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Mini review

Modes of action associated with uranium induced adverse effects in bone function and development

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ABSTRACT

Uranium, a naturally occurring element used in military and industrial applications, accumulates in the skeletal system of animals and humans. Evidence from animal and in-vitro studies demonstrates that uranium exposure is associated with alterations in normal bone functions. The available studies suggest that upon absorption uranium directly affects bone development and maintenance by inhibiting osteoblast differentiation and normal functions, and indirectly by disrupting renal production of Vitamin D. Animal studies also provide evidence for increased susceptibility to uranium-induced bone toxicity during early life stages. The objective of this review is to provide a summary of uranium-induced bone toxicity and the potential mechanisms by which uranium can interfere with bone development and promote fragility. Since normal Vitamin D production and osteoblast functions are essential for bone growth and maintenance, young individuals and the elderly may represent potentially susceptible populations to uranium-induced bone damage.

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1. Introduction

Uranium (U) is a naturally occurring alpha-emitting radioactive metal that is present in soil at a concentration of 2–3 ppm (ATSDR, 2013; Bleise et al., 2003; Craft et al., 2004). Naturally occurring uranium is a mixture of three isotopes, U-234, U-235, and U-238, all of which undergo radioactive decay by emitting alpha particles accompanied by very small amounts of beta particles and gamma emissions (ATSDR, 2013; IAEA, 2008). Uranium is present in all geologic materials and, consequently, in soil, water, plants, animals, food, and ambient air (ATSDR, 2013; NRC, 2008).

The primary source of exposure for naturally occurring uranium is through food and water consumption. However, due to its ubiquitous presence in the environment individuals may be exposed to uranium by multiple routes, including ingestion, inhalation, and/or dermal contact (ATSDR, 2013; Keith et al., 2007; Lariviere et al., 2013). Uranium uptake is low for all exposure routes, but once absorbed it undergoes oxidation and forms soluble complexes with bicarbonate plasma proteins (primarily transferrin) and citrate (Bleise et al., 2003; Craft et al., 2004; Keith et al., 2007). From the bloodstream, the dissolved uranium is rapidly

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distributed to target tissues, principally the kidney and bone, or excreted in urine (Eidson, 1994).

Animal and human studies have demonstrated that uranium accumulates in renal and osseous tissues (Adams and Spoor, 1974; Durbin and Wrenn, 1975; Fisenne and Welford, 1986). In humans and animals, uranium deposits in the skeleton in a dose- and time-dependent fashion (Arruda-Neto et al., 2004; Lariviere et al., 2013; Pellmar et al., 1999; Prado et al., 2008) and uranium accumulation in bones occurs at a higher rate in young individuals (Lariviere et al., 2007; Rodrigues et al., 2013). Thus, bone is considered to be the most significant, long term deposit of uranium.

Once deposited in bone, uranium may be retained for long periods of time (Brugge and Buchner, 2011; Zhu et al., 2009), with half lives in bone ranging from 70 to 200 days (ATSDR, 2013). Within the osseous tissue, uranium accumulates in areas of active bone formation, specifically the calcifying zones of skeletal cartilage, where it can mimic and replace calcium (Ca^{2+}) (ATSDR, 2013; Rodrigues et al., 2013).

As described below, various studies using mammalian and cell culture models report that uranium exposure interferes with normal bone functions. Furthermore, a human study reported an association between uranium exposure and biochemical indicators of bone turnover (Kurttio et al., 2005). This review evaluates the current evidence of uranium induced bone toxicity and the potential modes of action by which uranium exposure leads to adverse skeletal health.

2. Approach for literature search on uranium and bone toxicity

Medline, Web of Science and Toxline were searched for epidemiological and animal studies informative to the potential effects of uranium exposure in bones. The search terms used were: uranium and bone or bone growth or bone formation or bone toxicity or bone resorption or bone volume or bone remodeling or bone density or bone mineralization or osteotixicity or osteoblasts or Vitamin D or alkaline phosphatase. Titles and abstracts of retrieved publications were reviewed for relevance to uranium and bone health. The citation list of publications considered informative were evaluated to identify studies not captured in the scientific databases mentioned above.

3. Bone formation and maintenance overview

A brief review of the biological processes of bone formation and maintenance, which have been shown to be affected by exposure to uranium and other osteotoxic heavy metals, is presented below. This section is not meant to be an exhaustive review on bone biology and development of the skeletal system. More in depth reviews are cited herein.

The bones that comprise the skeletal system are rigid organs whose function is to maintain systematic mineral homeostasis, and to provide support, protection and mobility (Teti, 2011; Yang, 2009). The formation and growth of the skeletal system takes place during embryonic development and childhood (Karsenty, 1999). The process of bone formation and mineralization can be categorized into two types:

1. Endochondral ossification, in which the mesenchymal cells differentiate into chondrocytes which form the cartilage template for future bone, and are then replaced by osteoblasts (Karsenty, 1999; Teti, 2011).
2. Intramembranous ossification, in which bone formation occurs directly within the membranous tissue without the formation of a cartilage template (Franz-Odendaal, 2011; Mackie, 2003; Yang, 2009).

During early developmental stages, bones such as the skull, the mandible, and the pectoral girdle are formed via intramembranous ossification, while long bones are formed through endochondral ossification (Franz-Odendaal, 2011; Teti, 2011). The process of intramembranous ossification consists of three major stages: (a) cell induction to the skeletogenic lineage in which mesenchymal and epithelial cells interact and establish the eventual pattern of the skeleton, (b) condensation formation, in which mesenchymal cells aggregate until a critical size is reached, and (c) cell differentiation of osteoblasts which secrete bone matrix and promote bone mineralization (Franz-Odendaal, 2011; Olsen et al., 2000).

In both endochondral and intramembranous ossification, osteoblasts secrete bone matrix and the osteoblasts which become entrapped in the bone matrix are called osteocytes (Franz-Odendaal, 2011; Teti, 2011). Osteocytes form a network through the mineralized bone and their function is to maintain bone structure and metabolism by transducing stress signals from bending and stretching of bone as well as microdamage (Clarke, 2008; Teti, 2011).

Endochondral ossification consists of chondrocyte differentiation, proliferation and hypertrophy, followed by bone matrix secretion and mineralization. Enlarged chondrocytes secrete the matrix and form the bone cartilage model (Mackie et al., 2008). The hypertrophic chondrocytes then undergo apoptosis and are replaced by osteoblasts. The osteoblasts secrete osteoid, the unmineralized organic component of bone matrix, while osteoclasts remove the cartilage model (Karsenty, 1999; Mackie et al., 2008). Finally, the cartilage model is replaced by mineralized bone (Mackie et al., 2008).

Endochondral ossification also occurs during recovery from bone fractures (Shapiro, 2008). The histological appearance and molecular mechanisms involved in the process of fracture recovery are similar to the ones that regulate fetal and childhood skeletal development (Ferguson et al., 1999; Vortkamp et al., 1998). The process of endochondral bone repair also involves chondrocyte differentiation and hypertrophy, secretion of the cartilage bone model, osteoblast recruitment, and bone mineralization (Gerstenfeld et al., 2003; Shapiro, 2008). Endochondral bone repair is considered to recapitulate bone development during early life stages (Gerstenfeld et al., 2003) and, although fracture repair studies are carried out in a postnatal setting, they may be informative to the understanding of the effects of osteotoxic agents on early developmental bone growth.

Bone modeling and remodeling are two lifelong processes which allow growth and maintenance of the skeleton and damage removal (Clarke, 2008; Seeman, 2009). Bone modeling refers to the biological process by which bones change their shape and mineral content in response to physiologic and/or mechanical stimulus. Bone remodeling removes bone microdamage, maintains mineral homeostasis, and manages the extracellular levels of Ca^{2+}, and is governed by bone resorbing osteoclasts and bone re-synthesizing osteoblasts (Clarke, 2008; Seeman, 2009). During bone remodeling osteoblasts activate osteoclast differentiation through increased secretion of the cell membrane bound protein receptor activator of nuclear factor kappa (RANKL) (Karsenty, 1999; Komori, 2014). Upon erosion of the bone matrix by osteoclasts, the osteoblasts then re-mineralize the bone matrix (Anderson et al., 2011; Turner et al., 2012). Thus, osteoclasts remove the damaged portions of the bone, while osteoblasts secrete the bone matrix which is subsequently mineralized to form the new bone (Clarke, 2008; Teti, 2011). Bone remodeling replaces bone without altering its bone mineral content, with the exception of disease states such as osteoporosis where bone resorption occurs at a higher rate than deposition (Teti, 2011). Alterations in the rates of bone formation