Calcium and Bone Metabolism During Spaceflight

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INTRODUCTION

The ability to understand and counteract weightlessness-induced bone loss will be critical

for crew health and safety during and after space station or exploration missions lasting months

or years, respectively. Until its deorbit in 2001, the Mir Space Station provided a valuable

platform for long-duration space missions and life sciences research. Long-duration flights are

critical for studying bone loss, as the 2- to 3-week Space Shuttle flights are not long enough to

detect changes in bone mass. This review will describe human spaceflight data, focusing on

biochemical surrogates of bone and calcium metabolism. This subject has been reviewed

previously.[1-9]

BONE LOSS

Bone mineral is lost during spaceflight because weightlessness unloads the skeleton.[10-17]

This has been known for decades, but determining predictive factors or showing changes that are

consistent from subject to subject has proved difficult.

When changes in bone density are caused by unloading, the changes in different skeletal

regions do not necessarily correlate with the change in total body calcium or overall calcium loss.

Oganov et al.[16] found mineral losses averaging 2.8, 8.2, 5.0, and 6.2% in the tibia, greater

trochanter, femoral neck, and lumbar vertebrae, respectively, of 7 exercising cosmonauts who

stayed on Mir for 4 to 6 months. These 7 crewmembers had no change in total body calcium.

Both spaceflight and ground-based analog studies have shown that the loss of calcium from

bones varies among sites within a subject, and that the nature and degree of loss over time varies

between subjects.[12,14,17-20]

Virtually every astronaut on missions longer than 30 days has lost bone in some region. The constraints and difficulties of spaceflight research have prevented studies to date from finding any explanation for individual differences.

Whether factors such as exercise (type, frequency, technique, etc.), diet, and environment play a role in this variability has yet to be determined. Such factors may be critical in finding countermeasures for bone loss of spaceflight, or conversely, they may influence the effectiveness of a countermeasure once it has been defined. For instance, in the event that an exercise profile is defined that preserves bone during weightlessness, and a crewmember is not consuming enough calcium, then the countermeasure may appear to have failed. Given the small number of crewmembers available for study, this might prove to be a significant hindrance to resolving the problem of bone loss.

CALCIUM BALANCE AND CALCIUM METABOLISM

Negative calcium balance was observed during Skylab[11,21-23] and Mir[24] missions. Increased urinary and fecal calcium excretion accounted for most of the deficit.[11,14,21-23,25-27] Increased calcium excretion is a major contributor to the increased risk of renal stone formation during and after spaceflight.[25-27]

Recent studies with calcium[24] and strontium[28] tracers have shown that the calcium absorption of crewmembers decreased aboard the Mir space station. The calcium tracer studies included mathematical modeling of the calcium kinetics, which estimated a net bone calcium loss

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of about 250 mg/d.[24] This fits very closely with the Skylab calcium balance data, which showed

whole-body calcium losses of 200 to 300 mg/d.[1]

While early hypotheses suggested that space travelers' serum concentrations of total and

ionized calcium would increase, only very small changes have been noted, and those have had

only statistical rather than clinical significance.[24,29] Thus, despite the bone loss and

hypercalciuria associated with spaceflight, the body's regulation of circulating calcium levels

remains intact.

BONE METABOLISM AND BONE MARKERS

As a living tissue, bone is constantly subject to remodeling through the processes of bone

formation and bone resorption. The activity of these processes may be determined by a number

of methods, ranging from extremely invasive (bone biopsy) to noninvasive (markers found in

urine). The battery of biochemical markers available has evolved over the past 4 decades of

humans flying in space. Although more sensitive and specific markers have recently become

available, it is reassuring to find that the results of studies showing the effects of spaceflight on

bone metabolism are very consistent, essentially regardless of technique.

Bone formation is generally unchanged or decreased during spaceflight. Typically, blood

(serum) samples are required for assessment of bone formation markers, the most popular of

which are bone-specific alkaline phosphatase (BSAP) and osteocalcin. Studies from a few

astronauts and cosmonauts on Mir have yielded mixed results, but again, the general finding was

that these markers were unchanged or decreased compared to their preflight serum

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concentrations.[24,30,31,32] Kinetic studies with calcium tracers yielded similar results for bone

formation (i.e., it decreased in one crewmember and was unchanged in the other two).[24] In all of

these studies, unfortunately, the number of subjects was very small.

While bone formation may remain unchanged, or perhaps decrease slightly, during

spaceflight, bone resorption clearly increases. Several biochemical markers in blood or urine

samples reflect bone resorption activity. Increases in urinary calcium excretion, perhaps the

oldest of the markers, are consistently observed during and soon after spaceflight.[10,11,14,22-27]

During the Skylab 4 mission, calcium losses correlated roughly with calcaneal mineral losses

determined by bone density studies.[33]

Hydroxyproline in urine may be used as a marker of bone resorption. Posttranslational

modifications of collagen form this amino acid, which appears in urine when collagen breaks

down. As with all surrogates, hydroxyproline has its limitations. A key example: the metabolism

of dietary collagen can also produce hydroxyproline. Nevertheless, the finding that urinary

hydroxyproline excretion was elevated 33% after the 84-d Skylab 4 flight[23,34]corroborates other

evidence of bone resorption during spaceflight.

The 1990s brought the ability to measure collagen crosslinks, a family of compounds that

appear in the urine as a result of collagen degradation associated with bone resorption. Several

crosslink fragments can be measured by high-performance liquid chromatography, and many by

commercially available enzyme-linked immunosorbent assays. Fragments of interest include

pyridinoline, deoxypyridinoline, N-telopeptide, and C-telopeptide. In general, all provide similar

results. The advantages of using crosslinks include the fact that these compounds are formed

only in mature collagen, and thus their release reflects breakdown of mature collagen; the

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fragments are not absorbed from the gut, and thus dietary consumption does not confound results; and these compounds are extremely stable in frozen urine samples for a long period.

Data from spaceflight studies very consistently show increased levels of markers of bone resorption.[24,30,31,35,36] Calcium tracer kinetic data also indicated that bone resorption increased about 50% during flight.[24]

Because of the increasing use of collagen crosslinks as markers, a few comments are warranted about common perceptions and misconceptions. Critics of using collagen crosslinks often point out that they vary considerably from day to day and from subject to subject, and this criticism is well founded. However, the day-to-day variability may be minimized by extending the sample collection period, an action more easily accomplished in research than in clinical settings. With regard to the subject-to-subject variability, although this is indeed considerable, the response to intervention (e.g., spaceflight, bed rest, or exercise) is highly consistent between subjects. For example, although the amount of a collagen crosslink excreted in 24 hours can easily vary 5- to 10-fold between 2 subjects, if those same 2 subjects go into space, they will have the same magnitude of response compared to their preflight level.

Another common issue is that of normalizing crosslink excretion to creatinine excretion. Whereas in a clinical setting the collection of individual urine voids may make this necessary, in research it should be avoided wherever possible. This is especially, and perhaps obviously, true in cases where muscle mass and metabolism, or creatinine excretion, may change.

One clear limitation of using these biochemical markers is that they reflect changes in the entire skeletal system, and regional differences may be missed or masked. Because of this, whenever possible the bone markers should be determined in conjunction with other tests (bone

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density measurements, for example), to ensure that multiple perspectives are considered. However, the changes in spaceflight are clear enough to alleviate concerns about this potential problem.

ENDOCRINE EFFECTS

In an attempt to define the mechanism of weightlessness-induced bone loss, many studies have focused on the endocrine regulation of bone and calcium metabolism. In general, changes in the endocrine regulation of bone metabolism seem to reflect adaptation to the weightless environment (that is, the system functions normally to decrease bone mass).

The absence of ultraviolet light and decreased dietary intake of vitamin D during spaceflight diminish vitamin D pools in the body. This was observed during the 84-d Skylab mission[22] and the 115-d Mir mission.[24] However, on Skylab, the slight decrease occurred despite dietary supplements of 500 IU of vitamin D/d.[22] Crewmembers on the International Space Station are provided with vitamin D supplements, but this is done because of concerns about the amount of vitamin D provided by the food system. In other words, the supplements are intended to prevent a dietary deficiency, and are not expected to correct bone loss.

Circulating parathyroid hormone concentrations decrease during flight, albeit with some variability.[22,24,31,37] Decreased levels of the active form of vitamin D - 1,25-dihydroxyvitamin D - have been observed on long-duration flights,[24] and these changes occurred much earlier than changes in the vitamin D stores. Parathyroid hormone is required for synthesis of 1,25-dihydroxyvitamin D. Thus, the decreased concentration of 1,25-dihydroxyvitamin D

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observed during spaceflight seems to be related to decreased production secondary to decreased

parathyroid hormone concentrations, rather than increased disposal. No changes in circulating

vitamin D metabolites were observed on one Shuttle flight, but preflight concentrations varied

considerably.[37]

Changes in the endocrine regulation of bone metabolism seem to reflect adaptation to the

weightless environment. Decreases in calcium absorption and blood levels of parathyroid

hormone and 1,25-dihydroxyvitamin D are expected physiological responses to increased

resorption of bone. Resorption is likely stimulated as the body adapts to an environment in

which bones bear less weight. It is estimated, on the basis of limited available data, that recovery

of the lost bone will take about 2 to 3 times the length of the mission.[24] While more data clearly

are required to validate this hypothesis, it has significant implications as mission durations

increase. For planetary missions, the ability of a terrestrial partial g force (such as Mars' 0.38 g)

to reduce bone loss, or even allow recovery to begin, is unknown. While no data exist on

responses to partial g , the general consensus among investigators is that forces less than 0.5 g

(for example, the Martian 0.38 g) are likely to be of little value to bone.

DIETARY INFLUENCE

Several nutrients affect bone and calcium homeostasis. These include calcium, vitamin

D, vitamin K, protein, sodium, and phosphorus. Supplemental calcium is an important adjunct in

the treatment of patients with osteoporosis,[38] but it does not correct the problem of bone loss

during spaceflight. The importance of vitamin D was addressed earlier in this article. Vitamin K

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is responsible for carboxylation reactions in osteocalcin synthesis. The importance of vitamin K during spaceflight has been addressed in preliminary reports,[39] but the subject clearly requires further study.

Dietary sodium during spaceflight is also a subject of concern, as it is known to affect calcium homeostasis.[40-44] Dietary sodium also seems to exacerbate the calciuric responses to unloading: subjects consuming a low sodium diet (100 mmol/d) had no change in urinary calcium, while those on a high sodium diet (190 mmol/d) exhibited hypercalciuria.[45] Space diets tend to have relatively high amounts of sodium, and increased dietary sodium is typically associated with hypercalciuria (as reviewed by Nordin et al.,[42] and Heer et al.[43]).

COUNTERMEASURE POTENTIAL

The ability of many countermeasures to ameliorate spaceflight-induced bone loss has been tested. However, the countermeasured tested to date, including exercise, increased calcium and/or phosphate intake, vitamin D supplementation, exposure to ultraviolet light, and administration of early-generation bisphosphonates, have proved ineffective during spaceflight or bed rest.[5,46-49] Whether resistive exercise paradigms, newer anti-resorptive therapies, or other therapies involving bone-regulating proteins will prevent or reduce bone loss is yet to be determined. Ensuring adequate dietary intake, or in some cases ensuring adequate synthesis, of calcium, vitamin D, vitamin K, and other bone-related nutrients will be necessary, but does not appear to be sufficient to solve the problem of bone loss. Other factors that may also contribute to the degree of calcium loss are age, gender, fitness, genetics, and dietary history. The

importance of these in preventing (or hastening) bone loss has yet to be determined.

SUMMARY

Spaceflight-induced bone loss poses significant health risks for astronauts, both acutely and chronically. Future research is required to better understand the nature of this bone loss, to define the time course of its effects, and to develop means to counteract it. Successful resolution of these tasks will increase crew safety during spaceflight, will enable human exploration missions, and may provide insight into the treatment of diseases on Earth.

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