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Effects of selected heavy metals on the metabolism and healing processes of craniofacial bones

Vliv vybraných těžkých kovů na metabolizmus a procesy hojení kraniofaciálních kostí

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Abstract

Introduction: The healing of craniofacial bones is a complex and multi-stage process that can be influenced by many factors of endogenous and exogenous origin. These factors include heavy metals, which play a significant role in the metabolism of the human body. Fractures of the craniofacial bones carry a particular risk, both because of their proximity to many important anatomical structures but also because of the function they represent for the beginning of two important systems: the digestive system and the respiratory system. It is therefore important to restore full function and normal bone metabolism as soon as possible. **Objective**: The aim of this study was to review the scientific literature on the effects of selected heavy metals: cadmium, zinc, lead, mercury, iron on the metabolism and healing processes of craniofacial bones. **Material and methods**: An analysis of the available sources shows that cadmium, zinc and lead have a negative impact on the physiological processes leading to skeletal fusion. In contrast, iron play a positive role in bone-forming processes. The effect of mercury on craniofacial bone metabolism is not yet fully understood. **Summary**: In summary, it can be concluded that heavy metals affect the healing processes and metabolism of craniofacial bones to varying degrees. The impact of these substances is not always negative. It should be borne in mind that it is extremely important to minimise the supply of some of these substances during the healing process directed at bone fusion.

Key words: bone metabolism – heavy metals – metals – skeletal bone healing processes

Abstrakt

Úvod: Hojení kraniofaciálních kostí je složitý a vícestupňový proces, který může být ovlivněn mnoha faktory endogenního i exogenního původu. Mezi tyto faktory patří i těžké kovy, které hrají významnou roli v metabolizmu lidského těla. Zlomeniny kraniofaciálních kostí představují zvláštní riziko, a to jednak kvůli jejich blízkosti mnoha důležitým anatomickým strukturám, ale také s ohledem na jejich funkci v počátečních částech dvou důležitých ústrojí: trávicího a dýchacího. Je proto vždy důležité co nejdříve obnovit plnou funkci a normální metabolizmus kostí. **Cíl:** Cílem této studie byl přehled odborné literatury o vlivu vybraných těžkých kovů: kadmia, zinku, olova, rtuti a železa

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na metabolizmus a procesy hojení kraniofaciálních kostí. **Materiál a metody:** Z analýzy dostupných pramenů vyplývá, že kadmium, zinek a olovo mají negativní vliv na fyziologické procesy vedoucí k srůstu kostí. Naproti tomu železo hraje pozitivní roli v procesech tvorby kostí. Vliv rtuti na metabolizmus kraniofaciálních kostí není dosud zcela objasněn. **Shrnutí:** Souhrnně lze konstatovat, že těžké kovy v různé míře ovlivňují procesy hojení a metabolizmus kraniofaciálních kostí. Dopad těchto látek není vždy negativní. Je třeba mít na paměti, že je nesmírně důležité minimalizovat přísun některých z těchto látek během procesu hojení zaměřeného na kostní fúzi.

Klíčová slova: kostní metabolizmus – těžké kovy – kovy – procesy hojení kostí

Introduction

In a constantly and dynamically developing world, people are often exposed to substances that have a negative impact on their health. We can count heavy metals among such factors.

Heavy metals is a general term for metals and semi-metals with a high density (above 4.5 g/cm^3), often exhibiting toxic effects on the human body [1]. They can be delivered to the body through food, contaminated water, in the workplace through inhalation of contaminated air, or in smokers through inhaled tobacco smoke, which is rich in lead, mercury, nickel or cadmium, among others [1].

Bone healing after a fracture is a complex process and multistage process, which we divide into successive phases: inflammatory, proliferative, osseous formation and the ongoing remodelling and modelling phase. These processes lead to the restoration of tissue continuity. They may be influenced by the presence of substances physiologically not involved in the bone healing mechanism, such as heavy metals [2,3].

Heavy metals that can affect the healing processes of the craniofacial bones are: Cadmium, Zinc, Lead, Mercury, Iron.

Cadmium

Cadmium is considered to be one of the most harmful metals found in nature. As one of the main sources of cadmium in the diet are considered to be products of plant origin (75 %). Cadmium concentrations in cereals and plant roots reach 25 µg/kg. The concentration of this element in plants strongly depends on the growing region and the proximity of cadmium emitters to the environment, influencing the contamination of the area [4]. Potatoes, which are rich in this element due to the cadmium-rich fertilisers used in their cultivation, play a major role [5]. Another equally important source of cadmium is food products of animal origin, the main role being played by the offal of adult animals and certain shellfish. Fish meat and crustaceans contains cadmium at 0.01–0.02 mg/kg, in offal it is much higher, reaching values of 0.2 to 1.6 mg/kg [5].

Cadmium is one of the components of tobacco smoke, and the burning of one cigarette provides the smoker's body with approximately 0.1–0.2 µg of cadmium [5].

Cd enters the human body mainly via the oral or respiratory system. The oral cavity, as well as the entire craniofacial cavity as the first element of the respiratory system and the digestive system, is strongly exposed to the negative effects of this metal. Once cadmium enters the body, it accumulates in the liver, kidneys, testes and bones and it is in these organs that it causes the most damage [5].

An epidemiological study by Alfvén T et al found that even small, sustained doses of cadmium can affect bone structure, metabolism and density [6]. These studies were confirmed in experiments on rats administered $CdCl_2$ (1 mg/kg body weight) over a period of 49 days. On the day the laboratory animals were killed, an atomic absorption spectrometry (ASA) test was performed on the bones of these animals. The experiment proved that continuous exposure to even low doses of cadmium alters the structure of the spongy bone, which is abundant in craniofacial bones, among others [7].

Another issue is the effect of Cd on fracture incidence. In a study conducted in Belgium by CadmiBel in people with doubled U-Cd concentrations (in urine), a much higher incidence of fractures was observed, with a significantly higher frequency in women (RR = 1.73, 95% CI = 1.16–2.57). In contrast, in men, the rate was lower at (RR = 1.20, 95% CI = 0.75–1.93) [8].

Cadmium exacerbates the incidence of osteoporosis, which in turn affects the increased risk of fractures in the elderly. A study by Wallin et al demonstrated an association between high urinary cadmium concentrations and low BMD (densitometry) and an increased risk of osteoporosis-related fractures [9–11].

In a study by Sughis et al conducted on a group of 155 Pakistani school-aged children, it was noted that a doubling of urinary Cd concentration was associated with a 1.72-fold higher urinary DPD (Pyrylinks D) and a 1.21-fold higher urinary calcium content in the children studied. These results indicate a direct link between exposure to even low doses of cadmium and bone resorption also among adolescents [12].

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Zinc

Zinc has been known as an essential element since 1970. The daily requirement for this element is approximately 10 mg. 85 % of zinc is stored in bone and muscle [13]. Zinc is a cofactor for many enzymes, mainly metalloproteins, and has many physiological roles. The element stimulates bone-forming processes and inhibits bone resorption [14,15]. Zinc-dependent enzymes are involved in bone metabolism [16]. Zinc has been shown to activate alkaline phosphatases, which enable mineral deposition in bone [17]. The cellular mechanism of the beneficial action of this element is that it stimulates the differentiation and proliferation of osteoblastic cells [18].

In 2007, a study was conducted on the effect of zinc supplementation on alkaline phosphatase activity and bone fracture healing [18]. It was shown that zinc supplementation for 60 days had a stimulating effect on callus formation during fracture healing. Zinc stimulates protein synthesis in osteoblasts through the activation of aminoacyl-tRNA synthetase and enables the growth of bone components and an increase in calcium content [19].

Zinc supplementation is useful as a stimulant for healing of fractures of the facial bones and bones of the musculoskeletal system. [19]. Clinical studies have shown that serum skeletal alkaline phosphatase activity is used as an indicator of the rate of bone formation. Zinc additionally reduces the secretion of cytokines that inhibit the activation and formation of osteoclasts [20]. It has been shown that zinc supplementation can positively influence bone formation as it does not induce inflammatory processes, but affects the BMP protein [21].

In oral maxillofacial surgery, zinc alloy systems are used to stabilise bone fractures. Zinc is involved in the regeneration of hard tissues, it also promotes wound healing and keeps the periodontium healthy [22,23]. Zinc alloys and zinc itself have excellent osteogenic properties and low reactivity.

Ping Li et al. suggested that zinc-copper alloy is a good implant material for maxillofacial bone and improves cell proliferative activity [24]. The effectiveness of internal stabilisation of maxillofacial fractures with Zn-Mg-Fe alloy was also evaluated. In comparison with PLLA and Ti alloy, in addition to good stabilisation, it additionally enabled new bone formation due to the osteogenesis of zinc ions produced during degradation [25].

Topical injection of zinc ($ZnCl_2$) salts increases bone mechanical strength and stability after healing of bone fractures [26]. In contrast, Tokudome et al. found that topical injection around the alveolar bone of zinc stearate and zinc octanoate improves the formation of this bone and inhibits osteoclast activity within it [26].

Zinc is used for Guided Bone Regeneration (GBR) membranes. Membranes made of pure zinc with 300 μm holes showed the best osteogenic capacity in a rat model of cranial defect. This ability was compared to membranes made of Ti, as demonstrated by Guo et al in their study [27]. Chou and research group prepared a GBR membrane with Zn and HAp and compared its performance with collagen membrane and defects not filled by any membrane. Bone regeneration in the Zn-HAp group was significantly higher than in the other groups [28].

Zinc-doped bone subsytems also play an important role in maxillofacial surgery. These materials can release zinc ions to inhibit osteoclasts, stimulate osteoblast activity and form new mineralised tissue [26].

So far, no ideal agent has been found for the treatment of bone fractures and defects, but zinc and its compounds may act as a pharmacological tool to stimulate the healing of bone fractures in the craniofacial region.

Lead

The widespread presence of lead in the environment results in constant exposure of the human body to this element. Its effects depend on the dose received by an individual. The main sources of exposure to this element occur in environments such as: battery or paint factories, ferrous and non-ferrous metallurgy, ceramics, machinery and printing industries, scrap yards [29].

It is an element absorbed into the human body mainly through the respiratory tract, the skin, and to a lesser extent through the digestive system. Acute poisoning by this compound is rare, but chronic poisoning causes pathology in the nervous and digestive systems [30].

Lead has the ability to accumulate in the human body: 90–95 % of total lead in the body is stored in mineralised tissues such as teeth and bones, which is related to its ability to replace other divalent cations in the hydroxyapatite network (calcium, magnesium and iron). Lead is able to directly affect the mechanisms of bone mineralisation by acting on the activity of osteoclasts and osteoblasts, but it can also indirectly affect these mechanisms by damaging organs (e.g. kidneys) involved in calcium homeostasis. The strong inhibition of calcium assimilation caused by lead poisoning, together with the metabolic imbalances it induces, can lead to the development of various bone pathologies, such as osteoporosis. These changes in composition and structure have a direct impact on the mechanical properties of bones, reducing their hardness and resistance to external stresses and impairing their physiological function [31].

Studies by Terrizzi et al, Han et al and Kim et al also demonstrated the pathological effect of lead on the healing of the mandibular alveolar bone, with a consequent loss of volume linked to a pathology in the me-

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tabolism of calcium, which is a bone constituent quite important in the need for bone regeneration. This is due to the structure of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) of which calcium is the main component, it has osteoinductive properties and is one of the main building blocks of mineral tissues in the human body, so abnormal calcium metabolism will be the cause of insufficient or disappearance of hydroxyapatite [32,33].

The co-occurrence of additional periodontal disease with elevated lead levels in the body increased the likelihood of failure of craniofacial bone healing [32,33].

The study by Álvarez-Lloret et al. showed a significant decrease in bone mineral density (BMD) and bone volume/tissue volume (BV/TV) ratio in the trabecular bone of lead-exposed rats compared to the control group. SEM images also confirmed this impairment of the trabecular structure of the alveolar bone. Their study showed higher porosity and reduced bead density in the lead-exposed group, particularly in the inter-root area of the mandibular molars. Reduced traits of the trabecular microarchitecture of the alveolar bone are associated with an increased incidence of osteoporosis and fracture risk [31].

Mercury

Even in very low concentrations, mercury poses a threat to living organisms. There is currently no information on the metabolic functions of this element. Mercury can occur in organic and inorganic forms. Organic compounds can be up to ten times more toxic. By reacting with proteins containing sulfhydryl groups in their structure, they can interfere with most enzymatic reactions [30].

Mercury is an element which, together with Cadmium (Cd) and Lead (Pb), forms the so-called "trio of death metals". Its introduction into the body can take place by ingestion, inhalation as well as through the skin, the issue that differentiates mercury from the other two elements is its additional occurrence in amalgam fillings [34].

Mercury can accumulate in bone and cartilage tissue, which can cause osteoarthritis, especially in people with a genetic susceptibility to autoimmunity. Mercury is selectively captured by cells that are affected by rheumatoid arthritis and osteoarthritis. In addition, mercury is captured by fibroblasts in organs involved in multisystem connective tissue disorders. Mercury provokes autoimmune, inflammatory, genetic and epigenetic changes that have been described in a number of arthropathies and bone and connective tissue diseases [30].

The very easy availability of Hg results in its greater or lesser impact on the human body. The consequences of bone fusion pathology are that mercury can build up in place of calcium in carbonates or hydroxyapatites, which are the natural building materials of cartilage and bone, resulting in abnormalities when these tissues need to fuse/heal [35].

Paula Beatriz de Oliveira Nunes et al. conducted a study in which they investigated the effects of long-term exposure to inorganic mercury on the alveolar bone of adult rats [36]. Changes were observed in the physicochemical components of the alveolar bone of exposed animals. The bone changes represented a tissue response at the microstructural level, such as an increase in bone volume. However, no significant dimensional changes (bone height) were observed. Exposure to inorganic mercury at this dose may promote microstructural changes and alterations in the organic and inorganic components of alveolar bone [36].

Even in low concentrations, mercury poses a risk to living organisms, as any metabolic function of this element is unknown. Organic forms of mercury are more toxic (up to 10 times more toxic) than inorganic forms, and the distribution in the body depends on the type of compound and the time of exposure [30].

Iron

The human body needs balanced levels of iron, and both elevated and reduced levels of this micronutrient have their significant effects on osteoclast and osteoblast metabolism, contributing to loss of bone mass [37].

Iron deficiency is the most common micronutrient deficiency worldwide and has negative effects on pregnancy outcomes in women and on immune function and neurological development in children [38]. Iron excess, as well as iron deficiency, disrupts the balance between bone destruction and synthesis, affecting the differentiation and activity of osteoclasts and osteoblasts. Iron excess as well as iron deficiency is accompanied by weakened bones, suggesting that balanced bone homeostasis requires optimal iron levels [39].

Dietary iron comes in two forms: hem iron and non-hem iron. The main sources of hem iron are animal products, i.e. red meat, poultry and fish and seafood. The non-hemic form can be found in legumes, cereals and vegetables. Furthermore, iron bioavailability is dependent on the correct amount of hydrochloric acid. Which is especially true for non-hem iron, which requires a low pH for proper absorption [40,41].

A study was carried out, through which it was shown that approximately 7 out of 10 people with sickle cell bone disease (sickle cell SCD) with high iron levels had reduced bone mass. Thus, iron was found to have an inferior effect on a person's overall bone function. The most common form of hereditary haemochromatosis (HH) has a strong correlation with osteoporosis, its development being linked to iron. In addition, patients with

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this condition were characterized by a higher incidence of wrist fractures, as well as vertebral fractures [42].

In the case of menopause, we can see hormonal fluctuations and changes in iron metabolism. At the same time as estrogen reduction, an up to 3-fold increase in ferritin has been noted in postmenopausal women, while the rate of bone reduction itself is faster and in a manner closely related to ferritin intake. It has also been observed that there is an inverse relationship between ferritin and, more specifically, serum ferritin in the female sex at ≥ 45 years of age. With all these observations, it has been demonstrated that an increase in total iron may be an independent factor for increased bone reduction in postmenopausal women [37].

One recent study has shown that the effect itself of low iron levels may be biphasic, namely a mild low level of this metal stimulates the activity of bone-forming cells, while a low level of iron decreases their activity [36,43]. Confirmation of the deleterious effects of excessive iron is the higher prevalence of such conditions in people with haemochromatosis, a genetic disorder involving excessive iron absorption. In everyday clinical practice, excess iron is treated with iron chelators, and successful treatment can prevent osteopenia and osteoporosis. This significantly reduces the propensity for bone fractures in the future and accelerates bone healing processes [37,41,43]. Accumulation of iron contributes to the progression of osteoporosis by inhibiting osteogenesis and promoting osteoclastogenesis, impacting the risk of femur bone fractures [44].

Summary

Environmental and occupational exposure to heavy metals is very high in today's ever-evolving world. These elements affect the overall health of the body, including the healing processes of the facial bones and bones of musculoskeletal system. The impact of heavy metals on the healing of bone fractures will be the same for both facial bones and other bones in the human body. The presence of heavy metals affects the risk of developing osteoporosis, and consequently, the fragility of all bones, which may lead to bone fractures.

The role of specialists – including dentists – is to take into account the effects of heavy metals on the healing processes of the craniofacial bones and the patient's environmental exposure to these elements. Consideration of these issues is essential to properly plan treatment and speed up the patient's recovery.

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