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Perspective Article

Summary - Bone in Microgravity Environments: "Houston, we have a problem"

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With the recent change in leadership at NASA, a sea change in research priorities at the agency has occurred. Monies once dedicated to life science research have been dramatically reduced in order to provide resources for development of a new Crew Exploration Vehicle, designed to replace the aging shuttle vehicles. Bone loss during spaceflight, once considered a "show-stopper" when long duration exploration missions were more central to NASA planning, no longer commands center stage. The prevailing sentiment appears to be that changes in bone with short-term missions to the International Space Station (ISS) or to the lunar surface will be too small to impact on mission outcomes and will be successfully mitigated with current exercise countermeasures, perhaps in combination with bisphosphonate therapy. Strategies to minimize bone loss with long-term spaceflight (e.g., 2-3 years' duration) may not be necessary 10 years from now some speculate, given projections of improved pharmacological treatments or even the integration of artificial gravity on board exploration vehicles. It behooves bone biologists to carefully define the specific challenges to bone integrity incurred during (or following) the shorter 3- to 6-month Lunar or ISS missions planned for the next 10 years. Data presented during this session illustrate well that, with reference to microgravity effects on bone integrity, there is too much of "we don't know what we don't know".

The key health risk to working astronauts associated with the reduced bone mineral density (BMD) and altered bone geometry is bony fracture. A hip fracture could be devastating to astronaut health as well as mission objectives, and difficult to treat. Data recently published by speaker **Thomas Lang**[1] demonstrated significant decrements in BMD of femoral neck cancellous bone and dramatic thinning of the cortical shell in ISS astronauts; estimates are that 90% of the bone loss observed resulted from endocortical resorption. Using a patient-specific finite element modeling approach[2], Lang and colleague Joyce Keyack have performed safety factor analyses to predict the risk of fracture given these carefully quantified changes in astronaut crew members. The challenge of these analyses, of course, lies in the many assumptions that must be made to perform the modeling, introducing increasing levels of uncertainty. Although these analyses predict no increase in fracture risk for a fall to the side while on the Mars surface (3/8 g), they do reveal a significant increase in fracture risk in more than half of the astronauts on whom CT data were collected for a fall to the side upon return to the 1 g of Earth. In fact, the average factor of risk for all crew members studied (presuming a fall to the side in 1 g) matched that estimated for 70- to 80-year-old postmenopausal women. Given the documented perturbations in dynamic postural stability post-spaceflight, falling risk is presumably increased in the first days or weeks upon return to Earth, further increasing risk of fracture in the postflight period.

Recent reports on recovery of BMD[3] indicate that most astronauts slowly recover lost bone mineral, but require on average 3 years to do so. We have no available data to judge whether cortical thinning of the femoral neck is reversible, which also impacts on resistance to fracture at this site. If the multiple assumptions made in these finite element analyses are judged valid, it would be prudent to assume that all astronauts returning from flights of 5 or more months in duration are at much higher than average risk for fracture if a serious fall occurs in the ensuing months.

If a fracture does occur in-flight or on the Lunar/Mars surface, will it heal normally? Again, there is a real paucity of solid data on which to make a conclusion, with all of four peer-reviewed publications identified on this topic. Interesting data acquired in male adult rats subjected to tail suspension (a well-validated model for simulating microgravity effects on hindlimb bone) and then to a fibular osteotomy are presented by **Ron Midura**. In this model, fracture healing in the tail-suspended rats is impaired; the resulting callus is

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smaller and its strength inferior to those in normally weight-bearing rats subjected to the same osteotomy procedure. Intriguing evidence is presented that a primary mechanism for this impaired fracture healing is a reduction in osteoprogenitor cell populations in marrow harvested from tail-suspended rats. Given that astronauts will be performing significant work tasks to establish a Lunar landing base, work-related accidents that incur a high risk of fracture are a distinct possibility. Should the worst-case scenario evolve (a non-union fracture), serious health consequences might be incurred. There are no doubt many "unknown unknowns" in this area as well, and further research is justified.

Two papers address the primary countermeasure strategies for bone loss with spaceflight considered most feasible at this time: exercise and targeted pharmacological agents. This author (**Susan Bloomfield**) presents data collected by collaborator Michael Delp[4] demonstrating reductions in blood flow to most bone sites after short- and long-term tail suspension in rats, along with decreased perfusion pressure to the hindlimb. Data from Yi-Xian Qin's group[5] demonstrate that oscillations in intramedullary pressures, which derive in part from blood flow to bone, are intimately related to the osteogenic response to mechanical loading. Given the well-documented cephalic fluid shifts with microgravity, the reduced bone blood flow in simulated microgravity in rodents, and the continuing bone loss observed in ISS crew members[1], who are required to exercise on a daily basis, it is reasonable to speculate that fluid shear stress signals to bone cells are significantly reduced in the microgravity environment. That is, can mechanosensitive bone cells in the unloaded limbs effectively 'hear' the loading signal even during vigorous exercise? Promising results from Alan Hargens and collaborators testing the effects of lower body negative pressure (which pulls fluids into the legs) combined with treadmill running suggest that maintaining adequate bone perfusion pressures, at least during planned exercise, could better maintain bone integrity during exposure to microgravity[6].

Only oral bisphosphonates (of all FDA-approved osteoporosis agents) have been tested during bed rest campaigns of the last 10 years, with some degree of efficacy[7]. **Jay Shapiro** effectively outlines the list of "known unknowns" regarding the multiple physiological mechanisms that might account for altered pharmacokinetics of any drug administered during spaceflight. In addition, there are very few published data documenting how drug absorption, distribution and metabolism are affected by living in microgravity. In this area, there will be no effective animal substitute for actual testing of candidate pharmacological agents in humans during spaceflight. It would appear prudent to start verifying efficacy of those agents already tested and in use by millions of earth-bound Americans.

Beyond the practical problem of minimizing negative alterations in bone with prolonged microgravity, more basic studies on mechanisms for the altered osteoblast phenotype might suggest other effective strategies. **Laurence Vico** presents compelling data on alterations in the cytoskeleton and focal adhesion contacts in cultured osteoblasts exposed to real and simulated microgravity that result in alterations in cell shape and intracellular tension. Various regulators of cytoskeletal proteins, such as P21 Rho A, are implicated in these changes. This discussion effectively illustrates how microgravity-based research can contribute back to more basic inquiries into mechanotransduction. Any further reductions in funding for these basic gravitational biology inquiries represent a lost opportunity.

It is clear there is a plethora of unanswered questions about mechanisms for bone loss with spaceflight, about the true fracture risk and the potential for normal fracture healing even after ISS missions, and about the efficacy of exercise and pharmacological countermeasures (currently in use or proposed). Those charged with protecting astronaut health and safety, and those researchers interested in contributing to that goal, must work diligently to keep these issues front and center if we are to provide a reasonably safe working environment for those individual humans exploring new space environments.

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