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# Research Progress on the Relationship between Intestinal Flora Imbalance and Kashin-Beck Disease

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***Abstract:*** *Kaschin-beck disease (KBD) is an endemic bone and joint disease, and its etiology has not been fully understood. Gut microbiota constitutes an important basis for human physiology and immune system development, and the homeostasis of gut microbiota is considered to be a key factor for individual health. In recent years, intestinal flora imbalance has been associated with the occurrence of many diseases. More and more studies have found that the imbalance of intestinal flora may be related to bone and joint diseases. However, the specific role of gut microbiota dysbiosis in KBD remains unclear. Therefore, an in-depth understanding of the relationship between gut microbiota and Kashin-Beck disease helps reveal the pathogenesis of the disease and provides new ideas and strategies for the development of potential prevention and treatment methods.*

***Keywords:*** *intestinal flora; Maladjustment; Kaschin-beck disease*

## 1. Introduction

Kaschin-Beck Disease (KBD) is an endemic, chronic, deforming osteochondral disease with irreversible pathological process and clinical development, which mainly affects epiphyseal plate cartilage, epiphyseal cartilage of the limbs and articular cartilage in childhood, leading to degeneration and necrosis of articular cartilage and epiphyseal cartilage, which seriously affects the patient's ability to work, quality of life, and even leads to a permanent disabling deformities[1]. China has the largest number of patients with macrosomia in the world. However, processes such as apoptosis, adaptive immune defense, oxidative stress, and extracellular matrix remodeling have been found to play important roles in cartilage damage in osteoarthritis major [2-6]. However, the specific details of the etiology and pathogenesis of large osteochondromas remain poorly understood, and effective treatment options are relatively limited.

Gut flora is a complex and dynamic group of microorganisms present in the human gut, which consists of approximately 1014 resident microorganisms and more than 1000 species of bacteria, archaea, and fungi, among others, that maintain the homeostasis of the human gut microbial ecosystem[7]. Dysbiosis of the gut flora is associated with the pathogenesis of several diseases such as inflammatory bowel syndrome, obesity, and cancer [8, 9]. In recent years, the composition of intestinal flora and the concept of the flora-gut-bone axis involved in the development of osteochondral diseases have attracted much attention. Several studies have suggested that dysbiosis of the intestinal flora may be associated with the development of osteochondrosis major. Dysregulated intestinal flora and changes in their metabolite activity may alter the immune response, triggering an inflammatory response and damage to cartilage[10, 11]. However, the specific mechanisms by which dysbiosis of the intestinal flora leads to macrosomia are unknown and need to be explored by further studies. This review aims to review the recent literature on the potential relationship between intestinal dysbiosis and the development of kyphosis and to explore the relationship between intestinal dysbiosis and kyphosis in terms of intestinal dysbiosis leading to cartilage damage in KBD, the involvement of environmental factors such as selenium and Fusarium toxin in the development of KBD through modulation, and impairment of immunomodulation exacerbating KBD, to provide a future KBD treatment and preventive The purpose of this study is to provide a reference for the treatment and prevention of KBD in the future.

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## 2. KBD intestinal flora characteristics

The healthy intestinal flora is dominated by Bacteroidetes and Firmicutes, followed by Actinobacteria, Fusobacteria, and Proteobacteria, with the most typical genera being Bacteroides, Faecalibacterium and Bifidobacterium[12]. Under physiological conditions, the stability and regulation of intestinal flora are important factors in maintaining the integrity of the intestinal mucosal barrier, immune function, and nutrient metabolism. A study using 16SrDNA gene sequencing technology found that the composition of the intestinal flora of patients with kyphosis differed significantly from that of the healthy population and that the diversity of the intestinal flora of patients with KBD was significantly lower, and the relative abundance also differed significantly. These differences were mainly reflected in pathological phenomena such as a decrease in the abundance of beneficial bacteria and an increase in the abundance of potentially pathogenic bacteria[13]. Specifically, patients with KBD had higher levels of Clostridia and Anaplasma spp. and lower levels of Thickettsia spp. in their intestines. At the genus level, there was a significant difference in the abundance of 56 genera between the KBD group and healthy controls. Among the identified groups, the KBD group had significantly higher levels of Actinobacteria spp, Isoprevotella sp, Clostridium spp, and Prevotella sp-9 than the healthy control group. Consistent with the genus-level 16SrDNA analysis, the species showing greater differential abundance in most KBD patients based on macrogenomic sequencing belonged to the genus Prevotella. Similarly, Ning et al.[14]found that Prevotella sp-9, Lactobacillus sp, Coprococcus sp-2, Senegalimassilia sp, and Holdemanella sp were higher than those of healthy controls. This intestinal flora dysbiosis may be related to the pathogenesis and inflammatory response of KBD. Another study found that some specific metabolites were present in the intestinal flora of KBD patients. Metabolomic analysis revealed significantly higher levels of certain metabolites (e.g. cholesterol and bile acid metabolites) in the faeces of KBD patients[13]. This suggests that the intestinal flora of KBD patients may be related to cholesterol metabolism and the bile acid cycle. These preliminary findings suggest that the normal proportion of intestinal flora in KBD patients is altered with specific intestinal flora characteristics and that intestinal flora dysbiosis may be one of the key pathogenic factors in kyphosis. Further studies will help to gain a deeper understanding of the relationship between KBD and intestinal flora, reveal the pathogenesis of KBD, and provide new targets and strategies for treatment.

## 3. Possible mechanisms of intestinal flora dysbiosis leading to KBD

The intestinal flora is the largest micro-ecosystem in the human body and is involved in a wide range of physiological and pathological processes in the body and has an impact on the health of the host. It is currently believed that KBD is a disease associated with a variety of genetic, environmental, and nutritional factors. Dysbiosis of the intestinal flora is associated with the development of KBD, which may result from a variety of pathways that affect the intestinal immune system, nutritional factors, environmental factors, intestinal toxins, and inflammatory responses. These mechanisms may cause changes in the host's flora-intestinal-bone axis disorders, immune dysfunction, oxidative stress, nutritional deficiencies, inflammatory responses, and apoptotic necrosis, and may contribute to the development of KBD by altering the host's intestinal flora.

### *3.1 Intestinal flora and its metabolites damage chondrocytes*

Gut flora and its metabolites underlie human physiology, immune system development, digestion, fat storage, angiogenesis regulation, behavior, development, and detoxification responses[15, 16]. Studies have shown that dysregulation of the intestinal flora is associated with the onset and progression of cartilage-related diseases, such as osteoarthritis and rheumatoid arthritis[17, 18]. In particular, the thick-walled phylum, which is one of the most common bacterial phyla in the healthy gut microbiota, has been found to exhibit significantly lower levels in KBD patients compared to healthy controls[13]. Thick-walled bacterial phylum can produce high levels of short-chain fatty acids (SCFA), which act as signaling molecules involved in a variety of physiological processes in the body[19]. Among them, butyric acid is one of the main components of SCFAs, and it has been found that butyric acid can increase the activity of chondrocytes by activating the Wnt/β-catenin signaling pathway and the AMPK signaling pathway and promote the proliferation and differentiation of chondrocytes, which can contribute to the repair and regeneration of cartilage tissues[20, 21]. SCFAs can reduce the production and release of inflammatory factors by inhibiting inflammation-related signaling pathways, such as NF-κB and MAPK, and down-regulating pro-inflammatory stimuli maintained by regulatory T cells[22, 23]. These signaling pathways play an important role in sarcopenia. Therefore, the anti-inflammatory effects of SCFAs may contribute

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to the reduction of cartilage inflammation and damage in patients with greater tuberosity. In addition, SCFAs may also influence the healthy state of cartilage tissue by regulating the metabolism of the cartilage matrix, such as the synthesis and degradation of collagen and chondroitin sulfate. Overall, SCFAs may protect chondrocytes by promoting chondrocyte proliferation and differentiation, inhibiting the production of inflammatory mediators and inflammatory signaling pathways, and regulating the metabolism of the cartilage matrix.

On the other hand, Xi et al.[13] also found that streptococcus levels were significantly higher in patients with macroglossia than in controls and that streptococci can induce or exacerbate joint inflammation. The abundance of streptococci was significantly correlated with increased joint pain and severity of intra-articular effusion[24]. Streptococci can drive macrophage activation, a process thought to be associated with KBD-related pain and joint inflammation[25]. In addition, Streptococcus is a major producer of lactic acid in the gut[26], and studies have shown that high concentrations of lactic acid induce apoptosis and accumulate in chondrocytes[27]. In summary, intestinal flora dysbiosis is closely related to cartilage damage in osteochondrosis major. Dysbiosis of intestinal flora may lead to a decrease in SCFAs, which reduces the anti-inflammatory effect and activity of chondrocytes and further accelerates chondrocyte damage. Meanwhile, the increase of streptococci and the accumulation of lactic acid may hurt chondrocytes. Although there are insufficient studies on the effects of intestinal flora dysbiosis on chondrocyte damage in osteoarthritis major, these findings suggest that dysbiosis and disorders of the intestinal flora may play an important role in the occurrence and development of chondrocyte damage in osteoarthritis major.

### *3.2 Involvement of intestinal dysbiosis in KBD development through environmental factors*

Environmental factors can influence the composition of the intestinal flora, leading to differences in the physiological gut flora composition between individuals, with diet being recognized as one of the key environmental factors contributing to such differences[28, 29]. There is growing evidence that cartilage damage in patients with osteoarthritis major is the result of an interaction between genetic and environmental factors[30]. Several studies have found that patients with osteoarthritis major are mostly distributed in low selenium zones and that whole blood selenium, serum selenium, erythrocyte selenium, urinary selenium, and selenium in hair were lower in the diseased population than in the non-diseased population[31]. Zhai et al.[32] human found that the diversity and abundance of the intestinal flora were altered in selenium-deficient animal models, in particular, the abundance of certain beneficial bacteria was reduced, and selenium could be detected through an increasing diversity of intestinal flora in mice to protect the integrity of the intestinal mucosal barrier[33]. Additionally, selenium has been shown to improve gut health by increasing the abundance of beneficial bacteria such as Lactobacillus and Faecalobacteria[34, 35]. Therefore, selenium deficiency from environmental factors may lead to low selenium levels in patients with macrosomia, which may trigger disturbances in the intestinal flora and disrupt the integrity of the intestinal mucosal barrier. Probiotics are flora that are beneficial to the human body, commonly including lactobacilli, bifidobacteria, and yeast. Probiotics can benefit the human body by regulating the balance of intestinal flora, improving intestinal function, promoting nutrient absorption, alleviating inflammatory responses, preventing intestinal infections, maintaining the integrity of the mucosal layer, and increasing the abundance of beneficial bacteria. Probiotics are also able to accumulate trace elements such as selenium in large quantities and bind them to organic matter[36]. Probiotics have been found to enhance the efficiency of selenium absorption by regulating the balance of intestinal flora and also enhance the body's immune function by regulating the balance of the immune system to improve the efficiency of selenium utilization. These findings suggest that probiotics could be potentially effective in the prevention and treatment of selenium by improving selenium absorption and utilization.

Secondly, Fusarium toxins (T-2 toxin, deoxynivalenol, and fusarol) have also been found to be one of the major pathogenic risk factors for Hirschsprung's disease[37, 38]. Studies have shown that these Fusarium toxins are stable in gastrointestinal digestive fluids and cannot be efficiently transported through the intestinal epithelial cell monolayer. They can be efficiently hydrolyzed upon contact with human intestinal flora[39]. However, selenium-deficient patients with macrosomia undergo abnormal alterations in the intestinal flora, which affects the efficiency of hydrolysis of these toxins, ultimately leading to the release of masked Fusarium toxins as parental mycotoxins that enter the body circulation through the intestinal epithelial cells. These toxins and harmful bacteria can migrate from the gut to the subchondral bone marrow and penetrate deeper into the deeper zones of articular cartilage and the thickened layers of epiphyseal plate cartilage, which are the main lesion areas in greater tuberculosis. Finally, these risk factors trigger chondrocyte response genes that directly contribute to chondrocyte damage such as apoptosis and necrosis in greater osteochondritis dissecans. In conclusion, dietary

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nutritional imbalance and Fusarium toxin contamination in low selenium diets may be one of the important factors affecting the composition of the intestinal flora in patients with osteoarthritis major and may lead to the occurrence of damage and degradation of the articular cartilage in patients with osteoarthritis major by way of the flora-gut-bone axis. Therefore, to maintain a balanced and healthy intestinal flora, patients with osteoarthritis should follow a well-balanced diet with appropriate probiotics and selenium, as well as choosing safe food products and avoiding food contaminated with Fusarium mycotoxins as much as possible.

### *3.3 Dysbiosis of intestinal flora affects immunomodulation aggravating KBD*

Dysregulation of gut flora may affect immune regulation through several mechanisms, including altering the production of inflammatory mediators, affecting the differentiation and activation of immune cells, and affecting the function of regulatory T cells. These changes may lead to abnormal activation or suppression of the immune system, which in turn may damage joints and other tissues. There is growing evidence that greater tuberosity is a chronic inflammatory arthropathy whose pathogenesis is associated with abnormal activation and regulatory imbalance of the immune system[40, 41]. Several studies have found that the composition of the intestinal flora of patients with osteoarthritis differs significantly from that of healthy individuals, with the abundance of Prevotella being significantly higher in patients with osteoarthritis[13, 14]. Prevotella is one of the major bacteria in the human gut[42]. Prevotella has been shown to have the ability to activate immune cells and promote inflammatory responses[43]. It can stimulate immune cells such as macrophages and dendritic cells to produce inflammatory mediators such as tumor necrosis factor-a (TNF-a), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which can further activate and potentiate inflammatory responses of immune cells, thus leading to exacerbation of joint inflammation and cartilage damage. In addition, Prevotella is the main acetic acid-producing bacterium in the gut[26], and it has been demonstrated that acetic acid and its compounds (iodoacetic acid, etc.) can affect the immune response by altering the expression of type II collagen, matrix metalloproteinases, and related inflammatory response factors in chondrocytes, ultimately leading to chondrocyte damage [44]. In addition, a significant increase in Prevotella can also affect the integrity of the intestinal mucosal barrier, resulting in impaired intestinal barrier function and increased intestinal permeability, leading to the release of bacteria, toxins, and inflammatory mediators, as well as other potentially pathogenic factors from the intestinal tract, which enter the blood circulation and, in turn, stimulate the immune system to produce abnormal local or systemic immune responses [43]. Probiotics have been found to enhance the function of the intestinal immune system and improve human resistance[45]. They can activate and regulate the function of immune cells, promote the proliferation and activation of immune cells, and reduce inflammatory responses. In summary, dysregulation of the intestinal flora may affect immune regulation, which in turn exacerbates the development of microcephaly. A significant increase in Prevotella may lead to abnormal activation of the immune system and increased inflammatory responses, further exacerbating joint inflammation and cartilage damage. Therefore, regulating the balance of intestinal flora may help to improve the outcome of greater osteoarthritis.

## 4. Summary and Prospect

In summary, osteochondrosis major leads to intestinal flora disorders, which in turn creates a vicious circle between the flora-intestinal-bone axis, affecting the occurrence and development of osteochondrosis major. At the same time, intestinal flora disorders and their metabolites may affect the value-added and differentiation of chondrocytes, inflammatory response, and immune regulation in osteoarthritis, etc. Probiotics may play a positive role in the prevention and treatment of osteoarthritis by correcting the intestinal flora disorders caused by environmental factors as well as regulating the immune function of the human body. Although research is constantly evolving, KBD is a complex disease whose pathogenesis is influenced by a variety of factors, including genetic, environmental, and immunological factors, and the exact pathogenesis is not yet fully understood. The intestinal flora itself is also affected by many factors, and we still lack more direct evidence to clarify the relationship between intestinal flora dysbiosis and KBD, such as (i) whether there is an ordered causal relationship between intestinal flora dysbiosis and KBD; (ii) the specific mechanism by which intestinal flora disorders lead to KBD; (iii) which specific flora play an important role in the pathogenesis of KBD; and (iv) whether regulation of intestinal flora can be considered as a key factor in the development of KBD. intestinal flora as the direction of KBD treatment. Therefore, future research should focus on conducting large-sample, multicentre clinical studies as well as more consistent basic research to explore how the composition of the flora and metabolites specifically affect the pathogenesis of KBD. This will help us to better

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understand the regulation of intestinal flora and therapeutic approaches, and further provide more effective treatment and management options for patients with Hirschsprung's disease.

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