

# REVIEW

## Interventions to prevent bone loss in astronauts during space flight

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**Abstract.** This paper reviews the interventions to stabilize calcium balance and bone metabolism and prevent bone loss in astronauts during space flight. Weightlessness during space flight results in calcium, vitamin D, and vitamin K deficiency, increases urinary calcium excretion, decreases intestinal calcium absorption, and increases serum calcium level, with decreased levels of serum parathyroid hormone and calcitriol. Bone resorption is increased, whereas bone formation is decreased. The loss of bone mineral density (BMD) in the spine, femoral neck and trochanter, and pelvis is 1.0–1.6% per month. High calcium intake and vitamin D supplementation during space flight does not affect bone metabolism, but prevents an elevation of serum calcium level through increased calcitriol level, while vitamin K counteracts the reduction in bone formation. However, there are no data to show the efficacy of pharmaceutical agents for prevention of development of osteoporosis in astronauts during flight, although the preventative effect of bisphosphonates, testosterone, and vitamin K<sub>2</sub> on cancellous bone loss in the tibia or BMD loss in the hindlimb was reported in tail-suspended mature rats. It still remains uncertain whether these agents can prevent cortical bone loss caused by weightlessness in tail-suspended rats. Therefore, in addition to calcium, vitamin D, and vitamin K supplementation, agents that have both potent anti-resorptive and anabolic effects on cancellous and cortical bone may be needed to stabilize calcium balance and bone metabolism and prevent bone loss in astronauts during space flight. (Keio J Med 54 (2): 55–59, June 2005)

**Key words:** Bone formation, bone resorption, calcium, microgravity, osteoporosis

### Introduction

It is known that weightlessness during space flight causes osteoporosis. The loss of bone mineral density (BMD) in the spine, femoral neck and trochanter, and pelvis is 1.0–1.6% per month.<sup>1</sup> The loss of bone mass in the whole body and legs, which are rich in cortical bone, is 0.3–0.4% per month.<sup>1</sup> According to Collet *et al.*,<sup>2</sup> 6 months of space flight resulted in 13.2% loss of calcaneus broadband ultrasound attenuation (BUA), 4.5% and 2.9% decreases in tibia cancellous and cortical bone mass, respectively, but 0.2% and 0.5% increases in radius cancellous and cortical bone mass, respectively. Skull BMD increases after space flight.<sup>3</sup> Recently, Lang *et al.*<sup>4</sup> demonstrated that spinal integral

volumetric (v) BMD was lost during 4- to 6-month space flight at a rate of 0.9% per month and cancellous vBMD was lost at 0.7% per month, while in the hip integral, cortical, and cancellous vBMD was lost at rates of 1.2–1.5%, 0.4–0.5%, and 2.2–2.7% per month, respectively. Thus, bone mass changes may be site specific and bone loss seems to be greater in cancellous bone than in cortical bone especially in the leg.

Thus, the physiologic changes in bone in astronauts during space flight have been studied. Osteoporosis after space flight may lead to an increased risk of fractures in later life. To our knowledge, the effects of calcium, vitamin D, and vitamin K on calcium balance and bone metabolism during space flight in astronauts have been reported, and the efficacy of bisphosphonates,

parathyroid hormone (PTH), testosterone, and vitamin K<sub>2</sub> for bone metabolism and bone mass has also been studied in the tail-suspended rat as a model of astronauts. The effect of exercise on bone metabolism and bone mass has rarely been reported, although its efficacy is expected. This paper discusses interventions, except for exercise, to stabilize calcium balance and bone metabolism and prevent bone loss in astronauts during space flight based on a review of the literature.

### **Changes in Bone Metabolism and Calcitropic Hormones During Space Flight**

#### ***Astronaut study***

Smith *et al.*<sup>5</sup> analyzed numerous reports on changes in bone metabolism during space flight without any interventions such as medication and exercise. Weightlessness during space flight increases urinary calcium excretion, decreases intestinal calcium absorption, and increases serum calcium level, with decreased levels of serum PTH and calcitriol. Bone resorption is increased as indicated by increased urinary pyridinoline, deoxypyridinoline, and cross-linked N-terminal telopeptide of type I collagen, and urinary and serum cross-linked C-terminal telopeptide of type I collagen levels, whereas bone formation is decreased as indicated by decreased serum bone-specific alkaline phosphatase and C-terminal peptide of type I procollagen levels, followed by increased serum undercarboxylated osteocalcin level.

#### ***Animal model study***

Bone histomorphometric studies of bones from rats after space flight for various periods provided the time course of the cancellous bone cellular events; a transient increase in resorption and sustained decrease in bone formation.<sup>6</sup> A tail-suspended rat model has been used to study the changes in bone metabolism as well as cancellous and cortical bone loss induced by weightlessness. Tail-suspension transiently increases bone resorption as indicated by a transient increase in urinary deoxypyridinoline level.<sup>7</sup> Tail-suspension increases bone resorption and decreases bone formation in cancellous bone and/or decreases bone formation in cortical bone in young growing and/or mature rats.<sup>7-9</sup> With regard to weightlessness-induced bone loss in rats, suppression of bone formation seems to play a predominant role rather than acceleration of bone resorption.<sup>10</sup> Parfitt<sup>11</sup> proposed two mechanisms of bone loss; reversible bone loss due to increased bone turnover in terms of increased birth rate of osteoclasts and osteoblasts and irreversible bone loss due to overactive osteoclasts and/or underactive osteoblasts. We surmise

that the former may be observed in the early phase of weightlessness, while the latter may follow the former in the late phase with decreased bone formation.

### **Intervention for Bone Loss During Space Flight**

#### ***Astronaut study***

##### *Calcium and vitamin D*

Because bone loss during space flight may be partly associated with low calcium intake and vitamin D deficiency due to inadequate sunlight (ultraviolet light) exposure, calcium and vitamin D supplementation may be a reasonable intervention for it. However, high calcium intake and vitamin D supplementation during space flight do not prevent the development of osteoporosis, because they do not counteract the increase in bone resorption and the decrease in bone formation despite prevention of the elevation of serum calcium level through increased calcitriol level and subsequent increased intestinal calcium absorption.<sup>12-14</sup>

##### *Vitamin K*

Vitamin K is known to be involved in the formation of  $\gamma$ -carboxyglutamic acid (Gla) in proteins, such as the calcium-binding bone Gla-proteins osteocalcin and matrix Gla-protein. Space flight induces vitamin K deficiency as indicated by increased calcium-binding capacity of osteocalcin and urinary excretion of free Gla. Therefore, vitamin K supplementation may be a reasonable intervention to stabilize calcium balance and bone metabolism. It was reported that vitamin K<sub>2</sub> decreased the serum undercarboxylated osteocalcin level and increased the serum osteocalcin level, sustaining lumbar BMD and preventing fractures in patients with osteoporosis.<sup>15</sup> However, the effects of vitamin K<sub>2</sub> on bone metabolism and bone mass have never been reported. On the other hand, vitamin K<sub>1</sub> in astronauts during space flight has no effect on bone resorption as indicated by no alteration in urinary cross-linked C-terminal telopeptide of type I collagen level, but counteracts the reduction in bone formation as indicated by decreased serum bone-specific alkaline phosphatase level, and decreases the serum undercarboxylated osteocalcin level.<sup>16,17</sup> Because an increased percentage of serum undercarboxylated osteocalcin level correlates with the hip fracture rate in elderly women,<sup>17</sup> the effect of vitamin K<sub>1</sub> on serum undercarboxylated osteocalcin level may be important to prevent future osteoporotic fractures in astronauts. Vitamin K may play a significant role in bone turnover during space flight.

## **Animal model study**

### *Tail-suspended young growing rats*

Tail-suspended young growing rats have been well utilized to test the efficacy of interventions for bone metabolism and bone mass during weightlessness. The anti-resorptive agent pamidronate prevented an increase in bone resorption and prevented bone loss despite a further reduction in bone formation in cancellous bone (secondary spongiosa) of the tibia of tail-suspended young growing rats, but could not restore normal growth-induced periosteal bone apposition and bone strength in cortical bone because it did not affect the weightlessness-induced decrease in periosteal bone formation.<sup>7</sup> The preventative effect of pamidronate on loss of cancellous bone mass might be associated with the formation of a substantial amount of primary spongiosa as a result of suppressed bone remodeling in the conversion of primary spongiosa to secondary spongiosa carried out by micromodeling and remodeling.<sup>7</sup> It was confirmed that pamidronate was unable to restore normal periosteal apposition, but could restore cancellous bone mass. Thus, potent anabolic agents were expected to restore growth-induced periosteal bone apposition in tail-suspended young rats.

The potent anabolic agent PTH (intermittent administration) prevented a reduction in bone formation and prevented bone loss in cancellous bone (secondary spongiosa) of the tibia of tail-suspended young growing rats.<sup>8,18</sup> Surprisingly, however, it could not prevent a reduction in periosteal bone formation and therefore failed to prevent cortical bone loss.<sup>8,18</sup>

Both potent anti-resorptive and anabolic agents may not be able to prevent the marked decrease in growth-related periosteal bone formation in the tibia of tail-suspended young rats. Thus, exercise during space flight may be needed to counteract the decrease in periosteal bone apposition or enhance the effect of PTH on periosteal bone formation, because exercise could increase periosteal bone formation in young growing rats.<sup>19–21</sup>

### *Tail-suspended mature rats*

Tiludronate prevented bone loss despite a further decrease in bone formation in cancellous bone (secondary spongiosa) of the tibia of tail-suspended mature rats.<sup>22</sup> This preventative effect of tiludronate might be related to the alteration in bone remodeling with an increase in trabecular bone number in cancellous bone.<sup>22</sup> However, the effect of tiludronate on cortical bone in this model remains uncertain.

Testosterone is anabolic to osteoblasts and muscle and also decreases bone turnover. Serum testosterone level was markedly suppressed in tail-suspended

adult male rats, and this might partially contribute to weightlessness-induced bone loss.<sup>23</sup> Testosterone prevented loss of muscle mass and BMD in the hindlimb of tail-suspended mature male rats.<sup>24</sup>

Recently, anti-resorptive and anabolic effects of vitamin K<sub>2</sub> on bone *in vivo* were reported in ovariectomized, orchidectomized, sciatic neurectomized, or glucocorticoid-treated rats.<sup>25–28</sup> Vitamin K<sub>2</sub> prevented the elevation of bone resorption and the reduction in bone formation, counteracting loss of BMD or cancellous bone mass in the hindlimb of tail-suspended mature rats.<sup>9</sup>

The tail-suspended mature or adult rat model rather than the tail-suspended young growing rat model may be more suitable to study the interventions to prevent bone loss by weightlessness because of the less influence of bone growth on bone mass and metabolism. Although a preventative effect of tiludronate, testosterone, and vitamin K<sub>2</sub> on BMD and/or cancellous bone mass in tail-suspended mature rats was reported, the direct effect on cortical bone mass remains uncertain. Thus, further studies are needed to clarify whether these or other agents are able to prevent both cancellous and cortical bone mass in tail-suspended mature rats.

## **Conclusions**

Table 1 summarizes the alterations in bone mass and bone metabolism during space flight in astronauts.

Data on interventions to stabilize bone metabolism and prevent bone loss in astronauts during space flight are limited. A high calcium intake and vitamin D supplementation during space flight prevents an elevation of serum calcium level through increased calcitriol level, while vitamin K counteracts the reduction in bone formation. However, there are not data to show the efficacy of pharmaceutical agents for prevention of development of osteoporosis in astronauts during space flight. In an animal model of weightlessness, the tail-suspended mature rats, cancellous bone loss of the tibia was prevented by the bisphosphonate tiludronate, and BMD loss of the hindlimb was counteracted by testosterone and vitamin K<sub>2</sub> by preventing an increase in bone resorption and a reduction in bone formation. However, it still remains uncertain whether these agents can prevent cortical bone loss caused by weightlessness in tail-suspended rats. We surmise that in addition to calcium, vitamin D, and vitamin K supplementation, agents that have both potent anti-resorptive and anabolic effects on cortical and cancellous bone may be needed to stabilize calcium balance and bone metabolism and prevent bone loss in astronauts during space flight.

It remains uncertain whether or if possible, when

**Table 1** Alterations in Bone Mass and Bone Metabolism during Space Flight in Astronauts

Parameters		Alterations
Bone mass <sup>2-4</sup>	Spine, femoral neck and trochanter, and pelvis BMD	1.0–1.6% decreases per months
	Spine integral and cancellous vBMD	0.9% and 0.7% decreases per month, respectively
	Hip integral, cortical, and cancellous vBMD	1.2–1.5%, 0.4–0.5%, and 2.2–2.7% decreases per month, respectively
	Tibia cancellous and cortical bone mass	4.5% and 2.9% decreases for 6 months, respectively
	Radius cancellous and cortical bone mass	0.2% and 0.5% increases for 6 months, respectively
	Calcaneus BUA	13.2% decrease for 6 months
	Skull BMD	Increase
Bone metabolism <sup>5,12,16</sup>	Urinary calcium excretion	Increase
	Intestinal calcium absorption	Decrease
	Serum calcium level	Increase
	Serum PTH and calcitriol levels	Decrease
	Bone resorption (urinary PYR, DPD, NTX, and CTX)	Increase
	Bone formation (serum BAP and P1CP)	Decrease

BMD: bone mineral density, vBMD: volumetric BMD, BUA: broadband ultrasound attenuation, PTH: parathyroid hormone, PYR: pyridinoline, DPD: deoxypyridinoline, NTX: cross-linked N-terminal telopeptide of type I collagen, CTX: cross-linked C-terminal telopeptide of type I collagen, BAP: bone-specific alkaline phosphatase, P1CP: C-terminal peptide of type I procollagen.

bone loss caused by weightlessness during space flight in astronauts will be restored after reconditioning. Further studies are also needed to confirm this issue.

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