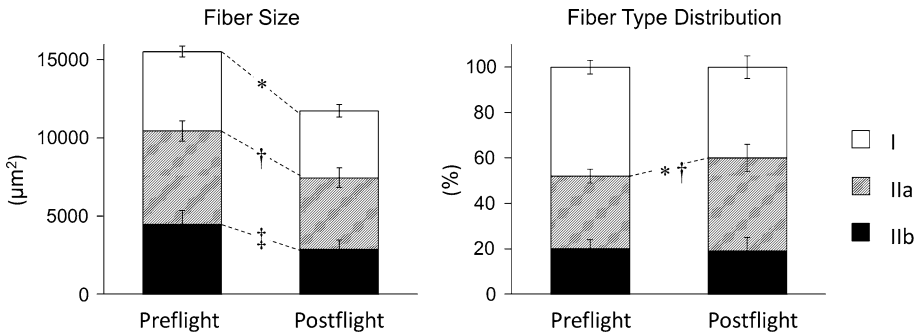

Fig. 2 Changes in muscle fiber size (*left panel*) and fiber type distribution (*right panel*) of the vastus lateralis in astronauts after 11 days of spaceflight (drawn from data in Ref. [28]). $*p < 0.05$ vs type I of preflight, $^{\dagger}p < 0.05$ vs type IIa of preflight, $^{\ddagger}p < 0.05$ vs type IIb of preflight

Unloading of the skeleton results in calcium leaving the bones. Within a few days of exposure to microgravity, urinary calcium excretion increases by 60–70% [36]. Densitometry of the calcaneus showed a tendency for increased bone mineral loss with longer spaceflight (−7.4% after 2 months of spaceflight, and −4.5 and −7.9% after 4 months of spaceflight) [37–39]. In the vertebral column, loss of bone mineral density (BMD) from −0.67 to 0.93% after 2–4 months, and −0.3 to −10.8% after 5–7 months of spaceflight were observed [36, 40]. The values are variable due to individual heterogeneity and variable methodology of measurements, but the decreases are twice those of bed rest, which is also unloading for the bones and a simulation of microgravity exposure [41, 42]. BMD decreases at weight-bearing points, such as the neck, spine, pelvis, and femur. In contrast, the upper extremities showed minimal or no decreases in BMD [43, 44] (Fig. 3). However, the skull exhibited increases in BMD [27, 45]. The trabecular zone is more susceptible to microgravity, and loss in BMD is larger than that in the cortical zone in the femur [40]. Thus, regional differences in BMD change are observed, and care should be taken in using metabolites as bone markers [46, 47].

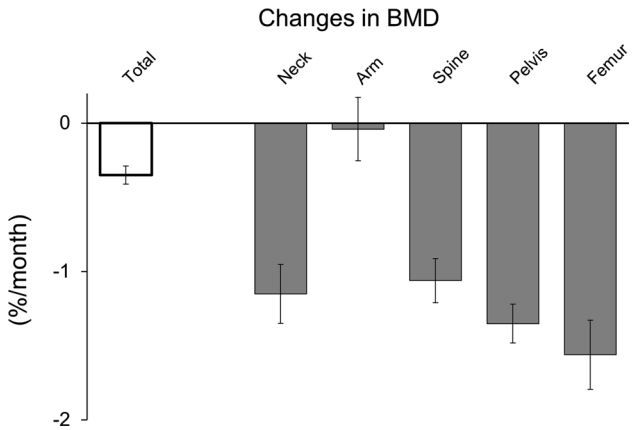

Fig. 3 Changes in bone mineral density (BMD) of various portions of astronauts after 4–14.4 months of spaceflight (drawn from data in Ref. [44])

Cardiovascular system

Humans live in an upright position about 16 h per day on Earth. The difference in posture from that of quadrupeds also affects cardiovascular condition. When posture is changed from a supine or recumbent position to an upright position, a hydrostatic pressure difference is observed along the longitudinal direction of the body [5]. Venous vessels are highly compliant, and the increase in intravascular pressure induces vessel distention and footward fluid shift [6, 48–52]. This fluid redistribution or footward blood shift may decrease the stroke volume of the heart [53]. To maintain AP, particularly in the head, heart rate (HR) and total peripheral resistance are raised reflexively [54]. In a microgravity environment or during spaceflight, the

hydrostatic pressure in the upper body is constantly as high as that during supine or recumbent posture. Thus, forehead thickness increases by 7% compared with that of preflight in a supine position [55], and intraocular pressure by 92% [56]. The heart size and stroke volume is increased temporally with the fluid shift [57–59]. In spite of the headward fluid shift, central venous pressure (CVP) decreases [58]. The change is opposite from that during simulated microgravity, such as head-down tilt and water immersion [60–62]. The decrease in CVP may be induced by change in the thoracic shape and reduction of intrathoracic pressure due to loss of gravitational compression for the thoracic cage and mediastinum [63–65]. Thus, the vena cava may be enlarged, and intravenous pressure is decreased, but the transmural pressure may be increased.

Apparent diuresis is not observed during spaceflight [66–68]; however, fluid intake is further decreased, and body fluid balance is negative. Eight and twelve days of flight decreased the plasma volume by −17%, probably due to the negative fluid balance and movement of the fluid to the extravascular space [69].

In a microgravity environment, large contractility of the heart is not required to send blood toward the head against gravity, and to maintain AP. Thus, the heart is atrophied by −8 to −10% after 10 days of spaceflight [70]. Figure 4 shows the relationship between averages of stroke volume and sympathetic nerve activity before and after spaceflight. They vary inversely, and a decrease in stroke volume induces an increase in sympathetic nerve activity. Stroke volume is largest and muscle sympathetic nerve activity is smallest during preflight supine position. With a change in position from supine to upright position, stroke volume decreased, and sympathetic nerve activity increased. Stroke volume significantly decreased, and sympathetic nerve activity increased after spaceflight even in the supine position. However, their relationship was maintained even after spaceflight [71] (Fig. 4). Even in the subjects who experienced presyncope during 10 min of standing test, the relationship was similar to that in non-presyncopal subjects after 4–215 days of spaceflight [72]. Stroke volume in presyncopal subjects at 6 min is 75% of that in non-presyncopal subjects, but HR is further increased. Thus, the relationship between stroke volume and HR is maintained even in presyncopal subjects (Fig. 5). As seen in these values, responses of sympathetic nerves or HR to changes in stroke volume, i.e., responses in the central arc of the baroreflex, are maintained at levels similar to those during preflight in spite of the decrease in cardiac size and blood volume control [71, 73–76]. Response in the peripheral arc of baroreflex control, i.e., decreased vascular contractility or responses in resistant vessels for sympathetic nerves, are also observed. Astronauts who could not complete 10 min of standing after 9–14 days of spaceflight revealed significantly reduced response of vasoconstriction [74]. The relationship between the low vasoconstrictive response and failure to complete stand tests was observed in an

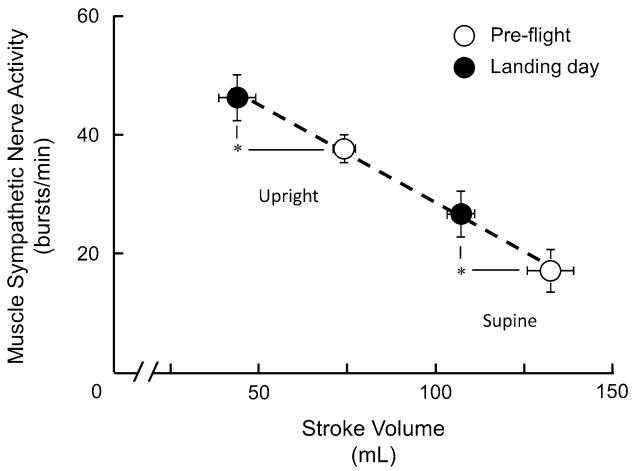

Fig. 4 Muscle sympathetic nerve activity plotted as a function of left ventricular stroke volume before and on landing day after 16 days of spaceflight (mean ± SE). With a change in position from supine to upright, stroke volume decreased, and sympathetic nerve activity increased. Stroke volume significantly decreased, and sympathetic nerve activity increased after spaceflight in both supine and upright positions. However, a relationship was maintained similar to that before spaceflight. $*p < 0.05$ for comparison between pre- and postflight muscle sympathetic nerve activity and stroke volumes (redrawn from data in Ref. [71])

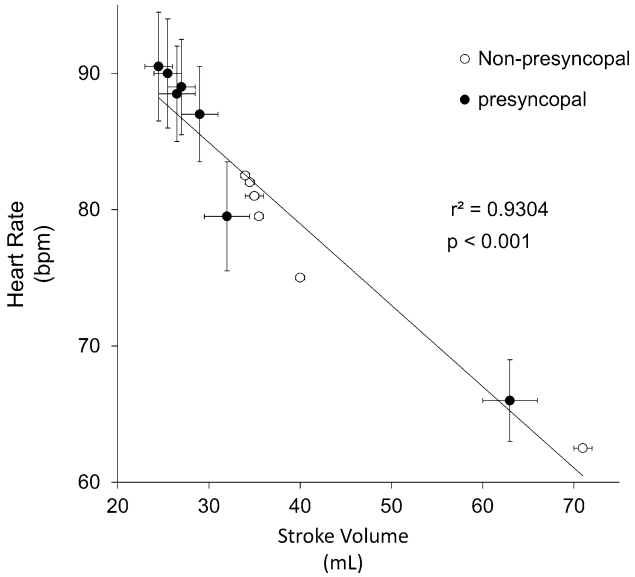

Fig. 5 Heart rate plotted as a function of left ventricular stroke volume during tilt test before and after 4–215 days of spaceflight in astronauts who completed 10 min of tilt test (non-presyncopal) and those who could not stand for the entire 10 min (mean ± SE). Values are plotted regardless of flight duration, and values during 6 min after the onset of tilt are plotted (drawn from data in Ref. [72]). The relationship between stroke volume and HR in presyncopal subjects is maintained, similar to that in non-presyncopal subjects after spaceflight

additional 87 astronauts after spaceflight [75, 77, 78]. However, the control of the AP may have been lost during the last minute of standing in those presyncopal subjects [72]. Thus, it is hard to determine whether the lowered vascular resistance is the reason or result of presyncope. Furthermore, vascular resistance is already elevated after spaceflight compared to that during preflight [71, 74, 75, 77, 78]. Since the capacity of vasoconstriction is finite, the elevated resting vasoconstriction associated with low circulating plasma volume and stroke volume may have represented a reduction in vasoconstrictive reserve. It is therefore unclear whether lower vascular contractility or simply lower vasoconstrictive reserve secondary to hypovolemia is being observed.

After 9–14 days of spaceflight and returning to Earth, orthostatic intolerance or orthostatic hypotension, i.e., acute drop of systolic AP more than 20 mmHg, has been observed in 64% of astronauts [74]. As described above, the orthostatic hypotension is considered to be induced mostly by cardiac atrophy, decrease in blood volume, and possibly decrease in vascular contractility [74, 75, 77, 78]. AP control at the onset of standing is importantly controlled by the vestibular system, particularly the otolith organs [50, 51, 79]. The otolith function or otolith-related control is considered to be weakened after spaceflight, and orthostatic hypotension at the onset of postural change may be induced by otolith deconditioning, as described in the next section [80–83].

Vestibular system

The vestibular system contains semicircular canals and otolith organs. Semicircular canals sense angular acceleration, and the otolith organs sense linear acceleration [84]. This system is important for equilibrium; in particular, the otolith organs contribute to the determination of body orientation with respect to gravity. This system also plays important roles in controlling posture via the motor neurons [4]. On Earth, 1-g acts in a vertical direction during any posture, but the gravity is zero in any direction during spaceflight. This unloading changes the characteristics of the vestibular system and its related functions.

The caloric test, the test for semicircular canal function, was performed before and after a 10-day spaceflight. The intensity of the response was similar to that measured on Earth [85]. The vestibulo-ocular reflex is involved in both otolith and semicircular canals, but head yaw oscillation in the test is sensed by semicircular canals only. A week of spaceflight did not change in the gain or the responsiveness [86]. For otolith function, an ocular-counter rolling test using a short-arm centrifuge during spaceflight showed a 10% decrease in magnitude [87]. In an otolith tilt-translation test, the difference in angle between real vertical direction and subjective vertical is measured. No difference was observed between the real and subjective vertical direction before spaceflight, but a difference of 15° was found after a 16-day spaceflight [88]. Postural equilibrium control measured by oscillation in the center of gravity was seriously disrupted immediately following 4- to 16-day spaceflight in all subjects [89, 90]. Thus, the function of otolith organs is more susceptible to exposure to microgravity than that of semicircular canals. However, the results from the center of gravity test may be exaggerated by the muscle atrophy described above. In order to evaluate the changes to otolith organs more accurately, function tests using less affected muscles will need to be done.

Countermeasures

Lower body negative pressure

A lower body negative pressure (LBNP) device applies ambient pressure lower than the normal atmospheric pressure to the lower portion of the body to induce footward fluid shift. The chamber is sealed, and the seal is attached to the iliac crest of the subject. The chamber pressure of −40 to −60 mmHg, which is below the normal ambient pressure, generates a force or weight bearing against the foot and footward fluid shift similar to that on Earth [50, 74, 91, 92]. With the fluid shift during −40 mmHg, renin was released [93], but lower negative pressure, such as −10 to −20 mmHg, did not affect the renin release, and cardiovascular impact was relatively small [94].

The LBNP device in the Mir space station did not have a saddle to support the body. Thus, negative pressure made the feet press against the bottom of the chamber and induced muscle contraction in the lower legs [95]. The contraction avoided venous distension and blood pooling in the legs. Thus, the fluid shift is considered to be less than that using the LBNP device with a saddle used during Skylab and the Shuttle program. The increase in HR was higher with the saddle compared to that without the saddle [95, 96].

The LBNP is used as a countermeasure with saline ingestion. LBNP with saline ingestion (6–9 g NaCl in 900–1200 ml water) during the last 2–5 days before landing subjectively improved orthostatic tolerance [95, 97]. About 1 l of isotonic saline ingestion and −30 mmHg of LBNP exposure 4 h a day prior to landing showed less HR increase and less decrease in systolic blood pressure compared with astronauts without LBNP during the simulated orthostatic test [98]. Thus, the program is beneficial for preventing orthostatic tolerance following landing, but a 5-h treatment for each astronaut makes it impractical to use.

Combined with treadmill running, the countermeasure for the musculoskeletal system, LBNP is proposed as both musculoskeletal and cardiovascular countermeasure [99–107]. The body needs to pull toward the treadmill in a microgravity environment during exercise. Bungee cords are used to strap astronauts, but they exert forces against the feet of only 75 and 54% of the body weight during walking and running, respectively, compared with those on Earth [108]. Pumping effect with the muscle contraction further enhances headward fluid shift. As described above, LBNP can generate similar force or body weight against the feet, and similar footward body fluid shift, as observed on the Earth. However, running and walking causes central fluid shift, and use of a LBNP device with no exercise is required as a countermeasure for cardiovascular deconditioning [104, 109].

Exercise

On the Mir space station, Russian astronauts or cosmonauts performed exercise using the bungee cord and treadmill 2–3 h on 3 of 4 days. The countermeasure was not effective for bone loss [44]. In addition to the treadmill, a cycle ergometer was also used on the International Space Station (ISS). Little information is available about the level of the force, but BMD was decreased by 4% in the lumbar spine and by 10% in the femur during a 6-month spaceflight [40]. Maximal voluntary contraction revealed a significant decrease of 17% during a 3- to 6-month spaceflight [110]. Thus, the devices are not effective as a countermeasure for bone loss during long-duration spaceflights.

Astronauts on the ISS allotted 2.5 h per day, 6 days per week for exercise countermeasures during the mission. The time also includes equipment set-up, reconfiguration, and personal hygiene [111, 112]. In microgravity, high-intensity interval training is much more effective than aerobic training [113]. For the first long-duration spaceflight on the ISS in 2000, the treadmill and cycle ergometer were used for exercise. After 6 weeks, the interim resistive exercise device (iRED) was assembled [114, 115]. In 2008, the advanced resistive exercise device (ARED) was launched to the ISS. The iRED provided the ability to perform eight exercises, i.e., squats, single-leg squats, heel raises, single-leg heel raises, deadlifts, Romanian deadlifts, upright rows, and bent-over rows [112]. The ARED included these exercises and added nine more, i.e., back squat, sumo squat, sumo deadlift, shrugs, shoulder press, bench press, bicep curl, triceps extension, and single-arm row [112]. The iRED had a maximum load equivalent of 1337 N, and the eccentric force was 60–80% of the concentric force. On the other hand, ARED had a greater load of 2675 N, and the eccentric force was 90% of the concentric force. Thus, ARED had greater resistance capability [116]. The combination of treadmill, cycle ergometer, and iRED did not maintain the muscle volume and peak power. After 6 months of spaceflight, the gastrocnemius and soleus atrophied by −10 and −15%, respectively. Their peak power had declined by 32% after the spaceflight [117]. The calf muscle volume decreased; the isokinetic strength decreased −16 to −31%, and the isometric strength also decreased −2 to −35% in 4 astronauts after 6 months of spaceflight [118]. By using ARED, the isokinetic strength changes were relatively improved in the thigh muscles, i.e., −9 to −20% with iRED and −4 to −15% with ARED during an ISS expedition of 60–190 days, but did not reach statistical significance [119]. With iRED, the BMD and bone mineral content (BMC) were still decreased in the pelvis and hip by −6 to −12% during 4–5 months of spaceflight. By using ARED, these changes were diminished, and the BMD and BMC in the pelvis and hip after the spaceflight were not significantly different from those before the spaceflight [112, 120]. However, the BMC and BMD of the lumber vertebral column significantly decreased by −0.2 to −5% with the use of either equipment. The changes in the vertebrae were not significantly different between the types of equipment. ARED was used with nutritional and pharmaceutical countermeasures, i.e., oral bisphosphonates (alendrone), calcium, and vitamin D [121]. Bisphosphonates block osteoclast activation and thus slow bone resorption. Moreover, they slow bone loss, improve BMD, and reduce fracture rates [122–124]. Bisphosphonates were started 3 weeks before the flight and continued throughout the flight [121]. They were taken at a dose of 70 mg/week, which is a dose for osteoporosis treatment and twice the dose for preventing osteoporosis [125]. About 400–800 IU of vitamin D_3 was taken daily, and 800 IU is a dose for postmenopausal women. More than 1000 mg of Ca was also taken daily, which is a similar dose to that given to postmenopausal women [121, 126]. Before the use of ARED and bisphosphonates, exercise with iRED decreased total hip BMD and BMC after spaceflight. However, the countermeasure using both ARED and bisphosphonates maintained BMD and BMC during 4.5–6.2 months of spaceflight (Fig. 6). Excessive load or training with squats, overuse injuries, and fatigue-related problems such as spine injuries still required attention [127], but the combination of nutritional and pharmaceutical countermeasures and ARED was effective in avoiding bone mineral loss for the lower extremities.

Future perspectives

Pharmaceutical countermeasures have been successful in preventing deconditioning of the skeletal system. However, exercise countermeasures as represented by ARED do not completely prevent muscle and cardiac deconditioning. Thus, atrophy of skeletal muscles and the heart is not induced by disuse only. Gravity-sensing or gravity-related mechanisms may be present, and the atrophy continues throughout the spaceflight [128]. Furthermore, the reflex via the gravity

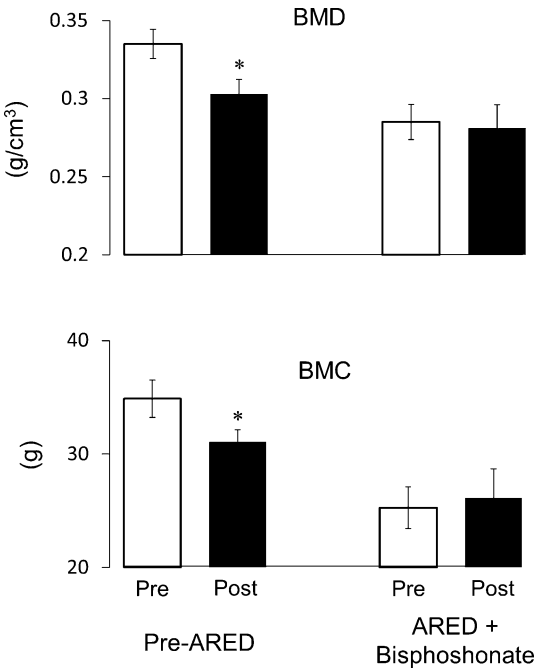

Fig. 6 Bone mineral density (BMD) and bone mineral content (BMC) in the total hip of before (pre) and after (post) 4.5–6.2 months of spaceflight (mean ± SE). Values are from astronauts who flew before the advanced resistance exercise device (ARED) was employed as a countermeasure (pre-ARED) and those who used combined ARED and medicated bisphosphonate (ARED + bisphosphonate). Before the use of ARED and bisphosphonates, total hip BMD and BMC decreased after spaceflight. However, a countermeasure using both ARED and bisphosphonates maintained the BMD and BMC during 4.5–6.2 months of spaceflight. $*p < 0.05$ vs preflight (drawn from data in Ref. [121])

sensors, such as muscle contraction for postural control [129, 130] and vestibulo-cardiovascular control during microgravity [79, 131, 132], is considered to change and leads to atrophy of the myocardium and skeletal muscles for standing. Artificial gravity with resistance exercise would resolve the deconditioning and be an important countermeasure [133–136], but the ability to provide such a device on a spacecraft will be an engineering challenge. In preparation for a Mars exploration mission, it will be necessary to develop an integrated and compact countermeasure for mission success. Further research on a combination of electric activating devices, such as galvanic vestibular stimulation and electrical stimulation of antagonist muscles to resist volitional contraction of the agonist instead of gravity, is expected [83, 137].

Conclusion

In this manuscript, we have summarized changes in the musculoskeletal, cardiovascular, and vestibular systems with exposure to a microgravity environment, and their current countermeasures. Spaceflight or exposure to microgravity immediately induces bone loss with an increase in urinary calcium excretion and muscle atrophy. The heart is also atrophied, and plasma volume decreases. Thus, decrease in stroke volume is considered to result in orthostatic intolerance. The otolith-related function also declines. As a countermeasure, ARED and bisphosphonates are effective for maintaining BMD and BMC, as well as effectively avoiding the deconditioning of bones, but they are only partially effective for muscles. LBNP and fluid loading do not completely avoid cardiac atrophy. Further ingenuity is needed to design countermeasures capable of preventing muscle and cardiac atrophy, and for maintaining vestibular function in future spaceflights.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The article does not contain any studies with human participants or animals performed by any of the authors.

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