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Advances in the Effect of Heavy Metals in Aquatic Environment on the Health Risks for Bone

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Abstract: Bone health is closely related to national life. The pollution of heavy metals in China is extremely severe, and a variety of heavy metals in aquatic environment would have an impact on health risks for bone. At present, studies involving the relationship between heavy metals in aquatic environment and bone health have been limited. Therefore, in this study, the relationship between heavy metals and bone health based on the possible pathogenic mechanism was explored. Meanwhile, the detection technologies for heavy metals applied in aquatic environment and clinical trials were discussed to provide theoretical support for the monitoring and governance of the heavy metal pollution, and supply the prevention and treatment of bone diseases based from heavy metals for information purpose.

1. Introduction

Bone health is critical to the overall well-being of people, since the bones function for support, protection, mobility, metabolism, hematopoiesis among others. According to the data from China's National Statistics Bureau, China sees constant rising of crude death rates from illnesses related to muscles, bones and connective tissues in its urban residents between 2013 and 2016. In particular, the morbidity of bone diseases including bone tumors, bone mineral density decrease, osteoporosis irrelevant to external forces accounts for significant proportions among all bone diseases^[1]. Relevant researches reveal that bones diseases irrelevant to external forces might enjoy certain relevance to pollution of heavy metals or metalloid elements such as arsenic, which has properties in between those of metals and nonmetals. Considering that the environmental effects and toxic actions of some metalloid elements are similar to those of heavy metals, therefore, certain metalloid elements have been included in the research on environment and health^[2]. Furthermore, heavy metal pollutants in aquatic environment are main causes for human bone diseases, entering the human body by means of drinking water, living water, enrichment in plants and aquatic animals, production water etc.^[3]. Hence, study on the relation between heavy metals in aquatic environment and bone health serves as important reference for heavy metal pollution supervision and governance as well as prevention and treatment of bone diseases in China.

China's rapid industrial and agricultural development is coupled with continuous increase of heavy metal content in pollutants discharged by various enterprises into the waters, leading to that heavy metal pollution constantly worsens aquatic environments with mercury (Hg), cadmium (Cd), chromium (Cr), lead (Pb), arsenic (As) being identified as main pollutants^[4]. Wang et al. have conducted research on content of trace heavy metals in part of rivers, lakes, seas of China and their changes, and found that rivers have higher such content than lake areas and suffer severer pollution, while the distribution of heavy metal in sea water is dependent on complex factors like atmospheric dry and wet deposition, runoff, salinity, pH and properties of the sea water itself^[5]. Frequent



occurrence of river heavy metal pollution incidents in recent years have been greatly concerned by the society, among which, Cd and Pb pollution incidents are the most serious^[6,7]. In addition, the Ministry of Environmental Protection figures show that 4035 and 182 persons were diagnosed as excessive blood lead and cadmium respectively resulting from heavy metal pollution incidents in 2009, including 32 group incidents. The *Heavy Metal Pollution Comprehensive Prevention and Treatment 12th Five-Year Plan* assessment results released by the authority reveals a general good implementation condition of heavy metal pollution treatment, however, the total discharge of heavy metal keeps running high^[8], which means China is still exposed to high risk of potential environmental dangers brought by heavy metals.

Presently, organs and neural system are main subjects of studies on the health effect of heavy metal pollution. As for bone health issues, Cd, Pb, Cr, As, and V are essential in the mechanisms. In this study, possible health risks posed by such five elements in the aquatic environment were reviewed, meanwhile, the detection technologies for heavy metals applied in aquatic environment and clinical trials were discussed to provide theoretical support for containing ecological risk from heavy metal in aquatic environment.

2. Toxicity effect of heavy metal on bone

2.1 Cadmium (Cd)

As one of heavy metal pollutants to the environment, Cd is widely used in chemical engineering, electroplating, nuclear industry among others. China faces rather serious Cd pollution with Cd content in industrial waste discharged each year as high as over 680 tons^[9]. Cd has a half-life period of between some 10 to 30 years in the human body with a low metabolic rate, can cause mutagenesis, carcinogenesis, and teratogenesis to multiple organs, thus it has been rated as IA carcinogen by the International Agency for Research on Cancer^[10, 11, 12].

Researches show that exposure to a low level of Cd affects osteogenesis and bone metabolism^[13], while long-term such exposure brings about osteopenia in human body, which in turn, incurs osteoporosis and osteomalacia, causes bone mineral density decrease in human body, i.e. postmenopausal women, thus, is prone to bone fractures, with higher disability rate induced^[14, 15]. Besides, Cd exposure can further lead to lower performance of intestines in calcium (Ca) absorption, speed up dissolution process of bone calcium, and finally bring about disorders in osteogenesis and normal bone metabolism processes^[16, 17].

Cd's effect on bone health is realized mainly by way of its impact on Ca metabolism. Currently, two mechanisms are assumed in Cd's effect on Ca metabolism. The first deems that Cd directly inhibits active transport of Ca through competition. The second assumes that Cd leads to decline of vitamin D₃ (1,25-(OH)₂-D₃) synthesis via impairing renal function, which indirectly impacts Ca metabolism^[18]. Besides, exposure to Cd quickens osteoclast cell (OC) proliferation, which leads to imbalance between bone formation and bone absorption^[19]. As kidney is the target organ of Cd accumulation in human body, renal damage is brought about in early stage of Cd exposure while osteoporosis and osteomalacia are frequently encountered in late stage, eventually results in spontaneous fracture^[20].

In 1986, "Itai-itai disease" was diagnosed among residents along the Jinzu River basin in Japan, who had eaten agricultural and aquatic products contaminated by industrial wastewater containing Cd. In 2012, excessive Cd concentration was found in the lower stream of Longjiang River Hechi Section with the peak value of Cd concentration 80 times surpassing the Water Quality Level III of China, directly threatened the water security of local residents, and the breeding industry of the region was also plagued. Bone diseases induced by Cd are not only found in areas with Cd pollution, but also are frequently encountered in occupational populations constantly exposing to cadmium^[21], for instance, plating operators and welding workers are frequent victims of cadmium poisoning. The abovementioned results were not only found in industry personnel exposed to high Cd level, the negative correlation between Cd exposure level and bone mineral density was established in general population. The group exposed to medium to high level of Cd has significant higher risk of suffering

osteopenia and osteoporosis than that exposed to low level^[22].

2.2 Lead (Pb)

Pb is one toxic heavy metal trace element nonessential to the human body and severely endangers human health. About 4 million tons of Pb is consumed worldwide each year, however, a mere fourth of which is recycled, and the rest is contaminating our environment in different ways^[23]. Presently, China's Pb discharge mainly comes from machinery manufacturing, printing, shipbuilding and car exhaust. Enjoying a long life in the environment, Pb intrudes into the human body through digestive tract, respiratory tract and skin, and undermines the human health^[24]. In China, Pb poisoning is claimed one of major occupational diseases, with the lead poisoned personnel in smelting and battery industries accounting for a shocking 66.03% of the total occupational population^[25].

Pb can exist in the form of soluble salt and combine with certain proteins in body fluid, with rapidly reduced toxicity and slower clearance. However, some 90-95% intruding Pb accumulates in bones, enjoying a half-life period of 5 to 10 years with relatively stable concentration^[26, 27]. Bones are main organs for Pb storage and target in human body. Pb accumulated in bones can combine with bone mineral and organic matrix, by means of higher bone turnover process, it is released to blood, causing increase of blood lead level^[28]. Since Pb has the similar metabolism with Ca, when the human body suffers from Ca deficiency or encounters change of acid-base balance, lead phosphate stored in bones transforms into lead hydrogenorthophosphate which has higher solubility, then Pb poisoning is caused^[29].

By lowering the levels of active vitamin D₃ (1,25- (OH)₂-D₃) and parathyroid hormone in plasma, Pb affects bone cell differentiation and function^[30]. It further inhibits the secretion of bone gamma-carboxyglutamic-acid-containing proteins (BGP) which functions to promote interaction between OB and OC as well as enhance new bone formation^[31, 32], interferes combination of osteocalcin with hydroxyapatite, thus hinders normal bone mineralization, finally affects normal development of bones^[33]. Studies reveal that Pb's competition with Ca in seizing the Glu-Malonate binding site on BGP while suppressing OB osteocalcin gene and its expression might be explained as one of mechanisms in which Pb inhibits BGP^[34]. Aside from the said mechanism, lead can directly curb OB in producing collagen, osteopontin, and osteonectin, inducing significant decline of bone-specific alkaline phosphatase, which is essential in bone mineralization^[35].

Clinical data indicate that where Pb concentration in drinking water is close to 50µg/L, the blood lead level in human body is about 30µg/L^[36]; with increased blood lead level of mothers, the breast fed babies experience rising lead level, which hinders bone development^[37]. Again, in 2009, lead pollution caused by illegal operation of smelting facility in Fengxiang County of Shaanxi Province led to excessive blood lead level of 84% local children^[38]. In 2010, excessive blood lead level was detected in locals of Neijiang City of Sichuan Province. With an aim to reduce the harm by Pb to human body, the Chinese *Integrated Wastewater Discharge Standard* and the *Standards for Drinking Water Quality* respectively stipulate that the total Pb concentration shall not exceed 1.0mg/L and 0.05mg/L.

2.3 Chromium (Cr)

Cr is mainly used in iron and steel, electroplating, leather, pharmaceutical, dyes, pigments, preservatives and other industries, the global annual output of Cr is about 7.5 million tons, and the Cr pollution caused therefrom should not be underestimated^[39].

Clinical studies on Cr are limited, mainly being carried out in vitro cells. OB is an important function index in the process of bone formation and bone tissue repair. Collagen Type-I, which plays an important role in fracture healing, is one of the early signs of OB differentiation^[40]. Chromium ion can inhibit the secretion of Collagen Type-I and its mRNA expression in OB; The study conducted by Ruan et al. has shown that, treated by different concentrations of chromium chloride (CrCl₃), the cell viability of mouse OB and human immortalized OB was decreased obviously^[41]. Studies on hexavalent chromium ion and orthopedic diseases have shown that Cr is cytotoxic to osteoblast-like cells and that toxicity is positively correlated with its concentration^[42], which may be explained that

high concentration of chromium ions stimulate OB to release the ligand of κ -B receptor activator and osteoprotegerin, and promote the ratio between the ligand and osteoprotegerin to increase, thereby reduce the OB vitality, then promote OC differentiation and maturity^[43].

In addition to industrial applications, as the main component of alloy for prosthesis, Cr is widely used in orthopedic surgery. Trivalent chromium ion can affect the proliferation and activity of OB, possibly because that cytokine interleukin-18 has been strengthened under the effect of trivalent chromium and the OB differentiation is thus inhibited^[44], so osteoporosis is caused around the prosthesis, then lead to prosthesis loosening^[45]. And at present, no effective alternative metal is available for clinical application. For orthopedic patients, the chromium alloy in the prosthesis may have slow release and accumulation of chromium ions under the mechanical friction and the patient's own bioelectrochemical environment, which may lead to OC activation and proliferation, result in osteolysis, trigger aseptic loosening and local osteoporosis, then ultimately affect bone healing of the patient^[46]. Therefore, paying close attention to the dynamic changes of Cr content in the body can play a positive role in the treatment of orthopedic patients.

In 1966, a serious Cr pollution accident happened in Jinzhou, Liaoning Province, in which, a ferroalloy plant discharged a large amount of hexavalent chromium, left the water Cr concentration significantly higher than the stipulated one in the drinking water standards of China, resulted in a significant increase in cancer mortality among residents in the downstream pollution area from 1970 to 1978. In 2011, a large number of livestock deaths^[47] were caused in Qujing, Yunnan Province due to illegal dumping which made the hexavalent chromium in water 2,000 times exceeding the stipulated figure.

2.4 Arsenic (As)

Arsenic is a metalloid element with three allotropes. Because the environmental effects of As and its toxic effects on living organisms are similar with heavy metals, the relationship between As and bone health was also discussed in this study. Generally speaking, As content in clean air, water and food is very low, with high As content being found in the air of coal-burning areas, groundwater of individual area as well as seafood^[48]. At present, As is generated from two sources, one is the natural source, mainly including rock weathering, arsenic volcanic magma eruption, etc., which well explains why the arsenic content of spring water and groundwater in individual area is high; the other comes from human activity, mainly involving mining, metal smelting, coal burning and pesticide application, etc.^[49].

After the inorganic arsenic compounds are taken into the digestive tract, they are absorbed in the gastrointestinal tract and entered into the blood, most of them are combined with the globin of hemoglobin, a small part of them are combined with the plasma protein, and ultimately stored in bones, hair and nails in the form of inactive arsenic^[50]. Excessive arsenic with protoplasmic toxicity can make a lot of important enzymes in the body lose their activity, which seriously affect the respiration, division and proliferation of cells. Although the toxicity of pentavalent arsenic is relatively light, animal experiments have shown that pentavalent arsenic has significant accumulation tendency in bones and excessive arsenic may aggravate skeletal fluorosis^[51, 52]. Presently, there is no clinical report on the direct toxicity of arsenic to bones. At the same time, there are limited studies on osteoblastic toxicity of arsenic at the cell and molecular level in China and abroad.

In 2007, an As pollution accident happened in Minquan County, Shangqiu City, the average As concentration of river water was up to 4mg/L, much higher than that stipulated in the drinking water standards of China (0.05mg/L)^[53]. Since 2008, the average concentration of As in Yunnan Yangzong lake water is 0.128mg/L, and the water quality is rated as an inferior Class V, which seriously affects the running of enterprises along the lake and daily life of residents (totaling 26596 persons)^[54]. In 2002, 60 regions out of 64 regions in Bangladesh were threatened by high concentration of As-containing groundwater, 28-62% of its nationals drank the polluted As-contaminated water, and more than 10,000 patients had been diagnosed as severe As poisoning, the overall health level of the nationals were seriously affected^[55].

2.5 Vanadium (V)

Being mainly used in steel and iron improvement, V is also dubbed as metal "vitamin". As a highly efficient catalyst, some vanadium oxides have been widely applied in the chemical industry. Besides, V is generally contained in fossil fuels, a large number of fossil fuel combustion emit large amounts of V to the atmosphere^[56], which not only has strong catalytic effect on sulfur dioxide, causing serious acid rain, but also enters into waters through rainfall and soil infiltration and other ways, which can result in V pollution in waters.

V is an essential trace element in the human body and plays an important role in cell growth and carbohydrate metabolism. Studies have indicated that V can lower blood glucose and play a role in treating osteoporosis, and also has a two-way effect on OB. The appropriate concentration of V can promote the growth of OB and stimulate its proliferation. At the same time, as V has similar structure with phosphoric acid, it can participate in many phosphate metabolism processes^[57]. Extremely high concentration of V can inhibit the activity of ATPase and Protein Tyrosine Phosphatase (PTP) of OB, leading to a variety of phosphorylated protein tyrosine residues aggregated in certain cells, thus inhibiting the proliferation of OB. In addition, since V can reduce PTP activity, inhibit the formation of OC, thus suppress osteolytic bone absorption^[58, 59]. Therefore, both deficiency and redundancy of vanadium may inhibit bone formation, while appropriate concentration of vanadium can promote bone formation and inhibit bone absorption. Vanadium compound may become a medicine for the treatment of osteoporosis.

Due to different industrial types, the emission concentration of vanadium also varies, which should be based on specific circumstances. In 2005, due to pollution of illegal vanadium smelter, it resulted in nearly 1000 persons suffered in Jianli County, Hubei, which seriously affected the normal production and life of local residents¹.

3. Method for detecting heavy metals

From the above analysis we can see that the effective detection towards heavy metals in water serves as an important means for evaluation of heavy metal pollution in whether it poses threat to the water environmental quality and the bone health of human. Therefore, in-depth study of water heavy metal detection method can provide a complete application system and technical support for monitoring and governance of heavy metal pollution in water environment, and further deliver theoretical basis for prevention and treatment of bone diseases caused by heavy metal pollution.

Currently, various detection methods are applied for testing water heavy metal, and the traditional detection methods are spectroscopy and electrochemical method, in which, the spectroscopy consists of Atomic Absorption Spectrometry (AAS), Atomic Fluorescence Spectrometry (AFS) and Inductively Coupled Plasma (ICP), while the electrochemical method is dominated by Differential Pulse Anodic Stripping Voltammetry (DPASV)^[60]. AAS is now quite mature and can detect almost all elements, but sample pretreatment is required to ensure its accuracy. AFS detection limit is lower than AAS and can simultaneously detect a variety of elements, but its application element range is much smaller than AAS. DPASV mainly includes Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES). ICP-MS enjoys such advantages as simple operation, rapid reaction, low cost and high accuracy, however, it is not suitable for monitoring metal ions that are not easily precipitated. Similar to AFS, ICP-AES can detect multiple elements simultaneously. Apart from the abovementioned methods, biochemical detection method is also developed at a rapid rate, in which, enzyme inhibition method, immunoassay method and biochemical sensor applications are particularly prominent. Compared with traditional methods, biochemical detection method is more convenient, fast and economical, and is more suitable for instant detection of heavy metal ions on site. In recent years, there are more and more studies combining biochemical detection technology with intelligent systems, which also provides a great possibility for online monitoring on heavy metal environment.

Nevertheless, along with the unceasing change of water environmental pollutants on a globe scale, the detection methods on heavy metal pollution in water environment need to be continuously updated

to meet the practical application need in contemporary scientific research and detection. Meanwhile, it is important to note that even though the detection technology of heavy metal in blood is quite mature, but for bone diseases, heavy metals are mostly concentrated in bones, not in the blood. And presently, the clinical detection of heavy metal in bone is very difficult. Hence, to develop more cost-effective detection methods on heavy metal to meet the needs of water environment monitoring and clinical testing has important practical significance for the prevention and treatment of bone diseases in China.

4. Conclusion

For the past few years, heavy metal water pollution accidents in water have happened frequently, in order to prevent and control the impact of heavy metal pollution on bone health of people, it is necessary to explore clinical detection methods and techniques of heavy metals and provide basis for prevention and treatment of bone diseases.

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