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Space Radiation and Bone Loss

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Abstract

Exposure to ionizing radiation may negatively impact skeletal integrity during extended spaceflight missions to the moon, Mars, or near-Earth asteroids. However, our understanding of the effects of radiation on bone is limited when compared to the effects of weightlessness. In addition to microgravity, astronauts will be exposed to space radiation from solar and cosmic sources. Historically, radiation exposure has been shown to damage both osteoblast precursors and local vasculature within the irradiated volume. The resulting suppression of bone formation and a general state of low bone-turnover is thought to be the primary contributor to bone loss and eventual fracture. Recent investigations using mouse models have identified a rapid, but transient, increase in osteoclast activity immediately after irradiation with both spaceflight and clinically-relevant radiation qualities and doses. Together with a chronic suppression of bone formation after radiation exposure, this acute skeletal damage may contribute to long-term deterioration of bone quality, potentially increasing fracture risk. Direct evidence for the damaging effects of radiation on human bone are primarily demonstrated by the increased incidence of fractures at sites that absorb high doses of radiation during cancer therapy: exposures are considerably higher than what could be expected during spaceflight. However, both the rapidity of bone damage and the chronic nature of the changes appear similar between exposure scenarios. This review will outline our current knowledge of space and clinical exploration exposure to ionizing radiation on skeletal health.

Keywords

osteoporosis; *fracture*; *ionizing radiation*; *radiation therapy*; *spaceflight*; *microgravity*; *space radiation*; *osteoclasts*; *bone*; *inflammation*

INTRODUCTION

The effects of microgravity and space radiation on astronaut bone health represent two of the most serious challenges present within the spaceflight environment. Loss of bone

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strength resulting from a reduction in bone mass or architectural stability can increase the risk of a serious fracture, threatening mission success. Countermeasures capable of both limiting the loss of bone and permitting the eventual recovery of bone strength post-flight are necessary to ensure astronauts' long-term skeletal health and productivity of extended space missions.

Bone damage is a known chronic (late) effect of exposure to therapeutic radiation. While animal models have long documented a persistent decline in bone volume after exposure, recent animal studies have demonstrated an early and transient increase in bone resorption followed by suppressed bone formation following exposure to spaceflight-relevant doses and qualities of radiation (Kondo et al., 2009; Willey et al., 2010). This initial bone loss can be prevented using the osteoporosis therapeutic risedronate (Willey et al., 2010), further demonstrating the role of osteoclastic bone resorption.

Skeletal unloading, due to extended periods of bed rest (Spector et al., 2009) or the microgravity environment of space (Lang et al., 2004), is a well-established cause of bone loss in both humans and rodent models (Bikle and Halloran, 1999). The bone loss that occurs as a result of unloading is characterized by both an increase in bone resorption and a decrease in bone formation. This mechanism stands in contrast to traditional forms of bone loss, such as post-menopausal osteoporosis, during which bone resorption and formation move in parallel, albeit with the former increasing to a relatively greater degree. The combination of microgravity unloading and spaceflight radiation may interact to enhance bone loss (Alwood et al., 2010; Hamilton et al., 2006; Kondo et al., 2010). As the mechanisms leading to radiation-induced bone loss are less well established than unloading-induced bone loss, this review will focus on the current state of knowledge regarding the influence of spaceflight and clinical radiation on the development of osteoporosis and bone health in the adult skeleton.

Radiation and Biological Damage

Energy absorbed from radiation sources, such as from electromagnetic or charged particles, has the ability to excite atoms to the point of generating an ion. Non-ionizing radiation will not eject electrons from an atom, while ionizing radiation can sufficiently excite electrons enough to eject the electron, creating an ionization event. The generation of these charged particles can potentially break molecular bonds and lead to biological damage, such as DNA strand breaks or membrane damage. Bonds can be broken directly by radiation, or indirectly through radiation-generated reactive oxygen species that result from the ionization of water molecules. Cells have a remarkable ability to repair radiation damage, but some cells inevitably die or propagate damage to progeny. Humans on Earth are exposed to natural, background sources of radiation (e.g., environment, space, medical imaging, internal radioisotopes) at doses that do not affect long-term health at a measurable level. However, as exposures increase, damage can lead to greater levels of cell death or radiation-induced phenotypic changes that may be heritable.

Absorbed dose of radiation (D) is measured in energy per unit mass with the SI unit being Gray (Gy = Joule/kg). It is also common to see dose expressed in the unit of rad, where 100 rad = 1 Gy (1 rad = 1 cGy). The degree of biological damage can vary depending on the quality of radiation exposure, which itself is influenced by factors such as linear energy transfer (LET); type of radiation, such as alpha particles, beta particles, gamma rays (X-rays), neutrons, or heavy ions; and energy. For example, exposure to 10 cGy of neutrons will be more damaging than exposure to 10 cGy of X-rays. To account for these varying degrees of damage to humans, Sievert (Sv) is the SI unit for absorbed dose equivalent (H), which is the quality factor (Q) (relative biological effectiveness: RBE) times the dose (H = D*Q). Generally, 1 Gy of X-rays is equal to 1 Sv (100 rad = 100 rem) (Hall, 2000).

Spaceflight and Clinical Radiation Environments

The space radiation environment consists of a complex mix of ions from solar particle events (SPEs), which are large mass ejections from the sun commonly known as “solar flares,” and galactic cosmic radiation (GCR), a type of background radiation that originates from outside the solar system. The majority of GCR flux is from protons. While only 1% of GCR is composed of ions heavier than helium, due to the high LET of these high charge (Z) and energy (E) particles (HZE), approximately 41% of the dose equivalent is predicted to be from HZE particles with approximately 13% being from iron alone (Bandstra et al., 2009). LET is the rate of energy lost per length of a particle track and varies as the charge squared divided by the velocity squared. During extended missions in space, estimated tissue dose-rates from GCR would be about 0.4-0.8 mGy/day and 1-2.5 mSv/day, respectively (NCRP, 2000). SPE dose-rates may reach as high as 50 mGy/hr inside a shielded vehicle and between 250 mGy/hr for an astronaut exposed during extra-vehicular activity in deep space. The cumulative GCR doses on a deep space mission of 400 days to a near-Earth asteroid would be 0.16 to 0.32 Gy or 0.4 to 1.0 Sv. For a large SPE lasting 8-to-24 hours, the whole body cumulative doses could reach the 1- to 2-Gy level for protons (1.0 to 2.0 Sv) depending upon the tissue site. For comparison, cancer patients will receive daily doses (fractions) of 1.8 to 2.0 Gy targeted locally to the tumor and delivered over a period of a few minutes, with the total dose to the tumor ranging from 50 to 80 Gy or more.

Radiation is also absorbed by normal tissues surrounding a tumor during the course of radiation therapy (RT) for the treatment of cancer. The absorbed dose can be substantial. For example, treatment regimens for gynecological or pelvic (e.g., anal) tumors commonly prescribe the administration of thirty 1.8 Gy fractions over six weeks, for a total dose of approximately 54 Gy to the tumor. Throughout the course of treatment, normal skeletal tissue constituting each “hip” (e.g., femoral neck, sacrum, acetabular rim) can receive as much as half of each fraction (0.9 Gy), totaling 27 Gy. While the primary concern in radiotherapy has always been curative treatment of the tumor, the incidental irradiation of normal tissues is not insignificant. Primary consideration has always been given to radiation effects on normal nervous tissue, reproductive structures, and hollow organs (i.e., esophagus, bowel), while concern for irradiation of bone was not a priority. Advances in surgical excision, concurrent chemotherapy, and modern RT modalities have afforded greater freedom to focus on minimizing the risk to bone and the potential for increased fracture risk.

Fractures of Irradiated Bones After Clinical Exposure

Ionizing radiation is an important and effective modality for the treatment of malignancies and has been a critical factor in the reduction of cancer mortality rates. With an increase in long term survivorship, however, the incidence of the long-term side effects caused by radiation damage to normal tissues near the tumor are of greater concern. Fractures at irradiated skeletal sites represent one such late effect. Bones within the irradiated volume exhibit a substantially increased fracture risk (Baxter et al., 2005; Brown and Guise, 2009; Florin et al., 2007; Guise, 2006; Oeffinger et al., 2006). Rib fractures have been documented in patients receiving treatment for breast cancer, with fracture rates ranging from 1.8% (Pierce et al., 1992) to as high as 19% (Overgaard, 1988). Similarly, patients receiving radiotherapy for various pelvic malignancies are at increased risk for hip fracture at the aforementioned pelvic skeletal locations that absorb dose (Baxter et al., 2005; Mitchell and Logan, 1998; Williams and Davies, 2006). A recent retrospective analysis of more than 6,400 postmenopausal women receiving RT for cervical, rectal, and anal cancers demonstrated an increased relative risk for hip (primarily femoral neck) fracture of 65%, 66%, and 214%, respectively, compared to women receiving non-RT cancer treatment such as surgery or chemotherapy (Baxter et al., 2005). These fractures were localized to the area

that absorbed dose, and did not occur at distant skeletal sites, such as the wrist. Therefore, while systemic or non-targeted radiation effects cannot be discounted, clinically, the response seems limited to the irradiated volume.

Deterioration of Bone Quantity and Quality After Irradiation

Deterioration of bone quantity and quality following direct irradiation is thought to be associated with traumatic and spontaneous fractures of bone (Baxter et al., 2005; Ergun and Howland, 1980; Howland, 1975). Reduction in bone mass and overall bone quality is dependent on a variety of factors, including the dose absorbed, the energy of the radiation beam, the fraction size of the radiation dose, and the age and developmental stage of the patient (Mitchell and Logan, 1998; Overgaard, 1988; Williams and Davies, 2006). For cancer patients receiving doses considerably higher than spaceflight exposures, osteopenia (defined as reduced bone density) is frequently reported in patients one-year post-therapy, although the observed timing and degree of bone mass reduction can be variable (Hopewell, 2003; Mitchell and Logan, 1998). Overall, demineralization of bone, thinning of bones, sclerosis, and loss of trabecular connections has been characterized as a consequence of radiotherapy (Ergun and Howland, 1980; Hopewell, 2003; Howland, 1975; Mitchell and Logan, 1998). Thickening of trabeculae can be observed within the irradiated volume (Williams and Davies, 2006). This coarsening of trabeculae is also observed from the marrow cavity of various animal models within weeks of exposure (Furstman, 1972; Sawajiri and Mizoe, 2003). Quantitatively, an approximately 30% reduction in bone mineral density from the third lumbar vertebrae was observed among a group of patients with uterine cervix carcinoma within five weeks following irradiation with either 45 Gy or 22.5 Gy total dose of high energy photons (Nishiyama et al., 1992). No subsequent recovery of bone mineral density was observed twelve months after RT.

While late observed bone loss has been documented for decades from irradiated animal models, recent studies have quantified rapid loss of bone that occurs following exposure to sub-clinical doses of both photon and particulate radiation. In particular, this bone loss can occur after exposure to doses and qualities of radiation relevant to long duration missions (Bandstra et al., 2008; Hamilton et al., 2006) and confirms long-term suppression of bone formation (Bandstra et al., 2008). A long-term reduction in trabecular bone quantity and quality occurs following a whole-body 2 Gy dose gamma-rays, protons, carbon, or iron ions (Hamilton et al., 2006). Bone loss persists at four months after irradiation with doses of protons as low as 1 Gy (modeling a solar flare), and at nine weeks after modeled galactic radiation of heavy ions <0.5 Gy (Bandstra et al., 2008; Bandstra et al., 2009). Functional bone loss has been identified as early as three days after a 2 Gy dose of gamma-rays (Kondo et al., 2009). In addition, an increase in osteoclast activity when mice are irradiated with a 0.5 Gy dose of iron ions during limb disuse has been observed, modeling the reduced loading of the spaceflight environment (Yumoto K, 2010).

Loss of Bone Strength in Animal Models After Irradiation

The primary concern regarding radiation-induced loss of bone mineral content or architecture is the weakening of the whole bone structure, leading to fractures. Such changes in bone strength following irradiation would account for the increased fracture risk among RT patients. Animal models therefore have been used to identify a reduction in bone strength after exposure with time and at various locations within the bone. These studies generally use clinically-relevant, higher dose exposures, rather than spaceflight-relevant scenarios. Radiation has been shown to produce relatively greater damage to spongy trabecular bone compared to dense cortical bone (Bandstra et al., 2008), however, heavy ion radiation at relatively low doses (50 cGy) does cause an increase in cortical bone porosity, cortical area, and polar moment of inertia (Bandstra et al., 2009).

Bone quality will be significantly compromised with damage to both trabecular and cortical bone, resulting in a cascade of changes throughout the structure. For example, the loss of trabecular bone will result in a greater proportion of the loads placed upon the skeleton to be transferred to cortical bone. The decline in polar moment of inertia represents a reduced ability of this cortical bone to resist both torsional and bending loads. Additionally, any defect in the structure, such as a porous hole, will cause a disruption of the load distribution resulting in a stress concentration that further compromises structural competency. These changes do not mean a fracture is imminent, even when combined with microgravity-induced bone loss; however, the probability of fracture later in life is greater, and depends upon future regeneration or degeneration and the loads placed upon the skeleton.

It is also important to comment on the effects ionizing radiation has on the body mass of irradiated subjects, as this can affect loading and therefore skeletal strength. High doses can affect the health and well-being of mice, causing them to temporarily or permanently lose body mass and/or be inactive (Willey et al., 2007). Chronic bone loss has been reported in rats nine months after exposure to high dose iron radiation (2 and 4 Gy), and these changes were attributed primarily to a reduction in body mass (Willey et al., 2008a). However, spaceflight relevant doses of ionizing radiation (<2 Gy of X-rays or protons; <1 Gy of heavy ions) do not change the body mass, activity level, or nutritional status of mice (Bandstra et al., 2008; Bandstra et al., 2009; Hamilton et al., 2006; Lloyd et al., 2008; Willey et al., 2010; Willey et al., 2008b).

A 2 Gy dose of iron ions causes a loss of vertebral stiffness as tested by compression loading and calculated by finite element analysis (FEA) (Alwood et al., 2010). Compressive testing of mouse distal femora showed a reduction of strength at twelve weeks after 5 and 12 Gy acute doses of X-rays (Wernle et al., 2010). Compressive strength at two weeks was greater in the irradiated animals, which corresponded with an acute increase in cortical bone volume and bone mineral content, despite virtual elimination of trabecular bone parameters (Wernle et al., 2010). The subsequent loss of strength as determined by compressive testing and estimated by FEA occurred despite a sustained elevation of cortical bone mineral content. Thus, the bone appeared to be more brittle. Thus, strength changes in bone after irradiation may be influenced by both architectural and material properties.

Radiation and Bone Cells

Vasculature—Bone loss following radiotherapy has traditionally been thought to be a result of physiological changes within the vasculature and bone cells (Bliss et al., 1996; Ergun and Howland, 1980; Gal et al., 2000; Hopewell, 2003; Konski and Sowers, 1996; Mitchell and Logan, 1998; Rohrer et al., 1979). The first report of radiation-induced bone damage (termed “osteitis”) described reductions in bone vasculature following obliterative endarteritis (Ewing, 1926). Early loss of vascularization occurs as a result of swelling and vacuolization of endothelial cells within the vascular channels of the osteons (Ergun and Howland, 1980; Hopewell, 2003; Rohrer et al., 1979). Ultimately, this results in the deposition of sclerotic connective tissue within the marrow cavity. Fibrosis of the sub-intima and replacement of vascular smooth muscle cells with hyaline-like material occur as late injuries, resulting in constriction of the vessel lumen. Bony elements such as the skull and jaw are considered especially at risk for vascular injury due in part to the inherent paucity of vasculature and their rather superficial location (Williams and Davies, 2006). Ablation of vasculature has been identified within the bone, including marrow cavity and Haversian systems, in a variety of animal models following radiation exposure (Cao et al., 2011; Furstman, 1972; Rohrer et al., 1979).

Osteoblasts and Osteocytes—Damage to osteoblasts and osteocytes is thought to be a primary contributor to reduced bone mineral density following irradiation (Ergun and Howland, 1980; Hopewell, 2003; Mitchell and Logan, 1998; Sams, 1966). Most studies have examined high, clinically-relevant doses of X-rays, but spaceflight-relevant doses and types of radiation have been shown to negatively affect osteoblasts as well (Kondo et al., 2009; Willey et al., 2010; Yumoto K, 2010). A reduction in the overall number of osteoblasts occurs following irradiation, along with reduced matrix formation (Cao et al., 2011; Willey et al., 2010). Both *in vitro* and *in vivo* data suggest that radiation can impair bone formation by inducing a decrease in osteoblast proliferation and differentiation, inducing cell-cycle arrest, reducing collagen production, and increasing sensitivity to apoptotic agents (Dudziak et al., 2000; Gal et al., 2000; Sakurai et al., 2007; Szymczyk et al., 2004). Radiation causes a decline in RUNX2 levels in osteoblast cultures stimulated with bone morphogenic protein-2 (BMP-2), indicative of impaired osteoblast differentiation (Sakurai et al., 2007). Receptor activator of nuclear factor kappa-B ligand (RANKL) mRNA levels tended to increase in osteoblasts following exposure to gamma rays, but not to carbon ions (Sawajiri et al., 2006). Osteoblast precursors are likely damaged by radiation (Kondo et al., 2009). Mesenchymal stem cell (MSC) numbers and colony forming ability under osteogenic stimulation are also reduced in directly irradiated bone after exposure, which would likely delay recovery of osteoblast damage (Cao et al., 2011). Oxidative stress appears to contribute to this early damage to osteoprogenitors (Cao et al., 2011; Kondo et al., 2009). However, others have indicated no loss of MSC viability within irradiated bone, but rather suggested a later effect, at the stage of terminal differentiation into osteoblasts (Schonmeyr et al., 2008).

The effect of radiation on osteocyte numbers and health remain unclear. Several studies have identified loss of osteocytes within irradiated bone following exposure to high doses (Ergun and Howland, 1980; Mitchell and Logan, 1998; Rohrer et al., 1979). Osteocytes were shown to be killed within the irradiated field inside cortical lamellar and Haversian bone of monkey mandibles irradiated with 45 Gy, although their numbers were not affected within trabecular bone. Overall, however, reports suggest that osteocytes are relatively radioresistant, remaining viable for several months after a single high dose of radiation in mice and rabbits (Jacobsson, 1985; Rabelo et al., 2010; Sams, 1966; Sugimoto et al., 1991).

Osteoclasts—Recent studies show that irradiation results in an early increase in osteoclast number and activity, which likely contributes to radiation-induced osteoporosis (Willey et al., 2010). Serum tartrate-resistant acid phosphatase (TRAP5b), a marker for osteoclast activity, is elevated as early as twenty-four hours after exposure to a whole body dose of X-rays. An increase in osteoclast surface of >200% and activity have been identified to occur within rodent bones three days after exposure (Willey et al., 2008b), with subsequent loss of bone within a week of treatment (Kondo et al., 2009; Willey et al., 2010). Serum chemistry and histological analyses show significant increases in TRAP5b, as well as osteoblast number and surface, during the first week of treatment. However, in these rodent models, the majority of the bone loss occurs during a time when osteoblast numbers and bone formation are unchanged relative to control (Willey et al., 2010). Suppressing osteoclast activity with the bisphosphonate antiresorptive risedronate has been shown to completely block radiation-induced increases in osteoclast activity and subsequent deterioration of bone at multiple skeletal locations (Willey et al., 2010). Decreased osteoclast activity has been noted at time points greater than one week post-exposure, with conflicting reports of recovery (Margulies et al., 2003; Sawajiri et al., 2003). This subsequent decline in both osteoclast and osteoblast activity, if persistent, could sufficiently suppress bone remodeling and turnover and result in impaired material properties of bone tissue (Burr et al., 2003), as described in rodents (Wernle et al., 2010). Taken together, it can be seen that a combination of an early and acute loss of bone via increased osteoclast activity, as well as a persistent

reduction in bone formation, contribute to osteopenia and bone deterioration following irradiation.

CONCLUSION

Radiation exposure represents a significant concern for skeletal health. During long duration spaceflight missions, astronauts could be exposed to low doses of radiation from cosmic and solar sources. These exposures could weaken bone and lead to mission critical fractures, especially combined with the significant bone loss associated with skeletal unloading in microgravity. From the oncological perspective, advances in cancer treatment, with improvements in radiation, chemotherapy and surgical modalities, have made concern for incidental radiation damage to non-tumor tissues a growing focus. Bone represents one such “normal” tissue concern. Clinicians are now considering normal tissue complication probabilities as part of the treatment planning process. One must note that radiation exposures outside the treatment volume may be substantially greater than those predicted for astronauts, and potentially at-risk volumes of bone need to be considered as critical structures rather than as neutral structures. Limited research has defined the magnitude and mechanisms behind bone loss-associated with radiation exposure. An inflammatory response does occur in response to radiation, and may represent a mechanism that induces early activation of osteoclast-mediated bone resorption. Ultimately, bone formation is also suppressed. Bone strength is thus compromised, which could leave individuals at a substantial risk for fractures, with accompanying mortality as a late sequela, particularly in geriatric patients. A clear need exists for effective countermeasures to radiation-induced bone loss, both for the astronaut population and the ever growing population of individuals taking advantage of highly effective cancer radiotherapy. More work is required to adequately define the molecular and cellular mediators of this response and to define targets for novel therapeutics.

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