Review Article

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Industrial and Environmental Toxic Exposures and Osteoporosis

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Abstract

Exposure of industrial and environmental toxic substances to air, drinking water, soil, plants, animals and food chains and their continuous release to the human environment have a negative impact on human health. When exposed to heavy metals due to these toxic exposures, many effects on body functions can occur. Generally, due to the long half-life of the metal in the body, it can accumulate biologically in soft and hard tissues/organs. Bone tissue undergoes a continuous remodeling throughout life. This involves the simultaneous action of resolution, synthesis and mineralization of the bone matrix. In general, metals have two effects on bone tissue: the first is their direct toxicity to bone cells and the second is their accumulation in the bone matrix. Their direct toxicity mainly affects osteoblasts, inhibits osteoblast differentiation, synthesis activity and mineralization of the extracellular matrix. Their effect on osteoclasts differs from that of metal, increases or decreases the activity of tartarate resistant acid phosphatase enzyme and prevents the maturation of the precursors. As a result, it causes imbalance in the bone remodeling process, reduces bone formation and contributes to the formation of bone diseases such as osteopenia and osteoporosis. Despite our knowledge of the effect of metals on bone tissue, many things are still unclear. Understanding the mechanisms of action will ensure that appropriate therapies are available to address their adverse effects on bone tissue.

Keywords: Heavy metal; Bone; Osteoporosis.

Industrial and Environmental Toxic Exposures and Osteoporosis

Contamination by air, drinking water, soil, plants, animals and food chains with metals has a negative impact on human health. Their toxicity and prolonged biological half-life is a serious problem due to their accumulation in the environment and living organisms. Metal exposure affects many systems in our body and has a negative impact on the skeletal system. Depending on the concentration and duration of the metal species, it may result in increased risk of osteoporosis and fracture.[1–4]

The aim of this review is to focus on the effects of toxic metals on bone tissue. It was to taking into account of the mechanisms of these metals with long/short term non-physiological deposition on the skeletal system.

Normal Bone Tissue and Osteoporosis

In addition to providing normal posture and bodily movements, bone tissue serves as a reservoir for many minerals, including calcium and phosphorus, to preserve important structures. Bone remodeling, which is a dynamic process, consists of bone resorption and construction processes.[3,4]

Osteoblasts are cells that originate from bone marrow (Mesenchymal), responsible for bone

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formation and mineralization. Active osteoblasts perform bone formation while inactive osteoblasts form cells that cover the bone surface. Osteoblasts synthesize the bone matrix, 90% of which consists of collagen. These matrix elements; Type 1 consists of collagen, osteocalcin, bone sialoprotein, osteopontin, proteoglycans, cytokines, growth factors and alkaline phosphatase. Alkaline phosphatases are responsible for the mineralization phase. During the mineralization phase, phosphate and calcium precipitate on the bone matrix. For intestinal absorption of calcium, 1,25 dihydroxy-vitamin D_3 is required.[5,6]

Osteoclasts are cells that originate from monocyte/macrophage precursors of the hematopoietic system. Osteoclasts are rich in lysosomal enzymes including tartrate-resistant acid phosphatase, collagenase, and cathepsins, and through these enzymes, they resorb the bone matrix.[6] Osteoprotegerin (OPG), which inhibits bone destruction, is the receptor activator nuclear kappa B (RANK), which controls the physiological and pathological bone resorption, and is the receptor in osteoclasts that causes bone destruction by stimulation with RANK ligand (RANKL).[7–9] The RANK, RANKL axis adjust osteoclast activity. Osteoprotegerin (OPG) binds to RANKL, inhibiting RANK activation and inhibits osteoclast formation.[10] Increased osteoclast activity leads to osteoporosis and osteopenia. Therefore, osteoclasts play an important role in bone hemostasis.[11]

Metal Toxicity in Bone Tissue

Chromium

Chromium (Cr) occurs in different states in natüre. It is commonly found as Cr (III) and Cr (VI). Chromium rock, soil, water and dust are also available. Especially chromium (III) is naturally found in some foods such as meat, fish, nuts, eggs, fruits and vegetables and is required in small doses for the human body due to its participation in carbohydrate metabolism. Chromium has been shown to reduce ALP activity and mineralization of osteoblasts.[4,12,13] The study in rats showed[14] that Cr (VI) accumulates in the femur. Some studies have shown that long-term supplementation with Cr (III) may have adverse effects on Fe metabolism, since these metals bind to transferrin.[15,16] Such interaction may also be observed between Cr (III), Zn and Cu due to similar mechanisms of absorption.[17,18] Therefore, over-administration of Cr may cause osteoporosis due to Fe, Cu and Zn deficiency.[4]

Lead

Lead (Pb) is found in various forms in nature including Pb salts (ionic Pb) and organic Pb tetraethyl lead compounds.[19] The main sources of environmental Pb contamination include the steel, metal and mining industries. When Pb content increases, physiological mineralization decreases.[20] The main target of Pb is the bone matrix, capable of replacing other divalent cations in the body such as Ca^{2+}, Mg^{2+} and Fe^{2+}, to a lower degree of monovalent cations such as Na^{+}. It may alter osteoblast function and thereby impair the hormonal regulation of calcification.[21] It inhibits the enzyme 1-hidroks-hydroxylase in the kidney. Affects vitamin D production. It results in hypocalcemia and hypophosphatemia.[22] Even subtoxic Pb doses may alter bone biomarker values such as alkaline phosphatase, collagen Type 1, osteocalcin and transcription factor 2, thereby preventing bone formation by reducing the differentiation of osteoblasts.[23]

Aluminum

Aluminum (Al) is a metal found everywhere. Aluminum is known to cause nervous system, hematopoietic system, renal osteodystrophy, hemodialysis encephalopathy, osteomalacia, osteoporosis and anemia.[24–28] Aluminum is accumulates on trabecular bone surfaces and on the surfaces of vascular ducts that penetrate the compact bone.[24,29] *In vitro* studies, there is evidence that aluminum prevents osteoblast differentiation. It inhibits type I collagen. Al, reduces expression of osteocalcin, bone sialoprotein, osteopontin.[30] Deposition of Al in the bone can reduce Mg, Ca and P levels and lead to inhibition of the bone mineralization process.[31]

Cadmium

Cadmium (Cd) is an environmentally and occupationally important contaminant. Cadmium compounds can be in powder and aerosol form. Toxic effects may result from chronic inhalation. Adverse effects on vitamin D levels and bone mineralization have been reported, particularly in the lung and kidney (renal tubular dysfunction, renal stone and hypercalciuria). Many studies have shown that increased risk of renal failure, osteoporosis and fracture can be triggered by exposure to Cd.[29,32–34]

Two mechanisms of action are mentioned: the direct effect of metal on bone cells. It has been reported that it directly affects osteoclasts

and causes the destruction of matrix tissue.[29,35–37] Cadmium causes renal failure first, increases excretion of calcium and phosphorus, decreases vitamin D synthesis and consequently decreases calcium absorption in the digestive tract and affects bone mineralization.[38–40] Studies have shown that chronic exposure to Cd reduces the mineralization of vertebral bodies and makes them more susceptible to fracture.[41] Youness E. et al. They found that a decrease in vitamin D_3, osteocalcin and bone-specific alkaline phosphatase activity and an increase in serum Ca, P and parathyroid hormone levels.[42] Other studies have shown that chronic exposure to Cd reduces bone volume and increases TRAP positive cells in the subchondral tibial bone.[43,44]

Mercury

Inorganic mercury (Hg) is absorbed by the lungs and accumulates in the brain, while methyl mercury is absorbed in the intestine and accumulates in the soft organ. Methyl mercury has been shown to reduce calcemia and directly affect the metabolism of bone cells.[4,29,45] Mercury inhibits the activity of both osteoclasts and osteoblasts. Prenatal poisoning of experimental animals with methyl mercury has shown that the rat fetus retards ossification and reduces long bone length.[46]

Iron

Iron (Fe) is one of the most abundant metals in nature and is required for many biological processes.[47,48] It catalyze the formation of free radicals in different cells. The RANK/RANKL/OPG system also showed a change, an increase in osteoclastactivity and osteoblastic dysfunction.[49] Iron overload also reduces the formation of mineralization and inhibits the growth of hydroxyapatite crystals by changing their crystallization.[29,50,51]

However, the exact mechanism by which Fe deficiency can affect bone health has not yet been fully understood. Some experimental studies have shown that Fe-deficient animals have reduced trabecular thickness and total bone volume compared to non-deficient animals.[52] Changes in iron metabolism inhibit osteoblast proliferation and osteoclast differentiation.[53] It has been suggested that there is a relationship between adequate Fe intake and bone health.[54–56]

Arsenic

Arsenic (As) is not a metal, it is a metalloid that occurs as inorganic As (III) and As (V) and organic arsenic species. Arsenic and Paget's disease have shown a relationship between them.[57] There are studies reporting that osteomyelitis and osteonecrosis of the alveolar bone develop as a result of the use of dental paste containing arsenic trioxide.[58] Chronic exposure to low-level arsenic can cause bone resorption by promoting osteoclast differentiation.[59] *In vivo* arsenic trioxide poisoning has been shown to alter bone resorption by decreasing the maturation of osteoclast precursors and decreasing osteoclastic activity. Non-cytotoxic doses of Arsenic have been reported to cause dysfunction of some signal transduction including steroid receptors due to osteoclast and osteoblast differentiation.[4,29] In addition, it has been reported that *in vitro* exposure of Arsenic may reduce osteoblastic activity and osteoblastogenesis, thereby affecting bone formation process.[60]

Nickel

In vitro studies have shown that high Ni concentrations inhibit alkaline phosphatase activity and bone mineralization.[61]

Titanium

Titanium (Ti) is used the production of orthopedic prostheses and dental implants. There are studies showing that titanium inhibits osteoblastic differentiation.[62] It was found to stimulate osteoclastogenesis and osteoclast activity in the presence of RANKL.[63]

Results

Various remains unclear as to the effect of metals on bone tissue. Understanding the mechanisms of effect will ensure that adequate therapies are available to address their adverse effects on the bone.

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