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Exploring the Pathogenesis and Therapeutic Approaches of Degenerative Joint Diseases Based on the Relationship between "Kidney Marrow" and the "Brain-Heart-Kidney-Bone" Axis

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Abstract: *The theory of "brain-heart-kidney-bone" axis suggests that brain, heart, kidney and bone are physiologically interlocked, with blood and essence as the communication, Shenming as the leader and Dugong vein as the link, which together nourish bones and joints; pathologically, brain-centre imbalance, heart-kidney failure, brain-kidney disorders together lead to limb impotence and dysfunction mainly. This paper combines the complex pathophysiological symptoms of degenerative joint lesions in the elderly, based on the theory of "kidney is the master of bone" and the theory of "brain-heart-kidney-bone" axis, to sort out the physiopathology, aetiology and mechanism of the disease, identification and typing, and treatment, and to seek a better diagnosis and treatment of degenerative knee osteoarthritis in the elderly. We will seek more ideas and methods for the diagnosis and treatment of degenerative knee osteoarthritis in the elderly.*

Keywords: *Brain-heart-kidney-bone axis; Osteoarthritis of the knee; Degenerative disease of the knee; Kidney is the master of the bone*

1. Introduction

Osteoarthritis (OA) is the most common degenerative disease in joints among elderly patients. Osteoarthritis is a kind of disease, which shows degenerative changes to articular cartilage and hyperplasia of bone and other connective tissues[1]. As well known, traditional Chinese medicine has accumulated rich experience in preventing and treating bone lesions in knee osteoarthritis., and Chinese medicine treatment not only relieves clinical symptoms and improve the function of the knee joint of patients but also delays the destruction of joint cartilage and prevents the rapid progression of knee osteoarthritis. Thus, traditional Chinese medicine (TCM) shows promising advantages in treating degenerative diseases and for anti-aging purposes.

Degenerative KOA is classified in Chinese medicine as "knee paralysis" and "paralysis", which belong to musculoskeletal diseases and are dominated by the kidneys, and the main causes of degenerative KOA are wind, cold, dampness, congestion of the meridians and collaterals, coupled with the deficiency of the liver and kidneys in old age, which leads to musculoskeletal disorders, and the deficiency of the functions of the spleen and kidneys. Phlegn-dampness, qi stagnation, and blood stasis are the major causes of OA[2]. Therefore, the deficiency of kidney essence is the fundamental internal cause of the disease, and the kidney-deficiency blood stasis runs through the entire pathological process of OA. To explain the aetiology and pathogenesis of degenerative knee osteoarthritis, Chinese medicine emphasises that "the kidney stores essence, the essence produces marrow, when the essence is sufficient, the marrow is born, and when the marrow is full, the bone is strong", It advocates treating the disease from the theory of the kidneys, the kidney essence and the kidney qi, and at the same time emphasises that 'the spleen and kidney are unable to perform and transform, and there is phlegm, stasis and congestion, and the qi and blood are not smooth'. At the same time, it emphasises that 'the spleen and kidneys are unable to transport and transform, there is phlegm and blood stagnation, qi and blood stagnation' will lead to bone and vein stagnation, and phlegm and blood stagnation is the key link in the pathology of the musculoskeletal system. However, modern medicine believes that the pathogenesis of degenerative osteoarthritis of the knee is complex, and in-depth exploration of its nature reveals that the

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decay and dysfunction of the "hypothalamic-pituitary-adrenal axis" is closely related to bone micro-immunity, etc.[3], which is similar to the 'cerebral-cardiac-nephro-osteo axis' and 'cerebral-heart-kidney-bone axis' of Traditional Chinese Medicine. This is similar to the 'brain-heart-kidney-bone axis' and 'brain-kidney metabolism' of Chinese medicine.As an important regulator of the bone-brain axis, in-depth study of the regulation of bone metabolism by GHRP can help to understand the pathogenesis of osteogenic diseases from the perspective of neuroendocrine network and provide new ideas for the prevention and treatment of bone diseases[4].

2. The Physiological Connection of the Brain-Heart-Kidney-Bone Axis

According to the theory of traditional Chinese medicine, "the heart stores the spirit," "the kidney governs the bone to produce marrow," and "the brain is the sea of marrow and the house of spirit[5], and the bones are directed by the marrow. The "brain-heart-kidney-bone axis" is united by the governing vessel, which acts as a link between the upper and lower parts. It is based on the foundation of blood and essence, governed by divine consciousness, and guided by the bones, forming an interconnected system. The functions of heart blood and kidney marrow are closely related and mutually influential, working together to maintain the functionality of the body's bones. "Degeneracy" and "derheumatism," attributed mainly to insufficient qi and blood, impaired blood circulation, and blocked meridians, leading to inadequate nourishment of the extremities. Thus, a deficiency in kidney-essence results in a depletion of the marrow sea, while a lack of kidney-yang leads to inadequate warmth nourishment and transpiration, rendering the brain susceptible to emotional and cognitive dysfunctions, and causing imbalance in the regulation of limbs, joints, meridians, and bones.

2.1 Communication between the Heart and Kidneys, and Connection of Blood Vessels.

The heart and kidneys communicate with each other, and the blood vessels are interconnected. The heart and kidneys are considered as two essential organs in Traditional Chinese Medicine. The heart governs the circulation of blood and controls blood vessels, while the kidneys store essence and regulate the production of bone marrow. The heart and kidneys have an inseparable relationship, as they work together to maintain the flow of blood and regulate the balance of yin and yang in the body. Simultaneously, blood vessels act as the connecting pathways for the circulation of blood, delivering necessary nutrients and oxygen to various organs and tissues. This mutual interaction between the heart, kidneys, and blood vessels plays a crucial role in maintaining the overall physiological functions of the human body.

2.2 Connection between the Heart and Brain, and Shared Mental Energy.

The heart and brain are interconnected, and they mutually utilize mental energy. In Traditional Chinese Medicine, the heart and brain are considered two vital organs that play significant roles in maintaining overall health and well-being. The heart is regarded as the "ruler" of the body, controlling mental activities, emotions, and cognition. The brain, on the other hand, is responsible for processing information, memory, and intellectual functions. The connection between the heart and brain allows for the exchange of energy and information, facilitating coordination and harmony in various physiological processes. Moreover, the heart and brain both rely on and contribute to the generation and utilization of mental energy, which is crucial for optimal mental and cognitive functions. This interplay between the heart, brain, and shared mental energy is essential for maintaining a healthy and balanced state of mind and body.

2.3 Governing Vessel Connection and the Heart-Brain-Kidney Axis

The "Brain-Heart-Kidney-Bone Axis" is connected by the Governing Vessel, serving as a bridge. The Governing Vessel passes through the brain, connects to the heart, and extends to the kidneys, strengthening the connection between the brain, heart, and kidneys. Additionally, there are direct or indirect connections between the brain, heart, and kidneys through the meridians. The Governing Vessel is considered the sea of yang meridians, governing the overall yang energy of the body. It nourishes the brain marrow with the essence and blood from the heart and kidneys, forming a link between them. This nourishment of the heart blood and kidney essence assists the brain marrow. Therefore, the Governing Vessel serves as the central connection in the theory of the "Brain-Heart-Kidney-Bone Axis".

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3. The Pathological Connection between the "Brain-Heart-Kidney-Bone Axis" and Degenerative Knee Osteoarthritis

The brain, heart, and kidneys are interconnected through the Governing Vessel, forming the "Brain-Heart-Kidney-Bone Axis." Its pathological characteristics are described as "weakening of one leading to the weakening of the other two.[6]" Most experts believe that the pathogenesis of degenerative joint diseases in the elderly is primarily due to deficiency in the root and excess in the branches[7]. The root deficiency primarily involves kidney qi deficiency, followed by the decline of kidney essence, marrow depletion, and the loss of nourishment to the limbs, tendons, and joints, leading to muscle atroph. The branch excess involves blood stasis, phlegm-dampness, and cold congealing[8]. The main clinical manifestations are joint pain, limited activity, and decreased muscle strength resulting in decreased motor control ability[9]. In the early stage of knee osteoarthritis, The main clinical manifestations are joint pain, limited activity, and decreased muscle strength resulting in decreased motor control ability[10]. With weakened vital energy and invasion of external pathogenic factors like wind, cold, and dampness, the meridians become blocked, leading to pain, numbness, and limited flexion and extension of the knee joint. The condition becomes chronic and persistent, exacerbated by long-term liver and kidney deficiency, further aggravating the above symptoms. Both the heart and kidneys play significant roles in nourishing and circulating blood in various meridians. The heart and kidneys exchange the essence and blood, filling the brain marrow, and are the source of spiritual activity. They maintain normal mental and emotional functioning as well as the smooth movement of limbs and joints. If the kidney essence weakens in old age, the production of marrow is insufficient, leading to a deficiency in the support of mental activity. The seven emotions primarily damage the heart and spirit, depleting heart blood. The deficiency of heart and kidney essence and blood weakens the nourishment to the brain marrow and prevents smooth circulation. Blood stasis blocks the meridians, impairs kidney qi control, hinders blood circulation, causes sluggishness, and results in stagnation of qi and blood. Moreover, the deficiency of essence and blood and the lack of nourishment to the spirit result in impaired brain function, manifested as mental fatigue, physical weakness, and prolonged disuse of tendons, bones, and joints.

4. The Close Connection between the Modern Research Mechanisms of Degenerative Joint Osteoarthritis and the "Brain-Heart-Kidney-Bone Axis"

The HPAA plays a role in the biological regulation of endocrine metabolism and bone-immune balance, which is closely related to the pathogenesis of osteoporosis in postmenopausal women, as postulated in the theory of the "Brain-Heart-Kidney-Bone Axis." Traditional Chinese medicine believes that these two are closely related. Modern medicine has clarified that the HPAA and the "Brain-Heart-Kidney-Bone Axis" play a role in bone metabolism and immune effects through signal transduction pathways, thus promoting the proliferation and differentiation of osteoblasts. In the pathological state of kidney essence deficiency and blood stasis, the dysregulation of the "neurohumoral and endocrine-regulated bone immune microenvironment mediated by the Brain-Heart-Kidney-Bone Axis" disrupts the bone immune microenvironment and ultimately leads to the occurrence of osteoporosis. In addition, the "Hypothalamus-Pituitary-Adrenal Axis" also plays an important role in regulating the secretion of hematopoietic stem cells and inflammatory factors, which are significant for degenerative joint diseases.

Stem cells are a type of pluripotent cells with self-replication ability[11]. They have the ability to regenerate and repair tissues after functional damage. Studies in life sciences have shown that the aging of the body is actually the aging or even death of stem cells, leading to changes in body morphology and functional disorders and degeneration. The HPAA can regulate the transplantation of stem cells into the bone defect area by releasing cell factors that promote synthesis, proliferation, regeneration, and migration, thereby nourishing the bone and improving bone and cartilage lesions. By creating a regenerative environment with the release of chemotactic factors, bone marrow MSCs might also drive endogenous stem cells to enter the cartilage defect and aid in the regeneration of damaged tissue[12]. It can also play a role in anti-inflammatory, immune regulation, and promote the repair and regeneration of bone and cartilage through the paracrine function of bone marrow mesenchymal stem cells.

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5. The Pathological Connection between the Modern Research Mechanisms of Degenerative Joint Osteoarthritis and the "Brain-Heart-Kidney-Bone Axis"

Articular cartilage and cartilage matrix degradation are key pathological changes occurring in the early stage of knee osteoarthritis (KOA)[13]. Its pathological features are mainly degeneration and destruction of articular cartilage, subchondral bone sclerosis, synovial hyperplasia, osteophyte formation, soft tissue contractures, etc[14]. The disease starts from the cartilage and affects the whole joint. The pathological and physiological studies of osteoarthritis, osteoporosis, and their combination have shown close correlations with various factors such as intra-articular ischemia, articular cartilage injury, stem cell aging, changes in estrogen levels, bone metabolism balance, and inflammation.

Ischemia Clinical studies have shown that ischemic lesions in bone-joint diseases are often associated with cartilage degeneration and defects. Research has shown that restricting the blood supply in the subchondral bone can lead to cartilage degeneration[15]. The supply of blood vessels in the bone marrow is the main source of nutrition for the distal end of the femur in knee osteoarthritis. Animal studies have shown that blocking the blood supply in the bone marrow, resulting in ischemia in the distal end of the femur, further worsens cartilage degeneration. Therefore, changes in blood supply to the bone-joint and subchondral bone may be one of the factors contributing to osteoarthritis.

Subchondral bone injury.

The occurrence of knee osteoarthritis is closely related to the pathological changes in articular cartilage. The pathological features include deformation, erosion, ulceration, and degeneration of the articular cartilage, subchondral bone degeneration, and the formation of osteophytes at the margins. Most of the cartilage tissue does not have blood vessels and nerve distribution, indicating limited ability for self-repair after cartilage injury. Therefore, both the intrinsic reserves and subsequent repair of cartilage tissue are extremely important.

Changes in estrogen levels.

Estrogen plays an important role in bone metabolism and is also involved in the metabolism of articular cartilage and subchondral bone[16]. Animal studies have shown that a decrease in estrogen levels is negatively correlated with subchondral bone turnover, accelerating cartilage injury and the progression of osteoarthritis[16]. Decreased estrogen disrupts the balance between bone formation and bone resorption, further exacerbating damage to articular cartilage and subchondral bone.

Stem cell aging.

From the perspective of stem cells, the renal essence nourishes the bone's physiological function, which can be understood as follows: Stem cells are the seeds for bone and cartilage regeneration and repair, and the renal marrow provides a microenvironment for the proliferation and differentiation of stem cells[17]. Studies in life sciences have shown that the aging or even death of stem cells is a cause of aging in the body, leading to changes in body morphology and functional disorders and degeneration. It has been found that transplantation of adipose-derived mesenchymal stem cells can achieve cartilage repair in knee joints[18]. Currently, the transplantation of mesenchymal stem cells for bone defects, cartilage defects, and inflammatory bone lesions to treat knee osteoarthritis and osteoporosis has become a major trend. The microenvironment of stem cell tissue is also crucial for the repair of bone joints. Transplanting stem cells to the bone defect area nourishes the bone through the release of cell factors that promote synthesis, proliferation, regeneration, and migration, improving bone and cartilage lesions. It can also release chemotactic factors to stimulate endogenous stem cells to participate in the regeneration and repair of bone and joint lesions. Furthermore, it can play anti-inflammatory, immune-regulating, and repair and regeneration-promoting roles through the paracrine function of bone marrow mesenchymal stem cells. Analyzing the "tonifying kidney and activating blood" method from the perspective of stem cells, it can mobilize more stem cells to participate in the repair of bone injuries, providing "seed" cells for tissue regeneration. It also ensures unobstructed cell migration, mobilization, and circulation by "activating blood." On the other hand, it plays an immune-regulating role by inhibiting the secretion of inflammatory factors and metal matrix proteases, reducing the interference of inflammation on stem cell proliferation, and controlling extracellular matrix degradation, maximizing the function of "tonifying kidney and activating blood."

ISSN 2616-5791 Vol.5, Issue 11: 49-55, DOI: 10.25236/AJMHS.2024.051107

6. Prevention and Treatment of Degenerative Knee Osteoarthritis from the Perspective of the "Brain-Heart-Kidney-Bone Axis"

According to the "brain-heart-kidney-bone axis" theory and the pathological conditions of degenerative knee osteoarthritis, treatment should follow the principle of harmonization among the brain, heart, and kidneys. Due to the complexity of the underlying mechanisms of elderly degenerative joint osteoarthritis and the varying degrees of deficiency in qi and blood, as well as the presence of phlegm, stasis, and pathogenic cold, it is essential to address the fundamental pathologies of heart, kidney, and qi deficiencies in order to strengthen the bones and maintain flexible tendons. Related studies have shown that the hypothalamic-pituitary-adrenal axis regulates the balance between osteoblasts and osteoclasts and is closely involved in bone metabolism and repair. Researchers such as Shen Ziyin have found that the pathological process of kidney yang deficiency is essentially a dysfunction of the hypothalamic central regulation. Another study by Ren Dawei and others, using moxibustion intervention in mice with hormone-induced kidney yang deficiency, found that moxibustion at the acupoint Shenshu (BL23) can improve the low function of the hypothalamic-pituitary-adrenal axis, providing evidence for the pathological mechanism of bone degeneration caused by dysfunction of the hypothalamic-pituitary-adrenal axis[19]. In addition, the hypothalamic-pituitary-adrenal axis also affects the regulation of hematopoietic stem cell secretion and inflammation, which is important for the prevention and treatment of age-related degenerative joint diseases, providing new insights into the prevention and treatment of bone degenerative conditions. Furthermore, in recent years, traditional Chinese medicine has shown advantages in the treatment of osteoporosis and osteoarthritis. Through clinical practice, certain effective ingredients in traditional Chinese medicine that promote osteoblast differentiation and inhibit osteoclast differentiation have been identified. Basic research has shown that kidney-tonifying herbal ingredients can effectively inhibit the excessive pituitary function caused by weakened ovarian function due to menopause and subsequent dysregulation of the autonomic nervous system, which leads to weight gain. Epimedium, as a representative kidney-ton.

7. Stage-Based Differentiation and Treatment

In the early stage of degenerative knee osteoarthritis, the pathogenesis is mainly due to pathogenic factors obstructing the meridians and affecting the circulation of qi and blood, leading to disharmony of tendons and bones, and imbalance of qi and blood. Treatment should focus on promoting qi and blood circulation while addressing the obstruction caused by stagnation of qi and blood. Herbal medicines such as safflower and peach kernel can promote qi circulation, activate blood circulation, and resolve stagnation. In cases of qi deficiency and blood stasis, qi tonics such as astragalus should be combined with blood-activating herbs like Chuanxiong, Danshen, and Chishao to promote blood circulation and resolve stasis.

In the middle stage, there is kidney essence decline, blood depletion, marrow deficiency, inadequate nourishment of the brain, and abnormality in the interaction between the heart and kidneys, leading to limb weakness. If there is kidney yin deficiency and insufficient nourishment of the meridians, blood stasis may occur. In such cases, treatment should focus on nourishing qi and yin, activating blood circulation, and resolving stasis. Herbal medicines such as ginseng and Ophiopogon can nourish kidney yin, while Danshen, Chishao, and blood-activating herbs can promote blood circulation and resolve stasis. If there is kidney yang deficiency leading to internal cold, treatment should include warming herbs like Aconite, Cinnamon, and roasted Licorice, as well as blood-activating herbs like Chuanxiong and peach kernel to dispel cold and resolve stasis. If there is deficiency of kidney qi and lack of Qi transformation, tonics such as Huangqi and Dangshen can supplement Qi and promote blood circulation. If there is deficiency of kidney essence leading to insufficient blood supply, herbs like Buguzhi, Rou Dou Kou, and Tu Si Zi can supplement the liver and kidney, while herbs like Danshen, Chuanxiong, and E Zhu can activate blood circulation and resolve stasis.

In the late stage, there is phlegm, blood stasis, and meridian obstruction, leading to poor circulation, muscle atrophy, spasms, and dysfunction. The treatment principle is to nourish the kidneys, promote blood circulation, and resolve stasis. Herbal medicines such as Danshen, Xianlingpi, Danggui, Chuanxiong, safflower, Licorice, Chishao, and Shudi Huang have kidney-tonifying and blood-activating properties. The combination of Chuanxiong and Danggui can promote the circulation of qi and blood without causing stagnation. The combination of Chishao, peach kernel, and safflower enhances the blood-activating effect.

ISSN 2616-5791 Vol.5, Issue 11: 49-55, DOI: 10.25236/AJMHS.2024.051107

8. Summary

Osteoarthritis is a degenerative bone and joint disease which is based on liver and kidney deficiency, with phlegm and blood stasis obstructing the meridians and external pathogens invading, leading to poor circulation of qi and blood in the limbs, obstruction of the meridians by stasis, and imbalance of tendons and bones, mainly manifested as paralysis and weakness. Traditional Chinese medicine focuses on the “kidney governing bones,” “dampness and cold evils mixed with obstruction,” and “treatment from the perspective of tendons and bones” in the diagnosis and treatment of degenerative bone and joint diseases in the elderly, aiming to tonify the liver and kidney, nourish essence and marrow, promote the circulation of tendons and bones, and dissolve stasis and relieve pain, easing the suffering of patients. This plays an important role in clinical practice. The “brain-heart-kidney-bone axis” in modern medicine, known as the HPA axis, also has a similar connotation in regulating bone growth, development, and physiological pathology. The “brain-heart-kidney-bone axis,” with the Governor Vessel as the link, connects the blood vessels and spirits, and the brain, heart, and kidney are also connected through the meridians. It regulates blood vessel circulation, prevents and treats blood stasis in meridians and blood vessels, regulates emotions, and promotes mental clarity and flexibility. It also regulates the essence and marrow of the kidneys and slows down the aging process of bones and joints. Treating osteoarthritis in the elderly from the perspective of the “brain-heart-kidney” axis has shown clinical efficacy. Therefore, future research should also explore this axis in depth, providing a theoretical basis and scientific evidence for clinical practice, and promoting the development of traditional Chinese medicine in the prevention and treatment of bone and joint diseases.

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