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PERSPECTIVE

Perspective: skeletal complications of space flight

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In October 1957, the Russians launched Sputnik 1, the satellite that marked the beginning of space flight. Only 12 years later, on July 20, 1969, the Americans were able to land two astronauts on the moon. During that period, many cosmonauts and astronauts orbited the earth in a variety of spacecrafts. Significant were the ten Gemini missions between 1965 and 1966. These missions put two astronauts in space for as long as 2 weeks. Following these missions, it was immediately apparent that the astronauts had severe vestibular problems, and it became clear that space travel, with exposure to prolonged weightlessness and cosmic radiation, as well as life in very tight environments presented a specific set of medical problems. The specialty of Space Medicine was born.

Numerous other medical problems arise in space flights. In addition to the dizziness of vestibular disturbances, muscle atrophy, circulatory problems, depressed immune response, severe fatigue, and psychological disorders occur. One particularly challenging disorder that the astronauts suffer is bone loss. The bone loss is similar to that which occurs in patients who have been on prolonged bed rest. This latter sort of bone loss was documented in an important study in 1948 [1]. In the early 1960s, astronauts were studied pre- and post-flight with the use of primitive bone density studies. Radiographs of the astronauts' hands were compared to containers with known calcium hydroxylapatite concentrations positioned adjacent to the bone. Even with this inaccurate method, bone loss after short periods of weightlessness was observed [2].

The Skylab project from 1973 to 1979 was the first U.S. space station. This vehicle allowed astronauts to spend as long as 28 days in space. Studies with single photon absorptiometry also documented bone loss in the space station astronauts. However, it was not until the Russian Mir spacecraft, launched in 1986, and the International Space Station, which began functioning in 2000, that astronauts could routinely stay in space from 4 to 6 months. Numerous animal experiments could also be performed in space. These long intervals allowed a more detailed understanding of bone loss.

Maintaining bone mass depends on a balance between bone formation and bone resorption during normal remodeling cycles. If the amount of bone replaced after a resorption phase does not equal the bone removed, bone mass gradually decreases and osteoporosis develops. This inequality of bone formation and bone resorption is the pathogenesis of almost all osteoporotic syndromes. In conditions of accelerated bone turnover, such as occurs in some women following estrogen withdrawal, the incremental deficit in bone formation leads to the more rapid development of osteoporosis.

The causes of diminished osteoblast function seen in osteoporotic syndromes are not entirely understood. Mechanical loading of bone, a factor not present in space flight, is one necessary factor in maintaining osteoblast function. Diminished osteoblast function is a critical factor in the bone loss that develops in weightlessness. Biochemical studies of astronauts in space (diminished serum osteocalcin levels) and studies of animals both before and after space flight or simulated weightless states provide evidence for diminished osteoblast function [3]. Studies have shown that there is a decrease in osteoblast number and activity after space flight [4]. This is most likely a result of interrupted differentiation of osteoblast precursors. This failure of mature osteoblast formation is mediated by a decreased synthesis of integrins,

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particularly beta-3 integrin. Integrins are synthesized locally after mechanical bone stress. They are signaling molecules to activate receptors for IGF-1, an important growth factor for bone formation. Without functioning IGF-1, osteoblasts precursors fail to differentiate into functional osteoblasts [5].

The causes of diminished integrin synthesis during weightlessness are not known. One theory is that shifts in body fluids during space flight are responsible [6]. The normal gradient of capillary pressure that occurs in normal gravity disappears in orbit. In space, capillary micropressure is reduced in the normally weight-bearing bones. Loss of pressure may diminish the bone formation phase in bone remodeling.

Although it is certain that osteoblast function is diminished in microgravity, there is strong evidence that osteoclastic activity is increased. Biochemical markers of resorption are elevated during space flight and remain elevated for several months after returning to gravity. Also, in flight, urinary calcium is increased, indicating bone breakdown. This combination of increased bone resorption with decreased bone formation leads to a high-turnover osteoporosis similar to that which occurs in some post-menopausal women.

As noted earlier, it was not until the landing of the Soviet Mir spacecraft in 1968 and the International Space Station in 2000 that astronauts remained in space for 4–6 months. Studies showed that bone loss begins immediately and that bones are not uniformly affected. Weight-bearing bones such as the lumbar spine and proximal femur are more susceptible. Earlier pre- and post-flight studies with DEXA showed a loss of 1% per month in the lumbar spine and 1.5% per month in the proximal femur [7]. However, quantitative CT studies showed a more severe loss, as high as 2.7%. This modality, now the preferable tool to study bone loss in space, shows most of the bone loss to be cortical. The 2.7% loss shown in the qCT studies is approximately six times the rate of bone loss that occurs in post-menopausal women. An astronaut, after only 6 six months in space, would lose of about 15% of skeletal mass, equal to the loss that would occur in an entire lifetime [8].

However, bone loss in space differs from person to person [9]. The cosmonaut Valeri Polyakov, after the longest continuous space flight on record (408 days), apparently suffered little bone loss. By contrast, U.S. astronaut David Wolf, after 135 days on the Mir spacecraft, lost 12% of his bone mass (he also lost 40% of his muscle mass and 23 lbs). This variability suggests the need for preflight screening for risk factors.

Replacement of lost bone begins on return to gravity, although the process is slow and may never be complete. Most astronauts fully recover their bone mass within 3 years [10]. During this interval, the bones are at risk of fracture. Indeed, despite normalization of density, as seen on DEXA, on the qCT the bones appear to have an altered bone structure that may render them permanently weakened. In microgravity, there is trabecular bone loss in addition to cortical thinning. Beyond a certain point, trabecular connectivity, a feature very important in bone strength, is lost. Although reparative bone may be added to existing trabeculae, normalizing DEXA results, trabecular connectivity can never be restored. Thus the skeletons of astronauts may be permanently weakened.

The observations of skeletal change indicate that bone loss is the limiting factor as to how long humans can be in space. Although the direction of the space program is currently unclear, the Administration still projects that a human voyage to Mars may launch in the year 2030. A voyage to Mars will require nearly 3 years of exposure to microgravity. This duration would be devastating to the skeleton. Much work needs to be done, and cutting back on the space program would hinder research on how to prevent bone loss. There are many possible preventative modalities that need to be further studied before long periods of weightlessness can be endured. In the early years, astronauts spent as much as 2 h/day in space exercising with stationary bicycles and weight machines. Unfortunately, these procedures did little to prevent bone loss. More recently on the International Space Station, exercises are performed on a treadmill with heavy straps to simulate gravity. This method is also not very effective. In addition to exercise, there is promise in vibrating platforms on which the whole body stands and a constant vibration is delivered that may stimulate osteoblasts. Indeed, these vibrating platforms are currently used to treat osteoporotic patients on earth. Individuals can buy these platforms for about $200.

Drug therapy is possibly another effective way to prevent bone loss. Astronauts could take long-acting bisphosphonates, such as Zoledronate, to slow down the bone resorption and the resulting bone loss. Another osteoclast inhibitor, osteoprotegerin, has been suggested. This drug is highly effective and works by inhibiting RANKL binding to its receptor on osteoclasts. Also, since exposure to cosmic radiation may contribute to bone loss, tightly shielding spacecraft from radiation may also slow bone loss. Finally, diets high in omega-3s and other antioxidants, such as those found in blueberries, may promote bone health in space.

At present we do not know if we will be able to prevent bone loss thereby allowing humans to have long periods of weightlessness. However, research in this area has a spinoff into general health. These studies of microgravity have emphasized the critical importance of mechanical forces on the skeleton to prevent osteoporosis [11]. This information will inform treatment of osteoporosis of aging and help us understand how to prevent bone loss in patients who must be immobilized.

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