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Space Medicine Considerations: Skeletal and Calcium Homeostasis

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I. Relevant Issues

A. Preventable Risks:

1. Short term
   a. Hypercalcemia
   b. Renal and other stones
2. Long term - Skeletal atrophy

B. Medical Questions:

1. Does hypercalcemia occur?
2. What are the changes in urine concentration?
3. What is the rate of an individual's bone loss?
4. How long does it take to recover bone after return to Earth? Is there a postcareer hazard regarding bone loss?
5. Is an exercise or pharmacological countermeasure needed for this length flight? Is the exercise or pharmacological countermeasure prescribed working?

C. Medical Operations Evaluation Requirements:

1. Ionized calcium determinations - in flight
2. Metabolic balance for calcium - collections in flight, analysis on Earth
3. Bone densitometry - in flight
4. Mineral and hormonal determinations - collections in flight, analysis on Earth

II. Background: Bone and Mineral Metabolism

Biomedical data from multiple U.S. and U.S.S.R. space missions are making it clear that there are continuous and possibly progressive changes in the musculoskeletal system. This effect appears in the way the body conserves calcium and other minerals which are normally stored in the skeleton. Loss of total-body calcium and skeletal changes have been observed in both animals and people who have flown from 1 week to more than 237 days in space. These alterations in bone and mineral metabolism may be among the most profound biomedical changes associated with long-duration space flight. Information on skeletal and mineral changes has been obtained from a variety of studies conducted in both simulated and actual space flight.

Bone Density Studies

During Apollo and Skylab missions, a precise method of photon absorptiometry was used to assess preflight and postflight bone mineral mass. The results of measurements of the central os calcis, which is almost all trabecular bone, for the Skylab Program (ref. 1) revealed that the largest losses occurred on the crew of Skylab 4 after 84 days of weightlessness. Bone mineral losses were not observed from the distal compact radius, however. Since these measurements were taken from different types of bone, they do not answer the important question of whether mineral loss occurs only in weight-bearing bones during space flight. Some suggestion is found from the U.S.S.R. space-flight measurements in which mineral loss was determined from the tubercle and plantar areas of the os calcis, predominately compact bone. Bone loss seemed to increase in rough proportion to the increase in mission length and ranged from -0.9 to -19.8 percent over periods from 75 to 184 days (ref. 2). Thus, both compact and trabecular bone is lost from the heel. Calcaneal mineral recovery is gradual and appears to take about the same length of time as the loss (ref. 3). This measured recovery was incomplete in at least one Skylab 4 astronaut, who, after 90 days back on Earth, had replaced only half his loss. Although U.S.S.R. investigators suggest that full calcaneal recovery occurs, spine mineral loss was seen in cosmonauts (using an x-ray computerized tomography technique) during the 6 months following flight, but, using the same technique, no loss of spine mineral was seen during flight (ref. 4).

Calcium Balance Studies

Studies of metabolic balance were conducted on the Skylab missions, during which dietary intake and urinary and fecal excretion were monitored. Daily reports of food ingested by individual crewmembers were communicated to dietary personnel, who calculated daily intake of calories, minerals, and other nutrients. Twenty-four-hour urine collections were mixed with a known quantity of a marker, and an aliquot was obtained and saved for analysis back on Earth. All stools were collected and returned for analysis. (However, enemas were used just prior to launch and the excreta discarded.) Sweat minerals were not measured, nor was any correction made for sweat losses. Vomitus may or may not have been saved for laboratory analysis. Despite the problems in balance technique, Skylab balance studies were more accurate than were the balance determination studies on the few crewmembers participating in the Gemini and Apollo missions. Results of these studies showed that space flight is accompanied by an increased excretion of calcium and phosphorus.

The changes in urine and fecal calcium content were measured in flight during Skylab 4 (ref. 5). The urine calcium content increased rapidly but reached a plateau after 30 days in flight. There was a small fecal calcium increase seen over the duration of the flight. Within 10 days in flight, the preflight positive calcium balances became less positive until the body as a whole began to lose calcium. The rate of loss was slow at first, but increased to almost 300 milligrams per day by the 84th day of flight. For the three Skylab 4 crewmen, the average loss was 25 grams of calcium from the overall body pool (about 1250 grams). Based on the trends in calcium loss during the first 30 days in flight, Rambaut and Johnston (ref. 1) calculated that 1 year in flight might result in the loss of 300 grams, or 25 percent, of the initial body pool. Similar conclusions can be drawn from U.S.S.R. research (ref. 6), in which an increased calcium excretion is attributed to weightlessness.

Results of the Skylab calcium balance studies suggest that the losses in bone mineral from the os calcis contribute relatively little to the overall calcium loss. A 4-percent loss observed in the os calcis after the 84-day mission would represent a loss of only about 100 milligrams of calcium, whereas overall calcium loss for this mission was 250 times greater. In one U.S.S.R. mission in which substantial exercise was performed by the cosmonauts, significant loss of os calcis mass was also seen, although the investigators think that an extensive exercise program on later missions did decrease skeletal loss (ref. 7). Thus, it is clear that other weight-bearing skeletal sites account for the major portion of the depleted mineral. Bone loss from other skeletal sites has not been reported.

Recovery of the lost calcium begins soon after return to one g. Urine calcium content dropped below preflight baseline by postflight day 10, but fecal calcium content had not dropped to preflight levels by 20 days after flight. The markedly negative calcium balance also had not returned to zero by day 20. Evidence from the studies on recovery of the os calcis mineral content after space flight, and evidence from bed-rest studies, suggests that after a period of some weeks or months, the astronaut would return to his/her normal os calcis bone mineral content. Nevertheless, it is possible that the calcium balance might return to zero long before the loss from space flight had been made up, and irreversible damage to the skeleton might result.

Biochemical Analyses

Analyses of in-flight urine, fecal, and plasma samples from Skylab missions revealed changes in a number of biochemical parameters (ref. 8). Urinary output of hydroxyproline gradually increased, indicating the deterioration of the collagenous matrix substance of weight-bearing bones. Output of nitrogen reflecting muscle atrophy also increased. The proportion of stearic acid in the total fecal fat increased throughout the flight as more and more calcium was available to form nonabsorbable salts. Urinary levels of catecholamines decreased but urinary cortisol was increased during space flight. Analyses of plasma revealed in-flight increases in calcium and phosphate; parathyroid hormone (PTH) levels were never increased and were decreased from preflight or early flight levels later in the flight (refs. 1, 9, and 10).

Ground-Based Simulation Models

Bed rest provides a good model for the changes of weightlessness on bone and mineral since the force of gravity is reduced on the longitudinal skeleton from one g to one-sixth g. Although the results from space-flight balance studies are not completely identical to the bed-rest model, a number of factors must be considered. These include the ability to perform a greater number of studies on Earth and thereby to minimize individual variations and the capability for more critical monitoring of subjects, minimizing mineral losses from sweat and vomitus during ambulatory control, bed rest, and recovery (compared to the lack of these controls in the astronauts before flight, during flight with early space motion discomfort or later exercise periods, and after flight during physiologic recovery). The lack of measurement of these mineral losses could become a standard error of the balance studies during space travel. Balances would initially appear positive and during space flight would remain positive, although less so. If the mineral losses from sweat and vomitus were not measured only during part of the space flight as would be seen with variation of cabin temperature changes, space motion discomfort, or exercise effort, mineral balance would appear to be inconsistent. Thus, space balance studies have pointed the way but must be interpreted with caution. Bed-rest studies have given reliable and reproducible results which have allowed us the opportunity to determine that bone loss continues unabated for at least 36 weeks with no evidence that the expected new steady state is produced. Total-body calcium stores decrease by 6 grams each month after the first month of bed rest, and by the end of 9 months, at least 50 grams of calcium have been lost. Additionally, bed rest allows us to determine results that bear on the mechanisms underlying bone loss during hypokinesic states.

Bed-rest studies have suggested a means to predict the amount of mineral that will be lost from the os calcis during bed rest or in space (refs. 11 to 15). The wide variability in the amount of lost mineral in bed-rested subjects can partly be accounted for by two other variables: (1) the initial os calcis mineral content and (2) the urinary hydroxyproline excretion rate (corrected for creatinine excretion). The regression of the prediction term (initial mineral divided by urinary hydroxyproline excretion rate) on the amount of mineral loss in subjects bed-rested for 59 days has been determined (ref. 3). The fact that data from two of the Skylab 3 astronauts fit well suggests that these variables also can be used to predict the effects of space flight on os calcis mineral content.

Studies of animals with immobilized limbs have suggested that disuse produces changes in both bone formation and bone resorption, depending upon the length of immobilization. For example, Landry and Fleisch (ref. 16) used osseous tetracycline incorporation corrected by changes in bone weight as a direct index of bone formation, and as an indirect index of bone resorption. They found a short initial phase during which formation decreased, and a second phase in which formation increased but bone weight decreased, indicating an even greater increase in resorption. After 49 days of immobilization, formation again decreased below normal levels.

Young et al. (ref. 17), through long-term immobilization of monkeys (*Macaca nemestrina*), demonstrated loss of not only trabecular bone but cortical bone in the weight-bearing areas. Moreover, full recovery of the cortical bone deficiencies may not have been complete even after 40 months of ad lib activity following restraint.

Didenko and Volozhin (ref. 18) exposed rabbits to 30 days of confinement in order to study changes in bone mineral composition. Levels of calcium in bone did not change, although calcium excretion increased. This effect was attributed to an inhibition of bone reorganization, in which bone mass was reduced without a corresponding alteration of crystalline structure.

The most pronounced changes are seen to occur in weight-bearing bones. Mechanical stimulation apparently has a critical effect on bone structure and metabolism, as numerous studies involving bone strain measurement have shown (ref. 19). There also appears to be an age-dependent variation in the relative rates of bone formation and resorption (ref. 20). Older animals show the highest net rate of bone loss during immobilization.

These and other results indicate that immobilization produces a number of time-dependent changes in bone accretion and resorption, and suggest that proportionately larger increases in resorption may be a key factor in the loss of bone mineral mass. Skeletal losses in space are likely due to relatively larger increases in bone resorption compared to bone formation (except in immature growing animals). Autopsies of the three U.S.S.R. cosmonauts who died after a 21-day flight revealed "a good number of unusually wide osteocytic lacunae," which may have been due to increased bone resorption.

In-Flight Animal Experiments

Studies of animals flown aboard the Cosmos satellites (ref. 21) and in Spacelab have also revealed changes in bone mineral content. Monkeys experiencing 8.8 days of weightlessness showed larger losses in bone mineral than did ground controls (ref. 22). Spacelab 3 rat studies as well as previous studies flown on the Cosmos biosatellites showed marked skeletal changes. For example, skeletal changes in rats exposed to as little as 7 days of space flight during Spacelab 3 included decreased bone growth, decreased mineralization, decreased bending strength, and decreased weight of the lumbar spines (L3) (refs. 23 and 24). Flight rats after 18.5 days in the Cosmos experiment showed a 30-percent decrease in mechanical bending strength (ref. 25) compared to a 28-percent reduction in rats aboard Spacelab 3 after just 7 days (ref. 26). In addition to these changes, other functional rearrangements such as depression in bone cell size and number at the bone surface have been documented (ref. 27). However, no change was seen in either qualitative or quantitative function of rat kidney calcitriol receptors and thus no causal or effectual role by the system in regulating renal calcium loss was suggested (ref. 28). These and other studies have suggested that the loss of bone mineral in growing rats might be primarily due to inhibited bone formation rather than increased bone resorption (refs. 29 and 30). Rats on the 22-day Cosmos 605 flight showed decreased metaphyseal bone in the vicinity of the epiphyseal cartilaginous plate, suggesting an inhibition of bone growth during flight. It is not yet possible to integrate these findings with the findings from hypokinesia studies on humans and animals in one g because of the complicating factors of time-dependent changes, species differences, and potential differences in the mechanisms by which bone is lost in space and in bed rest or immobilization.

Countermeasures

The major countermeasures being explored to reduce the effects of space flight on the skeleton are the use of various weight-loading exercises or artificial-gravity regimens that counteract the loss of gravitational and muscular stress, and nutritional and pharmacological manipulations. The crews of Skylab 3 and 4 exercised heavily in flight Three of these six people showed substantial mineral losses, which casts doubt on the effectiveness of the particular exercises used as a countermeasure. Findings of U.S.S.R. investigators regarding the effect of in-flight exercise during long-duration space flights have been inconsistent (ref. 7). Nutritional supplements of calcium and phosphorus for short periods of time, and drugs such as fluoride or clodronate, a disphosphonate, show some promise as countermeasures for the effects of bed rest on the skeleton and may be effective for space flight. Because of technical and hardware constraints, artificial gravity has so far been employed only in animal studies, but results have been quite promising. Centrifugation has been shown to prevent changes in calcium and phosphorus content of rat long bones (ref. 25) and to prevent osteoporosis (ref. 31).

Summary and Conclusions

Based on the information obtained from space missions, particularly Skylab and the longer Salyut missions, it is clear that bone and mineral metabolism is substantially altered during space flight. Calcium balance becomes increasingly more negative throughout the flight, and the bone mineral content of the os calcis declines. The major health hazards associated with skeletal changes include the signs and symptoms of hypercalcemia with rapid bone turnover, the risk of kidney stones because of hypercalciuria, the lengthy recovery of lost bone mass after flight, the possibility of irreversible bone loss (particularly the trabecular bone), the possible effects of metastated calcification in the soft tissues, and the possible increase in fracture potential.

For these reasons, major efforts need to be directed toward elucidating the fundamental mechanisms by which bone is lost in space and developing more effective countermeasures to prevent both short-term and long-term complications.

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