Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 7 Issue 1 January 2023

Review Article

Trace Elements and Bone Metabolism

Efstathios Koutsostathis*

Sotiria Hospital, Greece

***Corresponding Author:** Efstathios Koutsostathis, Sotiria Hospital, Greece.

DOI: 10.31080/ASMS.2022.06.1427

Received: November 23, 2022

Published: December 16, 2022

Abstract

Osteoporosis: Osteoporosis is a systemic disease that affects the skeleton and is characterised by reduced bone mass and deterioration of the bone structure. The direct consequence is increase in bone fragility, resulting in fractures even with little mechanical force. It is the most common complication of metabolic bone diseases. Simply put, osteoporosis is a systemic disease marked by increased incidence of fractures [1,2].

Osteoporosis is roughly divided into idiopathic and secondary. Idiopathic osteoporosis is further divided into type I and type II osteoporosis. These two types were previously known as postmenopausal and senile osteoporosis respectively [3].

Keywords: Osteoporosis; Menopause; Fragility

Introduction

Type I osteoporosis

It develops in middle-aged women, 15 years on average after menopause. It affects the cancellous bones. This often results in fractures of the vertebrae and the distal end of the radius. There is distinct and significant thinning of the trabeculae, especially the horizontal ones. In some parts, the vertebrae are stripped from bone. On the other hand, the trabeculae in other parts of the same bone swell up as counterbalance. Pronounced back pain, progressive loss of height, kyphosis and related fractures are the consequence of this loss of bone tissue process [4].

Type II osteoporosis

It occurs in older males and females, over 70 years of age, with a higher incidence in females. It primarily affects the cortical bones. Fractures of the peripheral skeleton, mainly of the upper thigh bone, are typical of this type [5].

The pathogenesis of osteoporosis relates to the interaction of genetic, metabolic and environmental factors. All these factors act on bone growth, affecting calcium homeostasis by regulating bone formation and loss. Age, physical activity, sex hormones (mainly oestrogens) and dietary habits are important modulators in the development and progression of the disease over time.

The concept of peak bone mass is extremely important in understanding the pathophysiology of osteoporosis. It is the maximum bone mass a person can reach. Achieving it depends on hereditary factors, the environment, hormonal disorders (PTH, vitamin D, sex hormones, thyroid hormones, cortisol, growth hormone). It is also affected by diet (coffee, alcohol, calcium), exercise and diseases, such as rheumatoid arthritis and inflammatory bowel disease.

The highest bone density value is reached approximately 10 years after linear growth is completed. It starts dropping as of the 4th decade of life, reaching almost half the maximum value at around 80 years. Failure to achieve peak bone mass contributes to skeletal fragility. Women lose 35% of cortical bone and 50% of cancellous bone, on the one hand due to ageing and on the other due to osteoporosis, with both conditions equally involved in the process. Taking into account that the peak bone mass is lower

in women compared to men and it is reached 3-5 years earlier, it becomes evident that osteoporosis predominantly affects the female population [6].

Trace elements and bone metabolism – Nitric oxide and osteoporosis

Over the past two decades, major strides have been made in understanding the mechanisms involved in bone metabolism. It is no coincidence that nitric oxide (NO) was named "molecule of 1992" and that the 1998 Nobel Prize in Physiology was also awarded to the research into the physiological effects of this molecule. NO has been shown to be involved in the regulation of osteoclasts, reducing their activity, while having a mild anabolic reaction in bone production, facilitating the action of the osteoblasts.

Figure 1 depicts the interactions between NO, cytokines and hormones.

Figure 1: The bone remodelling cycle. Osteoclasts differ from monocyte precursor cells as a response to RANK activation from RANKL, which is expressed on stratified cells. This interaction is inhibited by an OPG acting as a RANKL antagonist. Osteoblasts differ from mesenchymal precursors in bone marrow. (Adapted from van't Hof & Ralston, 2001).

Nitric oxide is a by-product of combustion of substances in the air, e.g. from car engines, fossil fuel energy production plants and lightning bolts. In primates, nitric oxide is involved in multiple pathophysiological processes, as a cell signalling molecule. It is a potent vasodilator molecule, with a short half-life in the blood, critically important as a mediator of vasodilation. Platelet factors (PDGF), acetylcholine and cytokines stimulate the production of NO by endothelial synthase (eNOS). The oxidation of L-arginine guanidinium nitrogen leads to the production of nitric oxide and citrulline. This reaction is catalysed by eNOS and is dependent on calcium, calmodulin and other co-enzymes.

In addition, NO is a neurotransmitter and is associated with neuronal avoidance learning processes, while it is believed to be a partial mediator of macrophage cytotoxicity against germ and cancer cells. It is also involved in processes such as septic shock, arterial hypertension, neurodegenerative diseases and stroke.

Nitric oxide appears to have a dose-dependent effect on bone metabolism. More specifically, low NO concentrations enhance IL-1, which induces bone resorption. In contrast, increased NO concentrations inhibit osteoclast formation and, therefore, osteoclast activity. In the first case, bone resorption is achieved through the action of endothelial synthase inhibitors, which is necessary for IL-1 induced bone resorption. In the second case, it has been proven that increased NO values facilitate the inhibitory effect of IFN-gamma on interleukin-1 and the tumour necrosis factor (TNF-alpha). The NO action both inhibits the formation and activity of mature osteoclasts, and induces the apoptosis of osteoclast precursors.

Increased NO concentrations are considered to have a strong inhibitory effect on the growth and differentiation of osteoblasts. Such concentrations are observed following stimulation by pro-inflammatory cytokines. These actions are partly caused by c-GMP action. However, there is research available to substantiate the autocrine effect of small amounts of NO to stimulate the maturation of osteoblasts and, therefore, bone reconstruction.

Studies at cellular level have shown that both osteoblasts and bone cells produce nitric oxide. At increased concentrations, this effect on osteoclasts leads to decreased bone resorption through the stimulation of osteoprotegerin, which is bound by the RANK ligand. The outcome of these and other more specific biochemical

interactions leads to decreased cellular absorption. Similarly, low NO concentrations facilitate osteoblast differentiation and growth. Although in animal models nitric oxide has clearly been associated with reduced bone loss, several research steps remain to prove that the same applies in humans. However, it is believed that biologically produced NO makes a positive contribution to skeletal health and also contributes to the prevention of osteoporosis, mainly in postmenopausal women. In contrast, nitric oxide from air pollutants does not have a clear biological effect; however, a negative effect on skeletal health cannot be ruled out [7].

Lead and osteoporosis

Lead exposure is found to be an important risk factor for osteoporosis, since it leads to an irreversible decrease in bone density and bone strength. Around 80-90% of the absorbed lead, from drinking water or inhalation, e.g. paint, but also from other sources, is stored in the bones. Part of the stored quantity of calcium is released into the bloodstream at periods of enhanced bone resorption, as is the case during menopause, pregnancy and breastfeeding. Therefore, postmenopausal women run a higher risk of being affected by the adverse effects of lead, due to the significant quantity released into the bloodstream. These negative effects include hypertension, acute and long-term renal failure, atherosclerosis and increased cardiovascular mortality, as well as considerable impairment of mental functions. There are also a number of studies that include other determinants of the harmful effects of lead, particularly in women. These include ethnicity, type of work, housing, tobacco, alcohol consumption, nutrition, etc.

Lead exposure occurs each day from a range of sources, including paint, contaminated dust and soil, roof tiles, games, cosmetics, herbal remedies and, of course, drinking water. Although acute exposure to high volumes of lead is relatively rare, chronic exposure is more likely. In adults, 80-95% of lead is stored in the bones. Note that its half-life is about 20-30 years. As a result of its slow release, the levels of stored lead in the bones increase with age. Interestingly, increased consumption of alcoholic beverages, particularly wine, is positively correlated to the amount of lead circulating in the bloodstream. A similar correlation occurs with smoking [8].

Cadmium and osteoporosis

There is plenty of epidemiological evidence highlighting the effect of cadmium on musculoskeletal health. Cadmium can increase bone breakdown and affect the potency of osteoclasts and calcium absorption, as well as kidney function, which, overall, and each separately, lead to the development of osteoporosis. In addition, it prompts the inflammatory response through the citrullination process, therefore acting on the “acute phase” protein [9].

Cadmium is practically a metal present everywhere. The annual emission of cadmium is estimated at millions of tonnes, which burden the atmosphere. Most of it is due to the production of fertilizers and pesticides, while incineration is just as burdensome. It is a fact that cadmium is found in most everyday objects, such as fridges, car seats, furniture, floor covers, plastic bottles, tyres, etc.

The air in urban centres is quite compromised and contains cadmium in concentrations up to 0.060 μg/m^3. Out of this, 70% enters the air through cigarette smoking. In addition to the air, this trace element also contaminates the water. Rivers and lakes are contaminated by industrial waste or by damaged galvanized pipes.

Food is another significant source of cadmium for humans. More specifically, eggs, fish, dairy products, tea and coffee contain cadmium. Fruit and vegetables may also contain significant amounts of cadmium. This is because of the extensive use of commercial fertilizers made from natural phosphate rocks.

Cadmium is practically toxic to the body. On a daily basis the human body takes in 50 μg of cadmium, the largest quantity of which is absorbed with the faeces. It blocks the function of enzymes containing the group (-SH), which depend on the presence of other trace elements such as Zn, Co, etc.

In summary, it has been reported that chronic accumulation of cadmium in the body causes chronic poisoning, which leads to disorders in several organs with a build-up of the element, e.g. kidney, lungs and bones, where increased accumulation of cadmium results in osteoporosis. The concept of acute poisoning also applies when the body is exposed to an increased amount of cadmium within a short period of time, so acute symptoms appear, such as vomiting, diarrhoea, spastic colitis and abdominal pain. It is important that its toxic effect is cumulative and its half-life is approximately 20 years, indicating the magnitude of its harmful effect on humans [10].

Exposure to increased amounts of cadmium may result in bone damage. It appears that the effects of cadmium on the bone are the

ultimate consequences of the toxicity of this element and are related to cadmium-induced nephrotoxicity, which results in disruption of vitamin D metabolism and loss of the ability to reabsorb many other trace elements, such as calcium, from the renal tubules [11].

Cadmium toxicity is also linked to the induction of oxidative stress in the human body. Oxidative stress is caused by the production of free radicals (ROS), as well as by the inhibition of cell proliferation and differentiation.

In addition, cadmium releases calcium from the bone within hours from toxic exposure, while its cytotoxicity ultimately leads to endoplasmic stress and mitochondrial collapse. The clinical profile includes osteomalacia, pseudofractures and osteoporosis [12].

Strontium and bone health

Strontium is a trace found in sea water. Therefore, the main nutritional source is seafood. Other foods containing strontium include milk, bran, meat, poultry, and root vegetables. The recommended daily intake has been calculated to be 1-3 mg.

Research on humans and animal models over the past 30 years have positively associated strontium intake at normal doses with good skeletal health and, in particular, increased bone strength and decreased incidence of fractures. Taking medicinal products containing strontium is believed to reduce the overall fracture risk by more than 20%. However, long-term administration of increased doses of strontium may lead to increased blood clotting, chronic diarrhoeal syndrome or even rickets [13].

DHEA and bone health

Dehydroepiandrosterone is a natural precursor of the sex hormones. DHEA preparations are widely available in pharmacies. They are thought to reduce the symptoms of osteoporosis, such as hot flushes, and are associated with a small increase in bone mass. In addition, they are believed to be associated with cognitive function improvement in postmenopausal women. The effects of progesterone appear to be similar, but not entirely substantiated in this case. However, some serious adverse effects have been associated with these medicinal products, even development of breast or ovarian cancer [14].

Aluminium and bone metabolism

Aluminium is the third most abundant element in nature and is present practically everywhere, including various foods. However, intake of normal amounts of aluminium, such as antacids and baby food, does not cause any problems. The intestinal tube and respiratory system act as barriers to the entry of this element into the bloodstream. However, parenteral nutrition, haemodialysis or even oral aluminium containing formulations administered to renal patients can lead to aluminium accumulation in the bones, parathyroid glands, liver, spleen and kidneys. Other sources of aluminium are calcium salts, phosphates, albumin medications and heparin. The toxic effects of aluminium on the bones include osteomalacia, osteoporotic fractures and hypoparathyroidism. In addition, they are associated with hepatotoxicity and cholestasis, microcytic anaemia and decreased activity of the active metabolite of vitamin D. Around 95% of the aluminium that crosses the natural barriers and enters the bloodstream is bound to transferrin [15].

The toxic effects of aluminium are depicted in figure 2 below.

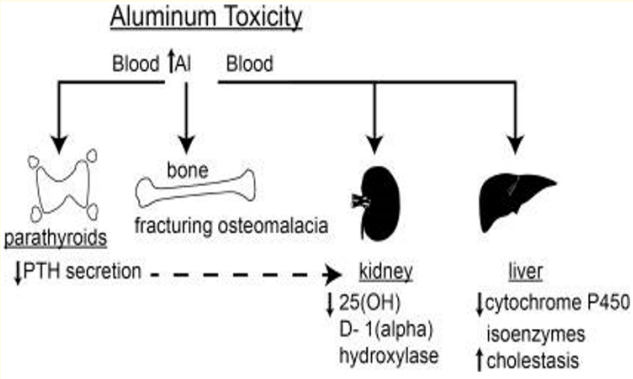

Figure 2: The toxic actions of aluminium on various organs, Aluminum toxicity to bone: A multisystem effect? Gordon L. Klein Osteoporosis and sarcopenia 5 (2019) 2-9.

Dioxins and bone disease

Dioxins are a family of chemical substances that are similar in structure and chemical properties to furans. Dioxin refers to 2,3,7,7-TCDD, i.e. 2,3,7,8-tetrachlorodibenzo-p-dioxin, which is the most hazardous chemical compound of this family. These compounds are associated with carcinogenicity and are particularly toxic to the human body. Their half-life is 3 to 30 years, while the primary source of their release is burning waste, especially polyvinyl chlorides. Waste of this type are water bottles, pipes, cables, etc. Dioxins have the propensity to accumulate in fatty tissue and act as endocrine disrupting chemicals, changing the ratio of oestrogens

and androgens in the body. They have also been associated with skin lesions, chlorines, liver disease and carcinogenicity. Recycling is considered the best way to prevent the adverse effects of dioxins [16-18].

A number of studies have shown a negative correlation between increased levels of dioxins in the human body and bone density (measured using the z-score) in women. In experimental models this has been attributed to a reduction in osteoblast activity. In addition, the mineralisation process of the vertebrae appears to slow down, combined with a decrease in vitamin D levels. The actions of dioxins on bone metabolism depend on gender, but also on the age when exposure to increased doses took place [19].

Conclusion

Furthermore, experimental data demonstrate the role of dioxins in bone metabolism. This way, they affect the integrity of the connective tissue, inhibit collagen type I synthesis and, by promoting oxidative stress, lead to increased concentration of pro-inflammatory cytokines, which activate osteoclast genesis. The effect of dioxins on oestrogen receptors, but also on receptors of other hormones, such as prolactin, thyroxine and corticosteroids, is extremely important [20]. This results in changes to oestrogen signalling, which include changes in gene expression (see Figure 3).

Figure 3: The relationship of dioxins to the food chain, from: The chemical compound of the month, Athanasios Valavanidis. Konstantinos Efthymiou.

Bibliography

1. "Consensus Development Conference Diagnosis, prophylaxis and treatment of osteoporosis". *The American Journal of Medicine* 94 (1993): 646-650.

2. Cummings SR and Melton LJ. "Osteoporosis I: Epidemiology and outcomes of osteoporotic fractures". *Lancet* 359.9319 (2002): 1761-1767.

3. Riggs BL., *et al*. "Differential changes in bone mineral density of the appendicular and axial skeleton with aging: Relationship to spinal osteoporosis". *Journal of Clinical Investigation* 67 (1981): 328-335.

4. Hiller TA., *et al*. "Height loss in older women: Risk of hip fracture and mortality independent of vertebral fractures". *Journal of Bone and Mineral Research* 27 (2012): 153-159.

5. Court-Brown CM and Caesar B. "Epidemiology of adult fractures: A review". *Injury* 37 (2006): 691-697.

6. Mundy G. "Pathogenesis of osteoporosis and challenges for drug delivery". *Advanced Drug Delivery Reviews* 42 (2000): 165-17355.

7. Elizabeth Culotta and Daniel E Koshland Jr. "NO news is good news. 9nitric oxide; includes information about other significant advances and discoveries of 1992) (Molecule of the Year)". *Science* 258 (5090): 1862-186455) Elizabeth Culotta and Daniel E. Koshland Jr (1992). "NO news is good news". 9nitric oxide; ear)". *Science* 258.5090 (1992): 1862-1864.

8. Anjani Manocha., *et al*. "Lead as a risk factor for osteoporosis in post-menopausal women". *Indian Journal of Clinical Biochemistry* Sept (2017).

9. Reyes-Hinojosa D., *et al*. *Environmental Toxicology and Pharmacology* 72 (2019): 103219.

10. Michalis Leotsinidis. "Levels of concentrations of lead, cadmium, chromium, nickel, zinc, copper in the hair of a semi-urban population of the NW Peloponnese, University of Patras, School of Health Sciences". *Department of Medicine* (1990).

11. Jesus M Lavado-García., *et al*. "Dietary Intake of Cadmium, Lead and Mercury and Its Association with Bone Health in Healthy Premenopausal Women". *International Journal of Environmental Research and Public Health* 14.12 (2017): 1437.

12. Edwin Aihanuwa Uwagie-Ero., *et al*. "Osteocyte viability and bone density in cadmium chloride-induced osteoporosis ameliorated with Pilostigma thonningii stem bark-extracted D-3-O-methy-chiroinositol". *Animal Models and Experimental Medicine* 2.1 (2019): 25-33.

13. Angelo Licata., *et al*. "Osteoporosis clinical updates, clinical information for health care professionals". Fall (2013).

14. "Aluminum toxicity to bone: A multisystem effect?" Gordon L. Klein Osteoporosis and sarcopenia 5 (2019) 2-9.

15. National Institute of Health (substance profiles): "2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD); "Dioxin" CAS No. 1746-01-6.

16. Commoner B (Greens.org): "The Political History of Dioxin".

17. World Health Organization: "Dioxins and their effects on human health" (Fact Sheet No 225, May 2010).

18. Junichi Fukushia., *et al*. "Effects of dioxin-related compounds on bone mineral density inpatients affected by the Yusho incident". *Chemosphere* 145 (2016): 25-33.

19. Sun Singh., *et al*. "Inhibition of dioxin effects on bone formation *in vitro* by a newly described aryl hydrocarbon receptor antagonist, resveratrol". *Journal of Endocrinology* 167.1 (2000): 183-195.

20. Darrell R Boverhof., *et al*. "Dioxin Induces an Estrogen-Like, Estrogen Receptor-Dependent Gene Expression Response in the Murine Uterus". *Molecular Pharmacology* May 69.5 (2006): 159901606.