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Original Paper

Research Progress of Drinking Water and Trace Elements in KBD Area

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Abstract

Kaschin-beck disease (KBD) is an endemic, chronic, and deformable osteochondral disease characterized by multiple degenerations and deep cell necrosis of epiphysis, epiphysis, and articular cartilage. The disease mainly affects children and adolescents aged 5-15, is concentrated in northeast and southwest China, involving 15 provinces, and extends into southeastern Siberia and North Korea. Although the etiology and pathogenesis of KBD are still not very clear, in recent years, more breakthroughs have been made in the supplement and update of its biogeochemical theory, especially in the analysis of hydrochemical characteristics and the study of the role of selenium and iodine in the pathogenic factors of KBD. Therefore, the present research results on the environmental geographical factors of Kashin-beck disease are reviewed in this paper.

Keywords

Kaschin-Beck disease, hydrochemical characteristics, Selenium, Iodine, Prevention and cure

1. Introduction

Kaschin-beck disease was named after two Russian Cossack doctors, Nikolai Kashin and Evgeny Beck (Stone, 2009), it is a kind of endemic, chronic, multiple and deformable bone and joint disease mainly characterized by degeneration and necrosis of growth plates and deep chondrocytes. The disease occurs mostly in childhood with a high disability rate. The condition usually appears in children and adolescents between the ages of 5 and 15 (Li, Liu, Li, et al., 2021; Zhang, Wei, Cao, et al., 2021). China has the

largest number of KBD patients in the world (Stone, 2009). The initial symptoms of Kaschin-Beck disease are mainly in the joints of the limbs, especially the ankles, knees, wrists, and elbows. Mild patients may experience joint thickening, deformation, dyskinesia, and pain. In severe cases, brachydactyly (toe), nanomelia, muscle atrophy, short stature, and even complete or partial loss of motor ability. Although KBD has been studied for more than 160 years, its specific etiology and pathogenesis are still not completely clear. Hypotheses about the etiology of KBD include trace element deficiency (low selenium and low iodine) hypothesis (Zhang, Li, & Luo, 2022; Wang, Li, & Yang, 2020), food mycotoxins (mainly T2 toxins) pollution theory (Li, Han, Guo, et al., 2016; Yu, Zuo, Sun, et al., 2022), and water organic poisoning hypothesis (Jiang, Gao, Xu, et al., 2021; Yang, Niu, Bodo, et al., 1993). Biogeochemical theory is one of the more popular hypotheses of KBD etiology. According to the biogeochemical hypothesis, the occurrence of KBD is related to a specific geographical environment, that is, excessive, lack or imbalance of certain chemical elements or compounds in soil, food, and drinking water in the KBD area environment will affect the normal metabolism of the body. And then cause human bone and joint lesions. It mainly includes three hypotheses: element deficiency, element surplus, and element imbalance. Water is one of the links between various natural factors and the human body, and the occurrence of endemic diseases is often related to the enrichment or lack of certain elements in drinking water. Among them, selenium deficiency is a relatively mature theory at present (Tan, Zhu, Wang, et al., 2002; Wang, Zhao, Yang, et al., 2020). Inspired by this selenium deficiency hypothesis, researchers have published a number of studies attempting to link KBD to various environmental factors, especially environmental hydrochemical conditions (Sun, Zhao, & Liu, 2012; Cao, Xu, Liu, et al., 2012). Other essential trace elements (ETE), such as copper (Cu), iron (Fe), manganese (Mn), molybdenum (Mo) and zinc (Zn), also have certain biological functions and play an important role in the pathogenesis of KBD (Wang, Ning, Yang, et al., 2017; Wang, Ning, Zhang, et al., 2019; Zha, Tian, Xiao, et al., 2022). This review will provide some reference for further research on the etiology and mechanism of Kashin-beck disease.

2. Hydrochemical Characteristics

At present, many studies have shown that the quality of drinking water is closely related to KBD. Surface water and shallow groundwater are the main sources of drinking water in KBD endemic areas. Huo et al. (1992) made a preliminary discussion on the hardness and content of calcium and magnesium ions in drinking water in KBD-affected areas of Zhashui County, Shaanxi Province, and found that the water in KBD-affected areas had low hardness and magnesium ion content, and the water hardness between the affected areas and non-affected areas was significantly different. According to a study conducted in 2002, the geological environment of KBD affected area is characterized by large topography fluctuation, intense surface erosion, strong water alternating cycle, and easy loss of some elements, resulting in low salinity, total hardness, and pH value of water in the affected area (Li & Jiang, 2010). In 2006, Wang and Xie (2006) also concluded that the environmental water chemical

characteristics of KBD-affected areas were mainly characterized by low salinity, and the pH value and hardness were lower than those of non-affected areas. Li, Xu, and Liu (2010) investigated and analyzed the drinking water quality in the KBD area of Zecqu River Basin in Rangtang, and concluded that the prevalence of KBD was closely related to the drinking water source, and the higher the total hardness, total alkalinity and total soluble solids of drinking water, the higher the incidence of KBD, while the pH value of water was negatively correlated with the prevalence of KBD. In 2015, the drinking water quality of KBD-affected areas in Malkang County was analyzed and studied, and the water quality in the affected areas showed low hardness, low mineralization, and acidic characteristics. All of the above studies indicated that the PH value of water in endemic areas of Kaschin-Beck was lower than that in non-KBD areas (Bell, 2015). This is because most elements are more mobile in acidic environments, pH directly affects biological processes in water bodies in a number of ways and is closely related to the behavior and properties of dissolved substances in water, including REDOX and complexation reactions, mineral dissolution and precipitation, and the characteristics of water-based species. It has been reported that in relatively low pH water, due to slow or stagnant water flow and the accumulation of large amounts of humic acid and other organic matter in the water body, a reducing environment is particularly conducive to the prevalence of KBD (Wang & Xie, 2006). The latest study found that the pH, TH and TDS values of surface water in KBD endemic areas were significantly lower than those in non-KBD endemic areas, and the hydrochemical characteristics of surface water were related to the prevalence of KBD (Zha, Tian, Xiao, et al., 2022). In 2016, Shi et al. (2017) analyzed the chemical composition of surface water in northwest Sichuan, China, combined with the prevalence of Kaschin-Beck disease, and found that the hardness and salinity of rivers flowing through KBD prevalence areas were usually low. Wang and Xie (2006) investigated the hydrogeological conditions of Rangtang County, an endemic area of KBD, and found that the groundwater and surface water had high organic content, weak acidity, and low hardness and salinity. The work of Sun et al. (2012) showed that the occurrence of KBD in the Zequ River area was related to the low salinity, low hardness, and high humic acid in the surface water. However, there does seem to be a pattern that the disease is more prevalent in areas where water pH, hardness, and salinity /TDS are lower. Although there are some differences between the results of different studies, after more than ten years of water treatment to prevent the occurrence and development of KBD, the prevalence of KBD has shown a steady decline.

3. Microelement

Trace elements in drinking water and daily diet are of special nutritional and health importance to humans, including zinc, copper, iron, etc. Among these trace elements, some elements are related to Kaschin-beck disease to varying degrees. As early as 1986, researchers pointed out in their study on trace elements that Se, Sr, F, Cr, Zn, and Mo in drinking water in KBD-diseased areas were lower than those in non-diseased areas, while Cu, Fe, and Mn were higher than those in non-diseased areas, and Pb was similar to that in non-diseased areas (Xiao, 1986). The comparative analysis of water quality

between KBD-affected areas and non-affected areas showed significant differences in copper, zinc, and sulfate in drinking water (Xiong, 1991). According to the 1992 Standard, the increased content of strontium in the plants of the central Urov River (East Baikal) is considered to be a risk factor for the onset of bone and joint diseases in animals and humans. Wang, Chen, and Jiang (1992) found in their study in Shanxi Province that zinc (0.021ppm) in water in diseased areas was lower than that in non-diseased areas (0.042ppm), with a significant difference. Zinc may be another important trace element besides selenium for Kaschin-Beck disease. Li (2007) also put forward the “low fluorine theory”, believing that the endemic areas of KBD were consistent with low environmental fluorine. It is suggested that low environmental fluorine is the original cause of KBD, and geological environment and low chlorine in drinking water contribute to the occurrence of KBD. A recent study showed that the concentration of most trace elements in surface water in towns affected by KBD was lower than that in non-KBD endemic areas (Zha, Tian, Xiao, et al., 2022). Although trace elements in the natural environment are present in low concentrations in the human body because these elements cannot be synthesized directly, elements such as iodine (I), copper (Cu), manganese (Mn), and zinc (Zn) are essential for health. Among the trace elements, essential trace elements such as manganese (Mn), iron (Fe), cobalt (Co), copper, and zinc, and potentially toxic elements have been associated with Kaschin-Beck disease in many studies. In some studies, many other trace elements including Sr, F, Fe, Cu, Mn, Co, and Zn are also associated with KBD; Zha et al. (2022) and Shi et al. (2017) found that there were significant differences in the concentrations of certain trace elements (such as Se, Fe-Zn and Mo) in drinking natural water between KBD endemic areas and non-endemic areas. A study conducted in 2022 tested the intake of essential trace elements in diet and drinking water in typical KBD endemic areas found that the oral intakes of iron, manganese, and zinc in the whole township in the study area exceeded and slightly exceeded, respectively, and the average daily intakes of molybdenum, copper and especially selenium were generally low (Zha, An, Gao, et al., 2022). It has been suggested that arsenic, selenium, and thallium are three types of metal elements of high concern in parts of China, as a lack or excess of these elements in the diet can lead to a series of endemic diseases (Li, Xiao, & Zheng, 2012). However, these correlations are not as well established as selenium and iodine. In particular, since Professor Mo first proposed the theory of selenium deficiency in 1972, a large number of studies have supported the theory of selenium deficiency Selenium is an essential trace element for the human body (Kieliszek, 2021; Rayman, 2012), which cannot be synthesized by the human body itself and must be absorbed through food and other ways. Selenium has many biological functions. In the human body, if there is a lack of selenium and iodine deficiency, there may be hypothyroidism, immune dysfunction, and other diseases. Selenium can synthesize glutathione peroxidase, thereby eliminating free radicals and protecting cell membranes (Hariharan & Dharmaraj, 2020). Selenium has an antioxidant effect in the human body, so appropriate selenium supplementation can remove lipid peroxides in the blood to a certain extent, so as to prevent and prevent the role of chondrocyte necrosis. The activity of glutathione peroxidase (GPX) and the content of selenium in the serum of patients with KBD were lower than

those of healthy people (Xiong, 2001). In China, endemic selenium deficiency is often accompanied by endemic iodine deficiency. All selenium-deficient areas in China are also iodine deficiency disease (IDD) areas (Ma, Guo, & Wang, 1993). Low levels of selenium and iodine in the diet are considered to be the most important environmental factors contributing to disease (Xie, Liao, Yue, et al., 2018). In the past few decades, selenium and iodine supplementation to prevent KBD has been carried out in the endemic areas of China, and the results have been reported in many articles (Zha, An, Gao, et al., 2022; Yu, Qi, Shang, et al., 2019). Until now, it has not been determined whether selenium and iodine are initiating or conditioning factors in the pathogenesis of KBD. Although selenium and iodine supplementation (selenium tablets, iodized salt) have been implemented in active areas of KBD as a means to prevent and treat the development of KBD, and have achieved good results, excessive selenium supplementation caused by high selenium poisoning is also worthy of attention.

3.1 Selenium and Kashin-beck Disease

The relationship between Kaschin-Beck disease and selenium has always been a hot topic in the environmental etiology of Kaschin-Beck disease. As early as 1972, scholars found that the selenium content in water and food in KBD-affected areas was significantly lower than that in non-affected areas. Since then, the relationship between selenium deficiency and KBD has attracted people's attention (Mo, Ding, Wang, et al., 1997). In 2003, the study of Moreno-Reyes et al. confirmed that severe selenium deficiency was an important risk factor for Kaschin-Beck disease. A subsequent study in 2008 found that the distribution of KBD was roughly the same as that of low-selenium cereals (Navarro-Alarcon & Cabrera-Vique, 2008). This further confirmed the widespread existence of selenium deficiency in KBD-affected areas (Li, Xiao, & Zheng, 2012). In 2013, Wang et al. conducted a systematic meta-analysis on the correlation between selenium and KBD and found that the selenium content in drinking water, wheat, soil, and corn in KBD-affected areas was lower than that in non-affected areas. The selenium content in whole blood, serum, red blood cells, urine, and hair of patients with KBD was lower than that of non-patients. Similar to the above studies, Lv et al. (2014) found that the soil selenium content in KBD endemic areas was significantly lower than that in non-KBD endemic areas. Similarly, Zha et al. (2022) sampled and analyzed the selenium content in the surface water of the Kaschin-beck disease area, and the results also showed that the selenium content in the surface water of the Kaschin-beck disease area was low. According to the 2022 study, the intake of essential trace elements in diet and drinking water in KBD endemic areas was tested and the results showed that selenium intake was generally low (Zha, An, Gao, et al., 2022). According to the China Health Statistics Yearbook 2020, more than 17,000 patients and more than 100 million residents are at risk of developing KBD (Ning, Wang, Ren, et al., 2013). KBD is mainly distributed in the semi-arid and semi-humid transition zone from northeast to southwest China, which is roughly consistent with areas of selenium deficiency (Farooq, Xiong, Irshad, et al., 2010). In recent years, a large number of studies have also shown that KBD patients are mostly distributed in geographical areas with selenium deficiency. A study conducted for three consecutive years (2017, 2018 and 2019) to detect the selenium

content in urine samples of children in KBD endemic areas found that the serum selenium content of KBD patients was significantly lower than that of healthy people (Kang, Liu, Gong, et al., 2022). However, some studies have also found that there is no significant difference in selenium content between some areas affected by KBD and non-affected areas (such as Banma County in Qinghai Province and Zhuoquan County in Shanxi Province) (Hong-Ying, Ding, Zhang, et al., 2004; Li & Zhao, 2006). In addition, there are still some areas such as Nanbu County, Sichuan Province, Finland, New Zealand, etc., although selenium deficiency occurs, there is no Kaschin-beck disease (Guo, 2008). Therefore, although selenium deficiency is associated with Kaschin-Beck disease, selenium deficiency is only one of the risk factors for Kaschin-Beck disease, rather than a direct factor.

3.2 Iodine and Kaschin-Beck Disease

Iodine is an essential element in the synthesis and metabolism of thyroid hormones. Lack of iodine can lead to reduced thyroid hormone production, which can trigger bone growth and developmental disorders. In addition, iodine deficiency may also lead to developmental disorders of the central nervous system and endocrine system, reducing antioxidant capacity. Therefore, iodine deficiency may be important in bone retardation (Zhu, Pang, Xu, et al., 2022). In recent years, studies have mainly focused on the relationship between selenium deficiency and Kaschin-Beck disease, but in China, endemic selenium deficiency is closely related to endemic iodine deficiency, and all endemic selenium deficiency areas are also iodine deficiency areas (Ma, Guo, & Wang, 1993). A geographical environmental study found that in addition to the low selenium content in the soil in KBD areas, iodine deficiency was usually associated (Shi, Pan, Feng, et al., 2017). One study showed that iodine deficiency, hypothyroidism, and low serum thyroid-binding globulin concentration were significantly associated with KBD. Another study showed severe iodine deficiency in KBD endemic areas, with 66% of residents having low urinary iodine levels, indicating that low iodine is another risk factor for KBD (Moreno-Reyes, Suetens, Mathieu, et al., 1998). In Gansu Province, the distribution of KBD and IDD has a good consistency. More than 90% of IDD patients live in KBD areas, and 46.7% of IDD patients live in serious KBD areas (Xu, Wu, Cheng, et al., 1999). A study evaluated the iodine and selenium status of 575 KBD children aged 5-15 years from KBD areas and non-KBD areas and found that 267 (46%) children had goiter, and the proportion of goiter and low urinary iodine concentration in KBD areas were significantly higher than those in non-KBD areas (Moreno-Reyes, Suetens, Mathieu, et al., 2001). Similarly, Li et al. (2004) found that the iodine concentration in drinking water in KBD endemic areas of Qinghai Province decreased significantly. Therefore, KBD was once considered a complication of iodine deficiency. These results suggest that iodine deficiency is also an important risk factor for KBD in areas with severe selenium deficiency.

3.3 The Relationship between Selenium and Iodine and Its Relationship with Kaschin-beck Disease

Selenium has a variety of protective effects, such as increasing the level of type II collagen (Chen, Chu, Cao, et al., 2011), anti-oxidation and maintenance of thyroid function (Yao, Pei, & Kang, 2011), promoting trabecular bone formation (Yao, Pei, Li, et al., 2012) and inhibiting inflammatory response

(Duntas, 2009). In addition, selenium supplementation can promote the repair of metaphyseal lesions, thus delaying cartilage degradation (Mo, Ding, Wang, et al., 1997). A number of studies have confirmed that the addition of selenium in food can effectively promote metaphyseal repair in pediatric patients with Kaschin-Beck disease, and selenium supplementation has therefore become a common means to prevent Kaschin-Beck disease (Zou, Liu, Wu, et al., 2009). Since we recognized the link between selenium deficiency in the environment and the prevalence of KBD, selenium supplementation has been used as a way to prevent KBD. Selenium supplementation can effectively prevent children from Kashin-beck disease. X-ray manifestations of metaphyseal and clinical symptoms of patients with KBD can also be improved (Jirong, Huiyun, Zhongzhe, et al., 2012). Selenium supplementation methods mainly include oral sodium selenite, yeast selenium, selenium salts, and plant spray selenium (Lv, Xu, Liang, et al., 2002). Many findings have shown that selenium supplementation is beneficial for the prevention of KBD in most of the areas affected by KBD (Li, Li, Tashi, et al., 2003; Deng, Li, Cai, et al., 1999; Wang, Pang, Xiao, et al., 1983). For example, a 1999 study found that selenium supplementation through oral sodium selenide tablets, wheat selenium injection, Selene-rich salt and other methods could improve the nutritional status of children in KBD areas with low selenium, improve the repair rate of finger diphysis lesions in children with KBD, and reduce the incidence of KBD (Xiong, 1990). However, some studies have found that in some areas affected by KBD, the effect of selenium supplementation is unclear. For example, a study in Aba County, Sichuan Province, found that from 1983 to 1998, the clinical detection rate of KBD dropped from 68.8% to 4.67%, and the X-ray detection rate in children dropped from 74.6% to 0.9%. Selenium content in hair increased from 0.051 mg/kg to 0.14 mg/kg. Further analysis showed that there was no dose-effect relationship between a decrease in Kaschin-beck disease cases and an increase in selenium content in hair. The increase in selenium content does not play a leading role in the control of Kaschin-beck disease (Deng, Li, Cai, et al., 1999). These results indicated that selenium supplementation could not completely eliminate the occurrence of KBD, and selenium deficiency may not be the dominant factor of KBD. Although selenium supplementation can reduce the incidence of Kaschin-beck disease, it can not control the occurrence of Kaschin-beck disease. Both selenium and iodine deficiencies exist in many KBD areas, and the two have an interaction. The interaction between selenium and iodine is mainly reflected in the synthesis and use of thyroid hormones. Selenium is an essential component of antioxidant defense and is involved in the lipoxygenase pathway in the organic antioxidant system, and selenium deficiency may increase thyroid destruction caused by iodine deficiency (Köhrle, 2015). Clinical studies have shown that simultaneous deficiency of selenium and iodine may lead to increased thyroid volume and/or thyroid stimulating hormone (Aydin, Kendirci, Kurtoğlu, et al., 2002; Giray, Hincal, Tezi ç, et al., 2001). According to clinical investigation, selenium and iodine supplementation can’t completely eliminate KBD. Therefore, selenium and iodine are the only environmental pathogenic agents. A lack of both selenium and iodine may lead to more severe thyroid damage and more severe disruption of the antioxidant system. Selenium and iodine deficiency

can impair bone and cartilage growth (An, Wang, Wang, et al., 1991). KBD is difficult to manage, and its prevention is more important than cure. The prevention and control measures of Kashin-beck disease are as follows: (1) Focus on prevention, strengthen the prevention and control of endemic diseases; (2) Implement iodine nutrition fortification in KBD endemic areas to reduce the occurrence of iodine deficiency disease; (3) The implementation of selenium nutrition enhancement, through selenium supplementation to prevent the occurrence of Kaschin-beck disease. Although supplementation of selenium and iodine is effective in the prevention and treatment of Kaschin-beck disease, there are certain deficiencies, and excessive use will cause harm to the human body.

4. Summary and Prospect

In summary, KBD is currently an endemic disease whose cause is not very clear, but one of the etiological hypotheses is the biogeochemical theory, specifically, the low content of trace elements such as water, soil, and grain in the external environment. Although the prevalence of KBD in China has largely passed into history, the cause and pathogenesis of the disease remain largely unknown. Environmental factors help to explain the etiology of KBD. The concentration of essential trace elements in the daily diet is also closely related to the prevalence of KBD and is also crucial for human health. Due to the complex etiology of KBD, other environmental influences may also play a role, such as landforms, vegetation types, and local climatic conditions that can have a significant impact on food mycotoxin poisoning and hydro-organic compound poisoning. The onset and development of KBD can not be explained by a single etiological hypothesis, it is caused by multiple factors.

Selenium and iodine are essential and key trace elements of the human body, but their content in the human body is very small, the body itself can not be synthesized, so their nutritional value and protein, sugar, vitamins and other nutrients are the same, its lack will affect the normal physiological function of the body, causing various diseases. On the problem of Kaschin-beck disease, the role of selenium and iodine is particularly prominent, and the relationship between them is close, with mutual influence and interaction. Many existing studies have confirmed that selenium and iodine play an important role in the occurrence and development of Kashin-beck disease. In recent years, a number of studies have shown that supplementation of selenium and iodine can significantly reduce the risk of Kaschin-beck disease. Therefore, an in-depth study of the influence mechanism of selenium and iodine on Kaschin-Beck disease and an in-depth analysis of how selenium and iodine supplements can jointly prevent the occurrence and development of Kaschin-Beck disease can not only provide new ideas for the prevention and treatment of Kaschin-Beck disease but also provide a new strategy for a reasonable supplement of trace elements in clinical practice.

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