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EFFECT OF SELECTED METALS ON BONE TISSUE OF THE MASTICATORY APPARATUS

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Abstract

The masticatory apparatus is a functional unit of the human body, which is mainly responsible for speech, chewing, and swallowing. It is built of bones, joints, ligaments, teeth, and muscles. In addition, the oral cavity and its hard tissues are the first ones to be exposed to exogenous factors during feeding and breathing.

The aim of the work was to review the literature of recent years on the toxicology of metals and their possible negative and sometimes positive effects on the metabolism of bones of the masticatory apparatus.

In summary, metals commonly found in the environment affect the bones of the masticatory apparatus to varying degrees. Attention should be paid to the sources of individual metals in the environment and to prevent their excessive, unwanted effects on the bones of the masticatory apparatus.

Key words: metals, toxicity, bone tissue, masticatory apparatus

Resumen

EFECTOS DE METALES EN EL TEJIDO ÓSEO DEL APARATO MASTICATORIO

El aparato masticatorio constituye una unidad funcional del cuerpo humano especializada en la regulación y coordinación de los procesos del habla, la masticación y la deglución. Está constituida por huesos, ligamentos, articulaciones, músculos y dientes. El tejido óseo de la cavidad bucal es el primero en estar expuesto a factores exógenos durante la alimentación y la respiración. El objetivo del presente trabajo es realizar una revisión de lo reportado en la literatura en los últimos años, con respecto a los efectos beneficiosos o nocivos de los metales pesados sobre el metabolismo de los huesos del aparato masticatorio.

En resumen, se evidencia que los metales presentes en el medioambiente afectan a estos huesos en diferentes grados. Se debe prestar especial atención a identificar las fuentes de donde provienen estos metales, para prevenir los efectos no deseados sobre el tejido óseo masticatorio generados por una excesiva exposición a ellos.

Palabras clave: *metales, toxicidad, tejido óseo, aparato masticatorio*

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Introduction

The masticatory apparatus, including stomatognathic system, is a functional unit of the human body, which is mainly responsible for speech, chewing, and swallowing. It is built of bones, joints, ligaments, teeth and muscles. The main elements of the skeleton that makes up the stomatognathic system include the maxilla and mandible, in which the teeth are inserted, and the temporal bone which connects the mandible with the skull by means of the temporomandibular joint. Bioelements and heavy metals enter the body in various ways. They can be taken together with food or water, and, in addition they can also be inhaled from cigarette smoke and polluted air, especially in highly industrialized areas.[1] The oral cavity and its hard tissues are the first to be exposed to exogenous factors during feeding and breathing. Excessive consumption of cadmium, chromium, cobalt, iron, as well as zinc, copper, and iron deficiencies of can cause metabolic disorders or destruction of bone tissue in the alveolar process of the mandible and other bones of the masticatory apparatus.[2] These metals affect calcium metabolism, which plays a strategic role in bone mineralization.

Cadmium

Cadmium (Cd) is the main heavy metal present in environmental and occupational hazards. Exposure to this metal can also occur as a result of food consumption (spinach, sunflower seeds, beef liver and peanuts), environmental, and industrial exposure, as well as during active and passive smoking.[3] As reported by Satarug et al., diet is the main source of Cd exposure, especially for people living in areas with high levels of Cd pollution.[4] The European Food Safety Authority (EFSA) has established a new PTWI (permitted tolerable weekly intake) of 2,5 μg / kg of body weight taking into account information on Cd intake in the diet. (0.357 μg / kg of body weight / Day).[5] The content of this element in the body of healthy people is approx. 5-40 mg and exceeding this value is associated with toxic effect of this metal on the body.

With respect to the human body, Cd affects homeostasis necessary for calcium metabolism.[1] Cd lowers bone mineral density (BMD), induces hypercalciuria, osteomalacia, and osteoporosis, increases the risk of fractures and chronic exposure to Cd causes Itai-itai Disease, which is associated with weakened and brittle bones. There is also evidence that Cd interferes with the activity of calcitropic hormones.[6] Another negative effect of this metal on human health is a decrease in the concentration of other elements in the liver, such as magnesium, iron and selenium, and increased levels of zinc, copper and manganese. Study of Engstrom et al. has shown that even low dietary exposure to Cd is associated with bone fragility in postmenopausal women.[7]

In the context of the masticatory apparatus bones, it is reported that human teeth are a site of Cd accumulation and possibly the source of exposure to the adjacent alveolar process bone. The results presented in the study of Browar et al. revealed that animals given daily doses of Cd (0.6 mg / kg / day) for up to 12 weeks showed significant time-dependent changes in the level of the periodontal bone as measured by the cemento-enamel junction (CEJ) - alveolar process bone crest (ABC) Distance. There was a significantly greater distance between CEJ and ABC when comparing 12-week-old animals exposed to Cd with saline-treated control group, indicating lower level of periodontal bone.[8] In another study, Browar et al. found that a greater accumulation of Cd in the alveolar process bone suggests that Cd may have a more direct osteotoxic effect in this bone compared to other types of bones.[9]

Another mechanism of the toxic effect of Cd is the intensification of oxidative stress in soft and hard tissues of the body. Cd affects bone metabolism by altering the oxidative-

antioxidant balance resulting in oxidative stress. As reported by Brzóska et al. the effect of Cd on oxidation-reduction processes in bone tissue depends on the level of exposure to this element and location of the bone. In the study of this group of researchers, Cd reduced the antioxidant capacity of bone and strengthened its oxidative state, causing oxidative stress and modification of oxidation proteins and / or lipids. In bones of rats treated with 5 and 50 mg / l Cd, there was a decrease in total antioxidant status (TAS) and antioxidant enzyme activity, as well as an increase in total oxidative status (TOS) and concentration of H_2O_2 and protein carbonyl groups (PC). Higher exposure to this metal led to an increase in the concentration of lipid peroxidation (LPO) and a decrease in all thiol groups (TSH). The results provide evidence that even moderate exposure to Cd induces oxidative stress and oxidative modifications in bone tissue.[10]

One of the main sources of Cd is cigarette smoke. After smoking one cigarette containing an average of 1-2 μg of Cd, 0.1-0.2 μg of this element enters the lungs with cigarette smoke.[11] Smoking 20 cigarettes per day is equivalent to providing 40 μg of Cd with food, showing that Cd consumption is doubled in this case.[12] Alhasmi et al. in a study involving both smokers and non-smokers with periodontal disease, found that the level of Cd in the teeth of smokers was higher compared to the teeth of patients without periodontal diseases.[13] Smoking is also associated with a high risk of delayed or lack of bone union. Preoperative smoking cessation is an important element in improving surgical prognosis. Changes in bone biology in smokers can persist for a long time even after smoking cessation, resulting in impaired fracture healing.[14]

Zinc

Zinc (Zn) is an essential nutrient that plays an important role in the growth, development, and maintenance of healthy bones. In an average person weighing 70 kg, Zn is the sixth most abundant metal in the body (2.3 g).[15] Deficiency of this element in the diet can change the standard distribution of Zn stored in the body. Zn is preferentially localized in bone, so when its access is limited with food, its serum level is maintained at the vital level due to the preferential mobilization of Zn from bones.[16]

Knowing the role of Zn in the development and growth of the skeleton, numerous studies have been conducted to determine the effect of Zn on the activity of osteoblasts. Common observation was that Zn promotes osteoblast proliferation in primary and established osteoblastic cell models.[17] Doses of Zn in the range of 1-50 μM favourably affect the activity of osteoblasts, while doses exceeding this range inhibit osteogenic activity, and below this range they do not induce measurable effects.[18] This fact is confirmed by the research of Azgin et al., in which it was shown that the number of osteoblasts was significantly higher in the Zn-treated group than in the control group without Zn in rabbits with maxillofacial fractures treated topically and intraperitoneally with Zn.[19] It should also be noted that Znis an important element in the process of bone remodeling by regulating calcitonin secretion, which leads to a decrease in osteoclast activity, collagen synthesis and activity of alkaline phosphatase (ALP), an strategic enzyme for the mineralization of the collagen matrix of the bone tissue. The important influence of Zn on bone development and growth is confirmed by studies of Hojyo et al. who found that mice with knockout of the Zn transporter Zrt/Irt-like protein 14 (ZIP14) had shorter long bones and showed dwarfism compared to wild-type mice.[20] Seyedmajidi et al. studied the effect of low levels of Zn consumption on the teeth, mandible and maxilla of rats during growth. In their experiment, the group with a low Zn content showed a significantly lower density of the trabecular bone compared to the control group, and a decrease in both body weight and growth of the craniofacial bones.[21]

A beneficial effect of Zn on bone tissue was also noticed by Tiffany et al. They described an increase in the mineral content in a class of mineralised collagen scaffolds developed for the regeneration of craniomaxillofacial bone by the incorporation of Zn ions to promote osteogenesis in vitro. Unrestricted compression tests showed that the inclusion of Zn ions affected the modulus of elasticity of the scaffold, with 5x Zn and 10x Zn scaffolds showing a much higher modulus of elasticity than traditional mineralised and 1x Zn scaffolds.[22]

The positive effect of Zn on bone metabolism is eagerly used in dentistry, specifically in the field of Implantology. As noted by He et al., bone formation is reinforced around the materials with changed surface containing Zn. Zn coating of titanium using various surface modification procedures increased bone adhesion around the modified surface material based on mechanical tests on rabbit models.[23]

Copper

Copper (Cu) is one of the basic trace elements involved in many biological processes, such as: enzymatic reactions, nucleic acid synthesis, antioxidant defense iron metabolism, and immune function. Cu deficiency can lead to impaired bone and cholesterol metabolism and cardiovascular disorders.[24]

In relation to bone metabolism, Cu acts as a cofactor of lysyl oxidase, one of the most important enzymes involved in collagen maturation. Collagen is the basic building block of the extracellular matrix of bone tissue, and integrity of the bone matrix is crucial for bone strength and plasticity.[25] Animal studies have shown that Cu deficiency is associated with decreased bone strength and bone quality deterioration leading to osteoporotic changes.[26] This fact is confirmed by the research of Marquardt et al. who observed that infants with short bowel syndrome and those on prolonged enteral nutrition developed osteoporosis and metaphysis changes caused by low levels of copper in enteral nutrition and diarrhoea. Cu supplementation improved or reversed bone disorders in these children.[27] Sierpińska et al. tested fifty patients with significant tooth abrasion matched to 20 people in control group with no tooth abrasion. Vertebral BMD and Cu content in tooth enamel, saliva, and serum were measured in all patients. Among people with advanced tooth abrasion, decreased vertebral BMD and significantly lower concentrations of Cu in the enamel were observed than in the control group. The researchers concluded that decreased lysyl oxidase activity may result in decreased collagen reticulation in tooth tissues. These conclusions were related to level of Ca in serum, osteocalcin and vitamin D. These researchers also concluded that reduced Cu levels may play a significant role in the pathophysiology of highly mineralized tissues in the human body.[26] It is worth paying attention to the research of Shi et al. concerning the role of Cu in implantoprosthetics. These researchers systematically evaluated mesoporous silica nanospheres doped with Cu, which, through in vitro biological evaluation in the immune environment, provided precise evidence that these nanomaterials can promote osteogenic / angiogenic factors and inhibit osteoclastogenic factors by immune cells. There is also an opinion that Cu is an antibacterial agent, which is crucial for the effective process of repairing inflammatory processes in the bones.[28]

However, not all studies report only positive effect of Cu on bone tissue. Sadeghi et al analyzed the relationship between Cu concentration in plasma and BMD in 135 women from Iran and concluded that plasma Cu levels were higher in patients with low BMD than in control group patients.[29] In another study, Qu et al. analysed data from 722 subjects and concluded that people with copper concentration in serum <98.5 μg/dl had lower total BMD by 0.049 g/cm^2 compared

to subjects with a Cu concentration of 98.5–114 μg / dl, while those with the highest serum Cu concentration (≥134 μg / dl) had an approximately 4-fold increase in risk of total fractures compared to subjects in the 98.5–114 μg / dl Cu concentration group. There was also a significant linear relationship between the increase in serum Cu concentration of 10 μg / dl and total fracture in men.[30]

Chromium

Chromium (Cr) is present in the environment at various oxidation states, with Cr (III) and Cr (VI) being the most common. Cr is commonly found in nature, in water, soil, rocks, volcanic ash and dust. Cr (VI) is a by-product of industries including electroplating, textiles, tanning and burning of fossil fuels.[31] Cr (III) is present in a variety of foods such as meat, fish, eggs, nuts, whole grains, vegetables, and fruit. It is necessary for normal functioning of the human body in small doses because it is involved in the metabolism and regulation of carbohydrates.

In bone tissue, Cr has been shown to affect the function of human bone cells. In vitro studies conducted by Shah et al. revealed that Cr (VI) is captured by osteoblasts, and more specifically by membrane transporters. It is then immediately reduced to Cr (III), inducing an increase of reactive oxygen species, oxidative stress, and DNA damage. These researchers also noted that Cr (VI) and Cr (III) reduce the activity of ALP and bone mineralization.[32] In another study, Andrews et al. revealed that Cr (VI) reduces osteoblast survivability as well as osteoclast number and bone resorption.[33] It has been proven that Cr (III) modulates the expression of chemokines and cytokines in bone cells by inducing osteolytic processes or changes in osteoblast migration along chemokine gradients.[34] Alrabeah et al. found that stimulation of osteoblastic cells with metal ions also enhanced the expression of Receptor Activator for Nuclear Factor κ B Ligand (RANKL). The ratio of RANKL / osteoprotegerin (OPG) was increased in cell cultures in experimental group exposed to cobalt (Co) Cr alloy. The altered ratio of RANKL to OPG induces an imbalance of bone metabolism, which is an important factor in pathological bone resorption. Therefore, the results of this study suggest that metal ions, including Cr and Co, can alter cellular components in osteoblast cells responsible for regulating osteoclast differentiation.[35] Zijlstra et al. also reported that the RANKL / OPG ratio increased after 72 hours of incubation of osteoblast cells in almost all tested concentrations of Co and Cr (1-100 ppb).[36]

Data from the study of Drynda et al. shows that divalent Co ions and trivalent Cr ions have different effects on bone-forming cells. According to the researchers, Co^{2+} ions decreased the expression of all three isoforms of TGF-β (transforming growth factor beta) in osteoblast-like cells, but their inhibitory effect on bone mineralization was not observed in the studied concentrations. The studied Cr (III) ions did not affect the expression of TGF-β, but strongly inhibited bone mineralization in vitro.[34] According to Arafa, who in his study examined eighty patients divided into two groups who received movable partial prostheses with titanium and chromium-cobalt connectors, bone loss ranged from 0 mm at the time of inclusion to 0.05 mm in the titanium alloy group and from 0.04 mm to 0.15 mm in the Cr-Co group. The difference in bone loss between the two groups was statistically significant ($p = 0.01$). The tissue response ranged from 0 to 0.02 in the titanium alloy group and from 0 to 0.16 in the Cr-Co group. The difference in tissue reaction was statistically significant ($p = 0.02$). These results indicate a negative effect of Cr and Co on bone tissue.[37]

Cobalt

In the natural environment, cobalt (Co) is found in sulfide, oxide and arsenic minerals. It is a trace element necessary for the synthesis of vitamin B12. Plant food products are the

main source of Co in the diet.[38] People working in the hard metal manufacturing industry, as well as gas turbine, space propulsion, base metal refineries workers, dental technicians, construction workers and the electronics industry workers are particularly exposed to Co. In the human body, Co ions interact with DNA and nuclear proteins, ultimately causing cell death. Co ions have the ability to penetrate the cytoplasmic membrane, accumulate in the cell nucleus, and then in the surrounding cytoplasmic structures.[39]

In relation to bone tissue, it has been observed that cobalt alloy is capable of causing extreme inflammatory bone loss in vivo. This mechanism is explained in several ways. As reported by Samelko et al. cobalt alloy implant residues act as a very strong danger signal known as danger-associated molecular pattern (DAMP), acting through the inflammasome pathway to produce IL-1β and that this DAMP alone is sufficient to induce inflammatory osteolysis.[40] Alrabeah et al. has reported that Co^{2+} ions in culture medium induce the production of pro-inflammatory cytokines in human osteoblastic cells, thereby inducing a shift of bone homeostasis towards bone resorption.[35] Another group of researchers, led by Drynda, suggests that the effect of Co^{2+} ions on bone homeostasis may be associated with inhibitory effects on the transcription of cytokines regulating bone formation, e.g. TGF-β1/3, and thus on bone-forming osteoblast activity, e.g. collagen production.[41] The results of the cell death ELISA test performed by Kanaji et al. show that exposure to Co ions induced osteocyte necrosis. In addition, fluorescence images provide qualitative evidence of a decrease in the total number of cells and a higher number of dead osteocytes exposed to Co ions at high concentration (0.50 mM).[42] Studies of Pajarinen et al. showed however, that the addition of Co ions to the cell medium caused a decrease in proliferation and function of osteoblasts and differentiation of mesenchymal stem cells into osteoblasts.[43]

Not all publications report a negative effect of Co on bone tissue. Liu et al. ascribed the type of effect of Co on the bone cells to its concentration. They found that Co at high doses (>10 ppm) had a significant negative effect on the growth of macrophages and BMSC (bone marrow stem cells). Lower concentrations (0.1-5 ppm) of Co had no toxic effects on BMSC, macrophages and PBMC (peripheral blood mononuclear cells). No systemic toxicity was observed in vivo in the low concentration groups (0.1-5 ppm). Cytokine profiles in multiple interacting systems were different in various dose groups, for example 1 ppm of Co had an optimal and complex effect on systemic osteoimmunomodulation, early angiogenesis, and regeneration of bone tissue.[44] Ignjatović et al. also reported a positive effect of Co. In their experiment, increase in the amount of Ca ions substituted with Co by 12 wt% corresponded to an increase in the rate of osteogenesis and the generation of newly formed and mature calcified bone. After 24 weeks of reconstruction using nanoscale Co-substituted hydroxyapatite with 12 wt% Co ions, intensive angiogenesis, vascularity, migration, and multiplication of bone-forming cells and maximum values of alkaline phosphatase and bone density were obtained.[45]

Iron

Iron (Fe) is a trace element that is essential for the proper functioning of human physiological and biochemical processes, such as electron transport, oxygen binding, and acting as a catalyst for hundreds of enzymes. The main sources of Fe in the diet include red meat and egg yolks.[46]

In bone physiology, Fe plays a key role in 2 processes: vitamin D metabolism and collagen production. Excessive Fe level, as well as Fe deficiency, are associated with bone weakness, suggesting that balanced bone homeostasis requires optimal Fe level. Numerous pieces of evidence suggest that high as well as low Fe levels affect the

differentiation and activity of osteoclasts and osteoblasts in a manner conducive to bone loss.[47] Diaz-Castro et al. conducted studies that proved reduced dietary Fe intake induces unbalanced bone turnover, the end result of which is bone weakness characterized by low BMD and reduced bone mineral content.[48] The same group of researchers reported in another study on animals that Fe deficiency reduces bone formation and / or increases bone resorption markers.[49] All of the above parameters were normalized after introduction of a normal or Fe-enriched diet. However, a thorough study conducted by Zhao et al. which consisted of examining human osteoblast cells to determine the effect of both excess and low Fe levels on osteoblast activity, revealed that the effect of reduced Fe levels is biphasic; mildly low Fe induces osteoblast activity, while very low Fe levels inhibit osteoblast activity. The researchers also concluded that excess Fe inhibits osteoblast activity in a concentration-dependent manner.[50] Studies on whether increased Fe stock affect bone health in postmenopausal women were conducted by a group of researchers led by Kim (it should be noted that about a third of postmenopausal women suffer from osteoporosis and subsequent osteoporotic fractures). These researchers proved that the annual bone loss rate correlates with ferritin level in plasma, indicating that increased total Fe stock in the body is an independent risk factor for increased bone loss in postmenopausal women.[51]

Attention should also be paid to the effect of iron on the induction of reactive oxygen species (ROS), which also have a negative effect on bone tissue. Fe participates in the production of ROS, and due to the fact that it is a highly transition metal, it also catalyses the formation of ROS. Some studies prove that Fe affects acceleration of the production of ROS, which play a key role in promoting osteoclastogenesis.[52] Recent experiment showed that Fe induces osteoclastogenesis of macrophages derived from bone marrow in a mechanism dependent on the production of ROS and activation of the NF-kB signalling pathway.[53] As noted by Tian et al., high doses of Fe in mice treated with Fe dextran resulted in increased ROS and bone resorption, resulting in disorders of bone structure and material properties and thus bone mass loss. In another experiment conducted by Balogh et al. in vitro, excess Fe inhibited osteoblast proliferation, differentiation, and activity, whereas Fe overload favoured differentiation of osteoclasts and bone resorption activity by accelerating ROS production.[54]

It should be noted that insufficient Fe during life fetal tissue may disrupt the integrity of the tooth tissue.[55]

Summary

Heavy metals, commonly found in the environment, affect bones of the masticatory apparatus to varying degrees. Some of them, even in a small concentration, have a negative effect on bone tissue, while others have a positive effect on bone and are used in modern medicine. Attention should be paid to the sources of individual metals in the environment to prevent their excessive, unwanted effect on bones of the masticatory apparatus. Due to increasing environmental pollution, concentrations of metals harmful to health should be strictly monitored. Dietary supplementation of bioelements also needs to be considered and consulted with the doctor.

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