Physiology of a Microgravity Environment
Invited Review: What do we know about the effects of spaceflight on bone?

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Turner, Russell T. Invited Review: What do we know about the effects of spaceflight on bone? J Appl Physiol 89: 840–847, 2000.—This review of the peer-reviewed literature focuses on the effects of spaceflight on bone. Studies performed in humans and laboratory animals have revealed abnormalities in bone and mineral metabolism that suggest that long-duration spaceflight will have detrimental effects on the skeleton. However, because of large gaps in our knowledge, it is not presently possible to estimate the magnitude of the health risk, individual variations in risk, effective countermeasures, or mechanism(s) of action. Specific recommendations are made for future research to ascertain risk and develop appropriate countermeasures.

gravity; osteoporosis; weightlessness; space travel; microgravity; mineral metabolism

The force imparted by Earth’s gravitational field (gravity) has shaped the form and function of biological systems. Life evolved on Earth exposed to a constant, nearly uniform gravity. Our species is no longer constrained by gravity; advances in physics during the 17th century and in spacecraft technology during the 20th century have made routine interplanetary travel theoretically possible. However, if we choose to travel to, live on, and explore other planets, it will be necessary for humans to adapt to changes in gravity. Our knowledge regarding human adaptation to long-duration spaceflight appears to lag well behind the physics, engineering, and hardware required for such travel. The purpose of this review is to evaluate our understanding of the skeletal consequences of long-duration spaceflight.

Portions of the human skeleton are subjected to large but transient mechanical loads that oppose the gravitational vector during normal activities such as walking and lifting. Because of the fundamental importance of dynamic gravitational loading, it is reasonable to expect that the skeletal system would be especially sensitive to changes in gravity.

The majority of space biology research involving the skeleton has focused on reduced loading and centrifugation. These ground-based studies suffer from incomplete validation and discrepancies with spaceflight (33, 52). Therefore, this review will focus on studies performed during spaceflight. This is not to diminish the importance of Earth-based models. They are essential for the most productive utilization of the limited opportunity to perform spaceflight research. However, by focusing on spaceflight studies, the gaps in our knowledge will become more apparent.

WEIGHT IS MORE IMPORTANT THAN GRAVITY

No space biology studies have been performed in a gravity-free environment. Similarly, the biological effects of increased gravity are purely conjectural. All animal and cell studies and all human space exploration, with the notable exception of lunar exploration, have been performed on Earth or in low Earth orbit.
There is no experimental evidence for or against direct effects of a gravitational field on biological processes (e.g., interaction with the putative “gravity wave”). There is, however, good reason to believe that the net force imparted by gravity on the skeleton (weight) and not the strength of the gravitational field is the important variable.

To review the relevant physics, the direction of the gravitational vector of an orbiting astronaut is identical to that of an individual standing on the Earth’s surface: both are pointed toward the center of Earth’s mass. The magnitude of this vector is dependent only on the distance of both individuals from the Earth’s center. For typical orbital spaceflight, the astronaut’s distance from the Earth’s center has increased <5% compared with an individual on the Earth’s surface. Thus orbital spaceflight results in minimal decreases in gravity. On the other hand, an astronaut is essentially weightless. This lack of weight is not because of a lack of gravity but rather is due to free fall, which means that the scale used to measure weight and the weight to be measured (the astronaut) are being accelerated (by gravity) identically. As a result, no weight is registered by the scale. Because gravity is little influenced by orbital spaceflight, whereas weight is dramatically decreased, it can be concluded that the biological effects of spaceflight are more likely to be due to changes in weight than to changes in gravity. Weight acts on the skeleton by imparting a mechanical load. Earth-based studies suggest that dynamic loading during walking and lifting is more important to normal growth and maintenance of the skeleton than resting loads.

WE DON'T KNOW MUCH ABOUT THE EFFECTS OF SPACEFLIGHT ON THE HUMAN SKELETON

Four decades of spaceflight have yielded a modest number of published peer-reviewed studies dealing with adaptation of the human skeleton to spaceflight (Table 1). On one hand, there are major difficulties that must be overcome to perform spaceflight studies. Investigations are limited to a small pool of potential subjects. The subjects’ age, nutritional status, and exercise levels, as well as flight duration, vary. Measurements and sampling that are taken for granted on Earth cannot be routinely performed during spaceflight due to inadequacies in procuring, preserving, and storing labile samples. On the other hand, this lack of progress is remarkable given that the detrimental musculoskeletal changes caused by chronic exposure to weightlessness are widely believed to be a limiting factor for long-duration space exploration. The outstanding successes of the space program in other areas lead to the conclusion that human bone biology has not received a high priority.

The most consistent observation made to date is that spaceflight results in chronic changes in calcium balance. A negative calcium balance is produced by a reduction of intestinal absorption and an increase in excretion through the gastrointestinal tract and kidneys (20, 23, 40). In contrast, the effects of long-duration spaceflight on bone mineral density show considerable individual as well as site variation. The greatest bone losses have been observed in the lower body, specifically in pelvic bones, lumbar vertebrae, and the femoral neck (21). The potential differential effects of spaceflight on cortical and cancellous bone have not been investigated. Evidence suggests that the magnitude of bone loss may be related to the duration of the flight, but no exact relationship has been established.

Mechanisms for the variations in bone loss are not understood. Studies of biochemical markers of bone turnover have been reported for a small number of subjects. Bone formation markers have been reported to increase, remain constant, and decrease after spaceflight (1, 6, 10, 23, 40). In contrast, bone resorption markers have been reported to be increased during flight (39) and unchanged or increased after flight (6, 10, 23, 40). Thus it is not clear whether the bone loss is associated with increased bone remodeling, reduced bone remodeling, or an uncoupling between bone formation and resorption. The reported differences need not be contradictory. Blood and urine were generally obtained after spaceflight; therefore,

Table 1. Effect of spaceflight on human bone and mineral metabolism

<table>
<thead>
<tr>
<th>Duration</th>
<th>Principal Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–84 days</td>
<td>Time-dependent decrease in BMD with failure to return to preflight values after 5 yr</td>
<td>43</td>
</tr>
<tr>
<td>28–84 days</td>
<td>Urinary calcium increased during flight</td>
<td>55</td>
</tr>
<tr>
<td>60 days</td>
<td>Urinary calcium increased during flight</td>
<td>56</td>
</tr>
<tr>
<td>51 days</td>
<td>Bone resorption markers increased; no change in bone formation markers</td>
<td>1</td>
</tr>
<tr>
<td>1 and 6 mo</td>
<td>Bone formation markers decreased; no change in bone resorption markers</td>
<td>10</td>
</tr>
<tr>
<td>4.5–14.5 mo</td>
<td>Decreased BMD in lower body; no change in upper skeleton</td>
<td>21</td>
</tr>
<tr>
<td>180 days</td>
<td>Serum PTH decreased; decreased formation markers and increased resorption markers</td>
<td>6</td>
</tr>
<tr>
<td>28–84 days</td>
<td>Urinary collagen breakdown products increased during flight</td>
<td>39</td>
</tr>
<tr>
<td>3 mo</td>
<td>Calcium intake and absorption decreased; urinary calcium increased; bone resorption and formation markers increased</td>
<td>40</td>
</tr>
<tr>
<td>21 days</td>
<td>Ionized calcium increased; serum 1,25-dihydroxyvitamin D decreased; bone formation markers decreased and resorption markers increased</td>
<td>23</td>
</tr>
<tr>
<td>30–428 days</td>
<td>Increased serum calcium and PTH; decreased calcitonin</td>
<td>20</td>
</tr>
<tr>
<td>115 days</td>
<td>Decreased intestinal calcium absorption; increased gastrointestinal and kidney calcium excretion</td>
<td></td>
</tr>
</tbody>
</table>

BMD, bone mineral density; PTH, parathyroid hormone.
biochemical markers of bone turnover may reflect variation in individual responses to restored weight bearing or to weightlessness. Additionally, a transient increase in bone remodeling followed by a net decrease in bone formation could yield dramatically different results, depending on the timing of the sampling. These conjectures merely serve to illustrate the pressing need for more longitudinal inflight measurements.

Published peer-reviewed spaceflight studies of laboratory animals are compiled in Table 2. Animal studies have several theoretical advantages over human studies for investigating the effects of spaceflight on bone and mineral metabolism: the experimental conditions can be more carefully controlled, the subject population

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Duration, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growing male rat; tibia</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; vertebrae</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; non-weight-bearing bones</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; $^{44}$Ca/$^{48}$Ca kinetics</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; femur</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; tibia and humerus</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; tibia and humerus</td>
<td>18</td>
</tr>
<tr>
<td>Growing male rat; tibia</td>
<td>18</td>
</tr>
<tr>
<td>Rapidly growing male rat; humerus and lumbar vertebrae</td>
<td>7</td>
</tr>
<tr>
<td>Pregnant growing rats; loaded (tibia and femur) and unloaded (thoracic and lumbar vertebrae) bones</td>
<td>5</td>
</tr>
<tr>
<td>Growing male rat; humerus</td>
<td>14</td>
</tr>
<tr>
<td>Growing male rat; vertebrae, calvaria, and mandible</td>
<td>12</td>
</tr>
<tr>
<td>Growing male rat; tibia and lumbar vertebrae</td>
<td>7</td>
</tr>
<tr>
<td>Growing male rat; humerus</td>
<td>7</td>
</tr>
<tr>
<td>Growing male rat; jaw</td>
<td>varied</td>
</tr>
<tr>
<td>Growing male rat; vertebrae</td>
<td>12</td>
</tr>
<tr>
<td>Growing male rat; humerus</td>
<td>12</td>
</tr>
<tr>
<td>Growing male rat; peridontal ligament</td>
<td>12</td>
</tr>
<tr>
<td>Growing male rat; tibia</td>
<td>7</td>
</tr>
<tr>
<td>Growing male rat; humerus</td>
<td>14</td>
</tr>
<tr>
<td>Growing male rat; tibia and metatarsal tendons</td>
<td>14</td>
</tr>
<tr>
<td>Growing male rat; tibia and lumbar vertebrae</td>
<td>14</td>
</tr>
<tr>
<td>Growing male rat; tibia, femur, and thoracic vertebrae</td>
<td>14</td>
</tr>
<tr>
<td>Rapidly growing male rat; non-weight-bearing (calvaria) and weight-bearing (long bones)</td>
<td>4, 10</td>
</tr>
<tr>
<td>Growing male rat; tibia</td>
<td>6</td>
</tr>
<tr>
<td>Growing male rat; femur and tibia</td>
<td>11</td>
</tr>
<tr>
<td>Rapidly growing male rat; humerus</td>
<td>4, 10</td>
</tr>
<tr>
<td>Rapidly growing male rat; femur, humerus, and calvaria</td>
<td>4</td>
</tr>
<tr>
<td>Rhesus monkey; iliac crest</td>
<td>11</td>
</tr>
<tr>
<td>Growing male rat; tibia</td>
<td>13–14</td>
</tr>
<tr>
<td>Growing male rat; humerus and caudal vertebrae</td>
<td>14</td>
</tr>
<tr>
<td>Rapidly growing male rat; thoracic vertebrae</td>
<td>14</td>
</tr>
<tr>
<td>Rapidly growing male rat; weight-bearing and non-weight-bearing bones</td>
<td>14</td>
</tr>
<tr>
<td>Growing OVX rats; tibia</td>
<td>14</td>
</tr>
<tr>
<td>Growing OVX rat; tibia and femur</td>
<td>14</td>
</tr>
<tr>
<td>Growing male rat; femur</td>
<td>14</td>
</tr>
<tr>
<td>Growing OVX rat; tibia and femur</td>
<td>14</td>
</tr>
<tr>
<td>Rapidly growing male rat; femur, tibia, humerus, vertebrae, and calvaria</td>
<td>14</td>
</tr>
<tr>
<td>Rapidly growing male rat; tibia, femur, and humerus</td>
<td>10</td>
</tr>
<tr>
<td>Chicken embryogenesis</td>
<td>7</td>
</tr>
<tr>
<td>Fetal rat; calvariae</td>
<td>9</td>
</tr>
<tr>
<td>Rapidly growing male rat; tibia, lumbar vertebrae, and femur</td>
<td>17</td>
</tr>
</tbody>
</table>

$OVX$, ovariectomized; IGF-I, insulin-like growth factor I; TGF-$\beta$, transforming growth factor-$\beta$. 

LABORATORY ANIMAL STUDIES HAVE PROVIDED LIMITED ADDITIONAL INSIGHT
is more uniform, and more invasive techniques can be used. However, the enormous potential for meaningful animal investigation has not been exploited. Only small numbers of immature animals have been flown at one time, and no longitudinal studies have been performed. Crew interaction with the animals during spaceflight has been uncommon. Thus most studies have been observational. Animal experiments have been of relatively short duration (4–18 days) compared with human flights aboard Skylab (up to 84 days) and Mir (≥1 yr).

With the exception of one spaceflight study in monkeys (62) and another investigating embryogenesis in chickens (42), the rat has been the animal model of choice for bone research. The rat is an established model for many aspects of human bone metabolism, but it has some limitations. The lack of a well-developed Haversian system renders most small mammals, including the rat, unsuitable for investigating the effects of spaceflight on cortical bone remodeling. All spaceflight studies have been performed in growing rats because either the investigator 1) was primarily

<table>
<thead>
<tr>
<th>Principal Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased periosteal bone formation; increased arrest line perimeter</td>
<td>34</td>
</tr>
<tr>
<td>No change in calcium and collagen content; increased keratosulfate content; delayed postflight decrease in calcium content and increase in chondroitin sulfate</td>
<td>17</td>
</tr>
<tr>
<td>No change in periosteal bone formation in the non-weight-bearing ribs and regions of mandibles covered by masticatory muscles</td>
<td>38</td>
</tr>
<tr>
<td>No increase in bone resorption</td>
<td>7</td>
</tr>
<tr>
<td>Impaired strength</td>
<td>41</td>
</tr>
<tr>
<td>Decreased cancellous bone volume and increased fat volume</td>
<td>26</td>
</tr>
<tr>
<td>Decreased periosteal bone formation</td>
<td>58</td>
</tr>
<tr>
<td>Abnormal matrix ultrastructure and hypomineralization</td>
<td>45</td>
</tr>
<tr>
<td>Impaired strength and altered composition</td>
<td>35</td>
</tr>
<tr>
<td>No change in bone mass; increased osteoclast surface on cancellous bone</td>
<td>51</td>
</tr>
<tr>
<td>No change in mechanical properties, geometry, or composition</td>
<td>48</td>
</tr>
<tr>
<td>Bone ash reduced in vertebrae but not non-weight-bearing calvaria or mandibles; impaired matrix-mineral maturation in calvaria as well as vertebrae</td>
<td>37</td>
</tr>
<tr>
<td>Nonsignificant tendency for decreased periosteal bone formation; no changes in cancellous bone</td>
<td>59</td>
</tr>
<tr>
<td>Minimal changes in morphology; impaired maturation of bone strength and stiffness</td>
<td>36</td>
</tr>
<tr>
<td>No impairment of function</td>
<td>28</td>
</tr>
<tr>
<td>Altered osteoblast and vasculature ultrastructure</td>
<td>13</td>
</tr>
<tr>
<td>Reduced maturation of cancellous bone</td>
<td>63</td>
</tr>
<tr>
<td>Altered bone geometry and impaired strength</td>
<td>48</td>
</tr>
<tr>
<td>Increased preosteoblast production 55 h after flight</td>
<td>19</td>
</tr>
<tr>
<td>Cancellous osteopenia in proximal tibial metaphysis</td>
<td>52</td>
</tr>
<tr>
<td>Fracture healing impaired</td>
<td>15</td>
</tr>
<tr>
<td>No change in bone geometry, composition, or strength</td>
<td>47</td>
</tr>
<tr>
<td>Less dramatic changes in osteoblasts and vasculature; tibial collagen disorganization of tendons</td>
<td>14</td>
</tr>
<tr>
<td>Increased height of proliferative zone and decreased height of hypertrophy/calcification zone</td>
<td>33</td>
</tr>
<tr>
<td>Reduced primary spongiosa width in tibia; evidence for physiological stress-induced changes</td>
<td>50</td>
</tr>
<tr>
<td>Time-dependent decrease in periosteal bone formation; reduced mRNA levels for bone matrix proteins and alkaline phosphatase</td>
<td>2</td>
</tr>
<tr>
<td>Increased mRNA levels for IGF-I, IGF-I receptor, and alkaline phosphatase; decreased mRNA levels for osteocalcin</td>
<td>5</td>
</tr>
<tr>
<td>Decreased periosteal bone formation and reduced mRNA levels for type 1 collagen and TGF-β; no changes in mRNA levels in cancellous bone</td>
<td>53</td>
</tr>
<tr>
<td>Time-dependent decrease in cancellous bone formation</td>
<td>46</td>
</tr>
<tr>
<td>No change in periosteal or endocortical bone formation or femur longitudinal growth; growth hormone increased bone formation at most sites in flight as well as in ground control rats</td>
<td>44</td>
</tr>
<tr>
<td>Decreased mineral apposition and surface</td>
<td>62</td>
</tr>
<tr>
<td>Cancellous osteopenia</td>
<td>16</td>
</tr>
<tr>
<td>Decreased cancellous bone volume and osteoblast surface in humerus; no change in cancellous bone volume and decreased osteoblast surface in vertebrae; no change in osteoclast surface</td>
<td>61</td>
</tr>
<tr>
<td>No change in mechanical hardness, BMD, or bone area</td>
<td>27</td>
</tr>
<tr>
<td>Altered trace element composition</td>
<td>60</td>
</tr>
<tr>
<td>Cancellous bone loss from proximal epiphysis</td>
<td>54</td>
</tr>
<tr>
<td>Cancellous osteopenia due to accelerated bone resorption; decreased periosteal bone formation and mRNA levels for bone matrix proteins; no change in cancellous bone formation and mRNA levels for bone matrix proteins, TGF-β, and IGF</td>
<td>9</td>
</tr>
<tr>
<td>Compartment- and matrix protein-specific changes in mRNA levels</td>
<td>18</td>
</tr>
<tr>
<td>Increased mRNA levels for specific cytokines</td>
<td>64</td>
</tr>
<tr>
<td>Bone- and compartment-specific deficits in bone mass and altered bone architecture</td>
<td>31</td>
</tr>
<tr>
<td>No decrease in periosteal bone formation, mass, and strength; IGF-I treatment increased bone formation, mass, and strength</td>
<td>3</td>
</tr>
<tr>
<td>Cartilage and bone formed normally</td>
<td>42</td>
</tr>
<tr>
<td>No change in collagenase and tissue plasminogen activator production after in utero exposure to spaceflight</td>
<td>12</td>
</tr>
<tr>
<td>No effect on bone formation</td>
<td>57</td>
</tr>
</tbody>
</table>

OVX, ovariectomized; IGF-I, insulin-like growth factor I; TGF-β, transforming growth factor-β.
interested in the effects of spaceflight on bone growth, or 2) was forced to use young rats because weight restrictions would result in inadequate statistical power if a smaller number of heavier, older rats were flown. The growing rat is an established model for studying the skeleton of growing humans but is a problematic model for the adult human. The principal processes that determine cortical and cancellous bone mass and architecture during growth (periosteal bone formation and endochondral ossification) differ from processes in adults (endocortical and cancellous remodeling).

The periosteal bone formation rate in bones in growing rats is often reduced during spaceflight, thereby resulting in a “relative” osteopenia (2, 9, 16, 34, 50, 58). The decrease has been reported in ovariectomized (OVX) and male rats. The term “relative” indicates that the deficit in bone mass was due to a failure to add as much bone and distinguishes the changes from those observed in adult humans in whom the osteopenia results from a net bone loss. Bone formation may be inhibited after as few as 4 days of spaceflight and is associated with decreased mRNA levels for bone matrix proteins (2, 5, 18, 53). The molecular mechanism is unknown, but there is evidence for changes in selected cytokines (e.g., transforming growth factor-$\beta$ and insulin-like growth factor 1) that have been implicated in the regulation of bone formation (5, 53, 64). Structural changes in the growth plate are consistent with disturbed longitudinal bone growth (33), but no changes in the rate of endochondral bone growth rate during spaceflight have been measured (44).

Impaired cortical bone mechanical properties have been observed after spaceflight (35, 41, 48). In part, the deficit appears to be due to altered bone geometry associated with an observed reduction in the periosteal bone formation rate (41, 48). However, evidence for altered bone matrix ultrastructure and mineralization has been reported, suggesting that spaceflight may result in a degradation of bone material properties as well (31, 32, 35, 37, 45). The altered geometry and abnormal material properties are associated with site- and gene-specific changes in expression of bone matrix proteins (5, 18).

The effects of spaceflight on material and mechanical properties of cancellous bone have not been investigated. However, spaceflight has been reported to inhibit bone formation and induce bone loss at cancellous sites in monkeys (62) and rats (16, 26, 27, 46, 51, 52, 59). One study suggests that spaceflight may inhibit normal bone repair following fracture (15).

There is minimal evidence that spaceflight increases bone resorption at either cortical or cancellous bone sites in growing male rats (7). In contrast to males, the osteoclast number increased in pregnant growing rats (51). Spaceflight accelerated OVX-induced cancellous bone loss in the proximal tibial metaphysis and induced bone loss in the epiphysis (9, 54). The bone loss in the metaphysis of OVX rats was due to excess bone resorption; there was no reduction in bone formation (9). These results suggest that there may be sex differences related to gonadal hormone levels that influence the skeletal response to spaceflight.

It is important to emphasize that skeletal abnormalities have not been observed in all spaceflight studies. There is evidence that nonweight-bearing bones are less affected by spaceflight than weight-bearing bones (28, 31, 37, 38) and that the skeletal effects of spaceflight are progressive (2, 46). However, changes are not always detected in weight-bearing bones after spaceflight (3, 14, 17, 27, 36, 44, 47, 48, 53, 57, 59, 61). These negative studies suggest that the effects of spaceflight may be influenced by caging conditions, age, or other unknown factors.

### Table 3. Effects of spaceflight on bone cell and organ cultures

<table>
<thead>
<tr>
<th>Cell/Organ Culture</th>
<th>Duration</th>
<th>Principal Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal mouse; long bones</td>
<td>4 days</td>
<td>No change in growth and collagen synthesis; decreased glucose utilization and mineralization; increased resorption</td>
<td>49</td>
</tr>
<tr>
<td>MC3T3-E1 cells</td>
<td>9 days</td>
<td>Decreased cell number, glucose utilization, and prostaglandin synthesis; altered morphology</td>
<td>25</td>
</tr>
<tr>
<td>Marrow-derived osteoblastic cells</td>
<td>5 days</td>
<td>Increased prostaglandin production and IL-6 mRNA levels</td>
<td>30</td>
</tr>
<tr>
<td>Alkaline phosphatase positive cells from caudal vertebrae</td>
<td>14 days*</td>
<td>No change in cell growth or matrix protein production</td>
<td>61</td>
</tr>
<tr>
<td>MG63 osteosarcoma cells</td>
<td>9 days</td>
<td>Decreased hormone-induced mRNA levels for type 1 collagen, alkaline phosphatase, and osteocalcin</td>
<td>8</td>
</tr>
<tr>
<td>MN-7 preosteoblasts</td>
<td>9 days</td>
<td>Altered cell ultrastructure; Decreased growth and $\Delta^{45}$Ca incorporation; no change in $\Delta^{45}$Ca liberation</td>
<td>4</td>
</tr>
<tr>
<td>Embryonic mouse; premetatarsal triads</td>
<td>2.5–43 h</td>
<td>Transient decrease in fibronectin synthesis followed by normalization</td>
<td>24</td>
</tr>
<tr>
<td>MC3T3-E1 cells</td>
<td>17 days</td>
<td>No change in growth, glucose utilization, collagen and PGE$_2$ synthesis, morphology, and mRNA levels for bone matrix proteins; decreased mRNA levels for TGF-$\beta_1$, TGF-$\beta_2$, IL-1$\alpha$, and IL-6</td>
<td>22</td>
</tr>
</tbody>
</table>

IL, interleukin; hFOB, human fetal osteoblastic. *Cells isolated and cultured following spaceflight.
IN VITRO STUDIES HAVE NOT PROVIDED ADDITIONAL INSIGHT INTO THE SKELETAL EFFECTS OF SPACEFLIGHT

Several in vitro bone cell and organ culture studies have been published (Table 3). These studies describe the growth and differentiation of organ cultures, primary cultures, and cell lines during or after spaceflight. A wide variety of results has been obtained, which may be due in part to differences in the culture systems. The propagation and expression of differentiated bone cell function during spaceflight may prove to be of value for biotechnological applications, but such studies to date have contributed no insight into the skeletal effects of spaceflight. In general, in vitro systems have proven to be of little predictive value as models for bone physiology. This is not surprising because the complex cell-to-cell, systemic, and mechanical interactions that define physiology are not preserved under culture conditions. The normal gulf between physiological bone remodeling and cell culture systems is further widened when cell culture is used for spaceflight research because of the great differences in loading conditions experienced by bone cells in vivo vs. in cell culture (11).

SUMMARY

Abnormalities in bone and mineral metabolism have been identified in astronauts after spaceflight, raising the concern that long-duration missions may have a negative impact on astronaut health. However, the magnitude of bone loss can be predicted for individual astronauts for neither skeletal site nor duration of flight. The inability to predict the magnitude of bone loss or recovery time makes it presently impossible to estimate the health risk. The skeletal changes during spaceflight are associated with altered calcium homeostasis and abnormal bone turnover, but the precise relationships between endocrine changes, reduced calcium absorption, increased calcium excretion, altered bone formation and resorption, reduced impact loading, and site-specific bone loss have not been established. Without an understanding of the mechanism(s) of action, effective prevention or treatment of bone loss is unlikely.

Spaceflight can disrupt bone growth, induce bone loss, and result in impaired bone material and mechanical properties in growing animals, but the flight conditions can influence the response. The effects of spaceflight on cortical and cancellous bone remodeling remain largely uninvestigated. Therefore, animal studies have been of limited value for modeling the effects of long-duration spaceflight on the adult human skeleton.

It is likely that a bone fracture will occur during spaceflight, eventually. The outcome of a fracture cannot be reliably predicted because of the paucity of research.

RECOMMENDATIONS

Applied to low Earth orbit or ground-based research, terminology such as microgravity, gravity free, zero gravity, and hypergravity has inadvertently impeded progress by encouraging investigators to conclude that any changes observed during spaceflight are due to altered gravity. This myopic view has discouraged consideration of the complex environmental changes encountered by astronauts, animals, and cultured bone cells during spaceflight. An improved appreciation of how the overall spacecraft environment interacts with weight change is likely to accelerate future progress in understanding the implications of long-duration space travel for the skeleton.

To understand the skeletal consequences of spaceflight and to validate countermeasures, it will be necessary to perform carefully controlled (age, gender, mass, nutrition, exercise, etc.) longitudinal studies in astronauts with long-term postflight follow-up. Frequent sampling of hormones that regulate bone mass, indexes of calcium balance, and biochemical markers of bone formation and resorption throughout many spaceflights is essential to elucidate time-dependent changes. Pre- and postflight measurements of bone mineral density are essential to evaluate site-specific changes in bone mass. Bone biopsies would be very valuable to evaluate the quality of the bone produced during spaceflight, as well as remodeling balance, architectural changes, and strength. It will be necessary to have suitable hardware for routine in-flight procurement and storage of blood and urine.

Long-term studies with appropriate animal models should be performed to uncover details of the cellular mechanisms that mediate spaceflight-induced bone changes, the knowledge of which is essential to design countermeasures. For example, antiresorbing agents are not an ideal choice as a countermeasure if the principal defect is reduced bone formation. Similarly, sex or age differences may preclude a “one countermeasure fits all” approach. Ground-based simulation models are valuable for exploring promising ideas but are no substitute for spaceflight because they do not result in weightlessness. It is imperative that hardware and crew time be made available to perform intervention studies during spaceflight. Carefully designed in vitro studies using validated cell models, while not capable of mimicking bone physiology, could advance our understanding of the mechanisms by which a mechanical force is detected by bone cells. No adequate in vitro models are presently available for weightlessness. Therefore, a high priority should be placed on attempting to improve and validate cell culture models for free fall.

The international space station could provide the platform necessary to perform the spaceflight studies recommended by the author. Failure to allocate sufficient resources to accomplish this task will impede advancement of knowledge in gravitational skeletal...
biology, which in turn will limit the capabilities of human space exploration.

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