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Mechanisms of Bone Loss in Space

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The unique conditions of microgravity and radiation exposure in space have a substantial impact on human tissue function, resulting in extreme bone loss. The goal of this project is to synthesize the current knowledge on bone loss in space for use in future research. There is clear evidence, based on past research, that microgravity, cosmic radiation, fluid flow, and mechanotransduction influence bone function during space travel and result in significant loss. However, there is a need for future research on how these factors relate to each other and their collective influence on mechanisms of bone regeneration and repair. In addition, there is a need for more research on potential solutions to prevent the bone loss seen during space travel.

Normal Mechanisms of Bone Regeneration and Repair

- Achieved through the actions of osteoblasts, osteoclasts, osteocytes, and bone lining cells
- Osteocytes detect bone damage to bone and signal this to bone lining cells via factors, such as PGE2, PG12, NO, and IGF-1
- Bone lining cells recognize and respond by recruiting osteoclast precursors to the site of damage
- Osteoclast precursors maturation mediated by RANK-L
- Osteoclasts digest bone through excretion of acid that degrades hydroxyapatite
- Undergo apoptosis – initiated by osteoprotegrin (OPG)
- Osteoblasts recruited to area of newly digested bone by growth factors: IGF-1, IGF-2, TGFβ1, and TGFβ2
- Osteoblasts deposit osteoid in cavity ➔ mineralized to form new bone

Potential Solutions

Combating Fluid Flow Effects
- Biophosphonate: inhibits osteoclast activity
- Intermittent Compression: improves blood flow to affected limb
- miR-33-5p Supplementation: promotes osteoblast differentiation
- mL1P8: promotes osteoblast proliferation

Combating Radiation Effects
- Amifostine: protects cells from DNA damage caused by radiation
- Antioxidant Supplementation: protects against reactive oxygen species

Effects of Fluid Flow and Mechanotransduction

- Microgravity reduces fluid flow within bone by two means: cephalad fluid shifts and loss of mechanical loading
- Loss of the gravitational pressure gradient increases pressure in the upper body and decreases pressure in the lower body
- Bone experiences unloading during space travel because it no longer bears the weight of the astronaut
- Decrease in fluid velocity and loss of loading-induced flow of interstitial fluid through the lacuna-canalicular network decreases the mechanosensitivity of the bone cells
- Osteocytes undergo apoptosis due to the lack of fluid shear force stimulation, resulting in a reduction in bone mass
- Unloading decreases proliferation of osteoblast precursor cells and causes resistance to parathyroid hormone (PTH) and insulin-like growth factor type 1 (IGF-1) in osteoprogenitor cells
- 1-type calcium channels in osteoblasts are inhibited under microgravity, blocking their major means of initiating bone formation
- Unloading caused osteocytic disuse leading to resorption
- Under microgravity conditions, this assembly of the cytoskeleton is altered because they do not have the gravity vector as a guide for growth
- Under microgravity conditions, cell growth is blocked either the G1 phase or G2/M checkpoint due to cytoskeletal changes

Effects of Cosmic Radiation

- Radiation environment in space is a mix of galactic cosmic radiation, solar particles, and geomagnetically trapped particles
- Galactic cosmic radiation (GCR) is “background” radiation originating from outside the solar system, but mostly from within the Milky Way galaxy
- Solar particles (SPE) come from solar flares and coronal mass ejections, when large masses are randomly ejected from the sun
- Geomagnetically trapped particles are protons and electrons within the geomagnetic field layer, which is the magnetic field surrounding the Earth
- As astronauts move further away from the Earth, the radiation exposure shifts from mostly geomagnetically trapped particles to GCR and SPE
- When GCR and SPE particles interact with spacecraft shielding, they can create secondary radiation and increase the potency of heavy ion irradiation

Cellular Response to Radiation

- The body responded to radiation through inflammation, DNA damage repair, and release of ROS scavengers
- Inflammation is activated by activation of stress-sensitive kinases, proinflammatory transcription factors, and upregulation of proinflammatory cytokine production.
- DNA repair mechanisms: base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and non-homologous end joining

References