Research Highlight

Treatment and Prevention of Skeletal Fluorosis

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Fluoride is soluble in water and accumulates in bone when absorbed by organism. Fluoride influences bone turnover by regulating certain factors, such as runt-related transcription factor 2 (Runx2) and receptor activator for nuclear factor-κB ligand (RANKL), which act as markers of osteoblasts and osteoclasts[1-2]. Excessive fluoride intake can destroy the processes of bone formation and resorption, which may lead to bone turnover disorders and result in skeletal fluorosis, a condition in which patients display various bone lesions, including osteosclerosis, osteoporosis, and degenerative joint changes. The damage caused by skeletal fluorosis is substantial. During the early stages, patients show fatigue, loss of appetite, and poor memory. Over time, as the illness progresses, fluoride accumulates in bone and may lead to dental fluorosis and damage other organs, such as angiocarpy, endocrine organs, and the nervous system. In recent years, the incidence of skeletal fluorosis has increased worldwide; indeed, skeletal fluorosis has been shown to be widely distributed throughout China and other countries, and researchers have focused on developing appropriate treatments for skeletal fluorosis[3].

Mechanisms of Skeletal Fluorosis

Bone turnover is a dynamic balance regulated by osteoblasts and osteoclasts. Excessive fluoride intake can disrupt this balance, influencing the differentiation of osteoblasts and osteoclasts and resulting in the development of bone lesions[4-5]. Many studies have evaluated the mechanisms of skeletal fluorosis. Previous studies revealed that fluoride mediates gene expression and cell viability through the mitogen-activated protein kinases (MAPK) pathway[6]. Additionally, the bone morphogenetic protein (BMP)/Smad pathway plays a role in cell differentiation induced by fluoride[7]. Li et al.[8] also found fluoride activates the Rho/ROCK pathway in ameloblasts. Moreover, fluoride can induce endoplasmic reticulum (ER) stress, leading to protein misfolding[9]. Fluoride not only mediates Runx2 and RANKL but also affects the expression of osteocalcin (OCN) and osteoprotegerin (OPG)[10]. Briefly, excessive fluoride alters the balance of bone formation and bone resorption by regulating related factors via certain signaling pathways, thereby leading to skeletal fluorosis.

Treatment of Skeletal Fluorosis

In the past few decades, studies have shown that ingestion of calcium, vitamin C, and vitamin D is effective for protection from fluorous toxicity[11]. However, intake of vitamin C alone has been shown to have little effect on skeletal fluorosis[12], and anti-inflammatory and analgesic drugs are harmful when taken long term. Many recent studies have evaluated treatment strategies for skeletal fluorosis. Blaszczyk et al.[13] demonstrated that methionine combined with vitamin E may have applications in the treatment of skeletal fluorosis. Methionine and vitamin E can reduce the effects of fluoride on soft tissues and prevent excessive accumulation of fluoride in the bone. Some nutrients have also been shown to affect skeletal fluorosis treatment. Zhao et al.[14] showed that choline attenuates damage to the chondrocyte matrix and to degradation enzymes in mice treated with fluoride. Choline can attenuate fluorous toxicity by influencing the expression of related factors. Moreover, taurine enhances thyroid gland function and renal antioxidant status in rats, resulting in restoration of fluoride-induced renal toxicity[15]. Additionally, Bouasla et al.[16] showed that pomegranate (*Punica granatum*) juice protects against fluoride-induced oxidative damages in liver tissues and erythrocytes of rats. These studies have shown that fluoride not only damages the bone but also injures other organs. More studies of the mechanisms of skeletal fluorosis have been conducted, providing a theoretical basis for the treatment of skeletal fluorosis.

In recent years, the incidence of skeletal fluorosis has increased in China. Most approaches using traditional Chinese medicine (TCM) have focused on treating bone lesions induced by fluoride.

doi: 10.3967/bes2017.020
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Zhou et al.[17] showed that the effects of acupuncture on the treatment of skeletal fluorosis are better than those of western medicine. Moreover, acupuncture was found to improve the range of joint motion and to relieve pain caused by skeletal fluorosis. Acupuncture has also been shown to stimulate urinary fluoride, which is beneficial for expelling fluoride from the body. Gu[18] showed that Cistanche has antioxidative effects and can regulate cell function. Cistanche reduces the increase in G protein expression in rats treated with fluoride, thereby alleviating skeletal fluorosis. Song[19] indicated that Gulingtongbi Wan has beneficial effects on purtenance and promotes Qi circulation, which can relieve the pain of bone joint affected by skeletal fluorosis treatment. Liu et al.[20] showed that anti-hyperosteogeny drugs stimulate urinary fluoride and enhance bone formation with a total effective rate of 95.8%. Moreover, Guo et al.[21] indicated that compound TCM also affects skeletal fluorosis treatment. Although TCM therapy is effective for the treatment of skeletal fluorosis, the accuracy of the dosage still needs to be improved in the future. According to the above studies, TCM therapy for skeletal fluorosis functions by improving immunity, promoting metabolism, and eliminating fluoride from the body through the use of some medicinal plants. Additionally, TCM can also relieve pain associated with skeletal fluorosis.

Although more studies have been performed, novel targeted therapies are still needed for the treatment of skeletal fluorosis. Based on the above studies, we found that western medicines used to treat skeletal fluorosis aimed to reduce fluorous toxicity in the body and repair damage to the body through consumption of tablets or nutrients. However, no approaches for decreasing the concentration of fluoride in the body have been developed. Therefore, these therapies may have inhibitory effects, but cannot cure skeletal fluorosis. For TCM therapies used to treat skeletal fluorosis, the mainly purpose is to reduce the concentration of fluoride in the body and improve the autogenous regulatory mechanisms protecting against fluorous toxicity in the human body; this requires long-term treatment. Therefore, comprehensive therapies incorporating western medicine and TCM treatment are expected to have significant effects in the treatment of skeletal fluorosis in the future.

Prevention of Skeletal Fluorosis

Fluoride is abundant in the environment and can be ingested through various mechanisms, leading to skeletal fluorosis. Drinking fluorous water is the primary cause of skeletal fluorosis worldwide because fluoride dissolves in water easily. Kharinar et al.[22] showed that most cases of endemic fluorosis occurring in Asia and Africa were caused by drinking fluorous water. Additionally, Fan et al.[23] indicated that fluoride can also accumulate in brick tea and that brick tea-type fluorosis is more prevalent in Tibet than in other regions. Moreover, Gao et al.[24] showed that fluorine in coal can be easily released into the atmosphere by burning and can then be taken in by breathing.

The prevalence of endemic fluorosis is related to several factors, including the environment, society, and living habits of the individual. Therefore, prevention of skeletal fluorosis may require comprehensive changes. First, providing safe drinking water can protect people against endemic fluorosis. In recent years, people have developed additional techniques to remove fluoride from water. Zhang et al.[25] indicated that the $CeCO_3OH$ nanosphere is a very viable technology to remove fluoride from drinking water in a highly effective manner. Second, improving the living standards of people will help prevent endemic fluorosis. Good living conditions will help people avoid intake of fluoride from water, tea, and coal. Additionally, education is more important for the prevention of fluorosis. Knowledge regarding the harmful effects of fluoride and the causes of fluorosis will help people pay more attention to their living habits. Moreover, nutritional supplements can improve human immunity and can contribute to treatment approaches. If these precautionary measures are taken, people living in areas with a high incidence of fluorosis areas will show reduced rates of endemic fluorosis and associated morbidities.

Conclusion and Perspective

Excessive fluoride accumulates in bone and may result in skeletal fluorosis. Further work is needed to disseminate information regarding the use of preventive measures. Thus, long-term efforts are needed to achieve appropriate skeletal fluorosis treatment and prevention strategies. For now, preventing is considered a more effective approach than curative treatment because it is difficult to fully cure the disease using skeletal fluorosis treatments. Further studies are also needed to elucidate the pathogenic mechanisms of skeletal fluorosis.

Bone formation is regulated by osteoblasts.

Osteoblasts originate from mesenchymal precursors and undergo well-defined osteoblastic differentiation processes[26]. Recent studies have highlighted the potential for bone mesenchymal stem cell (BMSC) transplantation in the treatment of bone lesion because of the low immunogenicity of these cells and the lack of matching problems[27-28]. We previously showed that fluoride inhibits osteoblast differentiation. Additionally, BMSC viability is influenced by fluoride[29]. Thus, excessive fluoride may suppress mature osteoblast activity and inhibits BMSC differentiation into osteoblasts, and introduction of BMSC therapy may have major effects on skeletal fluorosis treatment. BMSC transplantation may restore osteoblast viability and bone turnover balance in bone lesions induced by fluoride. With a deep knowledge of skeletal fluorosis, we believe that an effective solution for treating skeletal fluorosis will be identified in the future.

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Received: August 11, 2016;
Accepted: January 31, 2017

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