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Osteoarthritis of the Knee and Osteoporosis Therapy Advances in Chinese Medicine

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Abstract: *With the aging of the population, the incidence of osteoarthritis of the knee combined with osteoporosis is increasing year by year in China, and it is one of the main causes of joint pain and loss of working ability in middle-aged and elderly patients. There is a practical need and demand to actively investigate the prevention and treatment of osteoarthritis of the knee combined with osteoporosis. Modern medicine has not yet developed a holistic and unified treatment principle for this disease. Chinese medicine is experienced in treating this disease with obvious advantages and various modalities, including Chinese internal medicine, Chinese external medicine, Chinese physical therapy, Gong practice, and integrative therapy, which are hereby reviewed.*

Keywords: *osteoarthritis of the knee; osteoporosis; treatment progress; Chinese medicine; review*

1. Introduction

Knee osteoarthritis (KOA) and osteoporosis (OP) are both degenerative diseases that occur with age, and their development is mostly associated with biomechanical factors, cytokines, and growth factors, and they often appear together in middle-aged and elderly patients [1]. However, the relationship between KOA and OP is still highly controversial. In recent years, with continuous research, the following three views broadly exist: the first view is that there is a positive correlation between the two, i.e., OP can lead to the occurrence of KOA [2]; the second view is that there is a negative correlation between the two, i.e., the presence of KOA causes bone growth and thus reduces the occurrence of OP [3]; and the third view is that there is no correlation between the two [4]. However, most studies support a strong correlation between KOA and OP [5]. The vast majority of patients with KOA, accompanied by osteoporosis or bone loss, find that the two interact with each other and eventually form a vicious circle [6], which is one of the main causes of joint pain and loss of work capacity in patients. Studies [7] have shown that the prevalence of KOA combined with OP is as high as 30% in China. Therefore, there is a real need and demand for active prevention and treatment of KOA combined with OP. KOA combined with OP is a common disease in orthopedics and belongs to one of the primary diseases. Currently, non-surgical treatment is the first choice for this disease in clinical practice. The advantages of Chinese medicine for the treatment of KOA combined with OP are obvious, the efficacy is remarkable, and the side effects are less compared with western medicine treatment, so it has great potential promotion value, which mainly includes: Chinese medicine internal treatment, Chinese medicine external treatment, Chinese medicine physical therapy, gong practice, comprehensive therapy, etc., which are hereby reviewed.

2. Etiology and pathogenesis

2.1. Modern medical research

Osteoarthritis (OA) is a chronic arthritic disease characterized by degeneration and loss of articular cartilage and regeneration of articular margins and subchondral bone, with the initiation site in the cartilage, the most common cause of knee inflammation. A systemic bone disease with increased brittleness and an increased risk of fracture. It is believed that the initiating factor of cartilage lesions in KOA patients is due to biomechanical imbalance [8] and that it plays a role in the waterfall effect in the development and progression of KOA [9]. The theory of "uneven knee subsidence" suggests that the

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medial and lateral knee joints of KOA patients are subjected to unequal stresses, with the medial side being larger than the lateral side, thus predisposing the medial tibial plateau to osteoporosis and then to microfracture and subsidence, which provide the basis for the biomechanical imbalance in the mechanism of KOA combined with OP [10,11]. It was found [12] that NF-κβ, NF-α, and IL-6 expression were significantly elevated in KOA-OP model rats, thus confirming the involvement of inflammation in and regulation of the disease. Hormones can regulate bone and cartilage metabolism through direct or indirect pathways, and in the development of KOA combined with OP, hormones such as estrogen, parathyroid hormone, and calcitonin have very important roles in the balance of bone synthesis and resorption, which can regulate bone metabolism and inhibit cartilage degeneration [13]. In addition, studies have shown [14] that epigenetic mechanisms (DNA methylation, post-translational modification of histone tails, non-coding RNA, etc.) are also involved in bone and chondrocyte differentiation and mechanotransduction, and a variety of epigenetic abnormalities have been identified in patients with KOA with OP disease, but their true pathogenic mechanisms are still unclear [15]. In conclusion, the development of disease in patients with KOA combined with OP involves the regulation of multiple pathways, including biomechanical, inflammatory, hormonal, and epigenetic mechanisms, and these different factors interact with each other to play an important role in the development and progression of KOA combined with OP through a variety of complex mechanisms.

2.2. Chinese medicine etiology and pathogenesis

KOA belongs to the category of "paralysis" and "crane-knee wind" in TCM, while OP belongs to the category of "bone impotence" and "bone paralysis" in TCM. Wang Qingren's "Medical Lin Correction" puts forward the theory that blood stasis causes paralysis, and the treatment is to add and subtract the formula of body pain and blood stasis; Luo Tianyi's "Health Baojian" records: "The long-standing pain of the waist and knee in old age... is unbearable to walk, and the veins of the odd meridian, attached to the liver and kidney, are many."; Zhang Lu's "Zhang's Medical General: All the Pains" says: "The knee is the one that causes pain. In Zhang Lu's "Zhang's medical general: all pains", it is said: "Knee, tendons of the house, there is no one who is not due to liver and kidney deficiency, deficiency of wind, cold, and dampness attack. It is written in Su Wen, Theory of Impotence, that "The kidney is a water organ, and if water does not overcome fire, the bones are withered and the marrow is deficient, so the feet do not serve the body, and the bones become impotent"; "If the kidney is hot, the waist and spine are not lifted, and the bones are withered and the marrow is reduced, so the bones become impotent"; "Su Wen, Six Sections of Tibetan Elephant" "The kidney is the main dormant organ, the essence of the essence, and its flower is in its fullness in the bone"; "Suwen, the theory of reverse regulation" cloud: "the kidney is not born, the marrow cannot be full". In summary, the etiology of these two conditions is more or less the same, the pathogenesis is more or less the same, and the symptoms are similar, mostly caused by deficiency of the liver and kidney and blood stasis. If the liver and kidney are deficient and the essence and blood are not enough, then all the atrophy and paralysis will be complete, and the original atrophy and paralysis will result in this disease [16].

3. Chinese medicine treatment

3.1. Internal treatment of Chinese medicine

At present, the treatment of this disease by various medical practitioners mostly focuses on tonifying the liver and kidney and activating blood circulation. In other words, KOA belongs to the category of "crane-knee wind" and "bone paralysis" in Chinese medicine, and the disease is located in the tendons, and the knee is the capital of the tendons, which are dominated by the liver; OP belongs to the category of "bone impotence" and "impotence evidence" in Chinese medicine. OP belongs to the category of "bone impotence" in Chinese medicine; the disease is located in the bones and is dominated by the kidney. A comparative analysis of OA and OP TCM prescriptions [17] found that the prescriptions for OA and OP both contain tonic drugs for the kidney, such as Eucommia and Shu Di Huang, and at the same time include blood-activating herbs, such as Salvia. The difference lies in the different focus of their treatments, with the treatment of OA focusing on invigorating the blood and supplemented by tonifying the kidneys, and the treatment of OP focusing on tonifying the kidneys and supplemented by invigorating the blood. For the method of tonifying the kidney and invigorating the blood, Chen Haixia et al. [18] found that the pathogenesis of OA and OP was associated with the expression of interleukin 1, interleukin 6, insulin-like growth factor 1, and transforming growth factor β mRNA, while tonifying the kidney and invigorating the blood soup could cause downregulation of the

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expression of the inflammatory factors interleukin 1 and interleukin 6 mRNA in the cells and the expression of chondrogenic repair cytokines, insulin-like growth factor 1, and chondrocytes growth factor 1, and transforming growth factor β mRNA expression is upregulated in chondrocytes, thus promoting chondrocyte proliferation and protecting and repairing chondrocytes indirectly or directly. In a study conducted by Dai Shen et al. [19], the Chinese medicine Qing'e formula was found to alter the microscopic manifestation of articular cartilage and subchondral bone, regulate the indexes of subchondral bone tissue trabeculae and the expression levels of MMP3 and OPN, improve bone metabolism, delay early subchondral bone loss, and have a preventive and curative effect on KOA combined with OP. Bao Mingji et al. [20] treated KOA combined with OP by combining Douwuxiaosheng Tang with western medicine. 120 cases were treated in the control and treatment groups, and the total effective rate of the study group was 96.67%, which was higher than that of the control group (81.67%), further demonstrating the importance of the method of tonifying the kidney, activating the blood, and promoting blood circulation in relieving bone and joint pain, improving bone metabolic indexes, and improving patients' quality of life. In addition to traditional Chinese medicine tonics, proprietary Chinese medicines with similar efficacy also have good efficacy. It was found [21] that the bone and joint capsules (bone reinforcing fat, dog's spine, mulberry, epimedium, bone crushed tonic, sequestra, chickweed, frankincense, myrrh, and doklam) had an upregulating effect on bone density in SD rats with OA combined with OP. Zhu Yao et al. [22] also found that the application of bone pine pellets (Dihuang, Epimedium, Radix Rehmanniae, Radix Paeoniae, Rhizoma Chuanxiong, Curcuma, Trigonella, Zhi Mu, and Calcined Oyster) in the treatment of patients with KOA combined with OP significantly relieved their pain and improved their quality of life. In addition, some researchers have also used the method of "reconciling Shaoyang" to treat the disease. The study group was treated with Chinese medicine and Shaoyang, and the formula was Chai Hu Gui Zhi Tang plus reduction, while the control group was treated with glucosamine hydrochloride capsules plus alendronate sodium tablets. Levels were improved, as was knee joint function [23]. This study demonstrates the theory that "Shaoyang dominates bone" and provides another way of thinking about the clinical treatment of KOA combined with OP.

3.2. External treatment in Chinese medicine

Wu Shangxian, a famous doctor in the Qing Dynasty, said, "The theory of external treatment is the theory of internal treatment, and the medicine of external treatment is the medicine of internal treatment; the only difference is the method. The external treatment methods of Chinese medicine mainly include: Chinese medicine acupuncture point application, Chinese medicine fumigation, Chinese medicine ion introduction, Chinese medicine sealing treatment, Chinese medicine directional permeation, acupuncture, acupuncture knife, tui na therapy, Chinese medicine acupuncture point injection, and other methods.

3.2.1. Chinese medicine acupuncture point application

Based on the basic theory of Chinese medicine, Chinese medicine acupuncture point application therapy is based on the diagnosis and treatment of the symptoms to dispatch the prescription, make the medicine, and apply it on the corresponding acupuncture points, so as to achieve the purpose of soothing the meridians and opening the channels, slipping the joints, and treating the disease through the medicinal effect of the medicine and its stimulating effect on the acupuncture points. Xu Hao et al. [24] treated 26 cases of KOA patients with acupuncture point application. After treatment, the serum and joint fluid SOD levels and joint fluid GSH levels in both groups increased significantly compared with those before treatment, and the serum and joint fluid MDA levels decreased significantly compared with those before treatment, especially in the observation group. Ma Junyi et al. [25] treated 40 cases of postmenopausal osteoporosis patients with Chinese herbal acupressure, and the efficacy was remarkable. The efficacy of Chinese herbal acupressure in patients with KOA combined with OP is significant, it is easy to operate and apply without any adverse effects, and there is value in further research.

3.2.2. Chinese medicine fumigation

Chinese medicine fumigation therapy is the use of Chinese medicine steaming out of the medicinal gas fumigation of the knee joint, thus playing a role in reducing swelling and analgesia and promoting vasodilatation, which in turn enables faster metabolism of painful substances and can well relieve and improve the symptoms of the affected area. Huang Tao [26] randomly divided 120 patients with KOA combined with OP into an observation group and a control group, 60 cases in each group, and treated the disease with a combination of sodium vitrate injection into the knee joint, oral drug treatment, and

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Chinese medicine fumigation therapy. The results of Wang Jihong's study [27] were also similar to the above study. Thus, it can be seen that in the clinical treatment of patients with KOA combined with OP, the addition of Chinese herbal fumigation will not only effectively relieve patients' pain but also help to improve the clinical efficacy.

3.2.3. Chinese medicine ion introduction

Chinese medicine ion introduction therapy is based on traditional Chinese medicine theory, based on human meridian science. Through the application of bioelectric stimulation of meridians or subcutaneous acupuncture points, the drug is conducted into the body, and the directional impetus given to drug ions makes the active ingredients of the drug more deeply and effectively penetrate through the skin mucosa and quickly enter the organism, where they act directly on the knee joint, thus achieving the therapeutic purpose. Liu et al. [28] found that Chinese medicine ion introduction therapy could regulate the level of inflammatory factors in KOA patients, accelerate the recovery of knee joint function, and facilitate the early recovery of patients. Zhuang Shiwei et al. [29] treated 44 cases of osteoporosis patients with Chinese herbal acupuncture point ionization, of which 40 cases were significantly effective and 3 cases were effective, for a total effective rate of 97.73%. Chinese medicine ion introduction therapy is an organic combination of Chinese medicine and medical physics and a new method for treating this disease, which can effectively relieve knee pain and promote the recovery of knee function.

3.2.4. Chinese herbal medicine package therapy

Chinese herbal medicine package therapy is heated and then directly applied to the affected area, so that the medicinal power is conveyed from the outside to the inside, layer by layer, and enters the joint, exerting its effect of dispersing cold and removing paralysis, relaxing tendons, activating the muscles, reducing swelling, and causing analgesia. It not only has the external treatment effect of Chinese medicine but also has the effect of heat therapy. The study [30] found that compared to the use of non-steroidal anti-inflammatory and analgesic drugs, Chinese herbal medicine sealing package therapy combined with glucosamine sulfate capsules for early and middle stage KOA could significantly relieve knee pain and improve knee function, as well as improve the clinical efficacy of the drugs, reduce the adverse effects of the drugs, and improve the quality of life of patients. Liu Hua et al. [31] found that the combination of the Duoyu rubbing method and Chinese herbal medicine sealing package for the treatment of osteoporotic low back pain in the elderly could increase bone density and improve PINP and CTX levels. The direct and concentrated effect of herbal sealing therapy not only accelerates the metabolism of soft tissue, stimulates the regeneration and repair of cartilage tissue, but also improves the function of cartilage cells, which is a practical and effective conservative treatment method.

3.2.5. Acupuncture

Acupuncture has the function of unblocking the meridians, harmonizing yin and yang, supporting the positive, and eliminating the evil. In clinical treatment, acupuncture points are selected using the principle of proximal acupuncture. Since the disease is closely related to liver and kidney deficiency, relevant acupuncture points on the liver and gallbladder meridians are often selected for treatment with the A-Yi point, which is in line with the therapeutic principle of tonifying the liver and kidney, and the A-Yi point is a key point for pain. Li Langming et al. [32] treated 12 cases of osteoarthritis of the knee joint caused by osteoporosis using multiple acupuncture points, with a significant effect in 9 cases and an effective effect in 3 cases, for an overall efficiency of 100%. Meanwhile, a meta-analysis by Chen Rilan et al. [33] also showed that electro-acupuncture for KOA had definite recent efficacy and could exert positive effects on patients' pain symptoms and joint function with few adverse effects. It has also been found [34] that the warm acupuncture method can effectively improve knee joint function and reduce serum TNF and IL-1β levels in patients with wind-cold damp paralysis type KOA, with better efficacy than the conventional acupuncture method. Meanwhile, a meta-analysis on moxibustion for KOA showed that the efficacy of moxibustion for KOA was better than that of conventional Western medicine therapy [35]. Acupuncture not only tonifies the kidneys and activates the blood, but also regulates the function of the patient's internal organs and restores the flow of qi and blood, which in turn balances the mechanics between the ligaments around the knee joint and improves and restores the function of the knee joint.

3.2.6. Needle Knife

Needle Knife is a new type of therapy that integrates acupuncture therapy and minimally invasive closed surgery, which can effectively peel off and loosen the locally adherent soft tissues, cut open the

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scar, restore the original dynamic balance of the knee joint, and at the same time unblock the local paralysis of the meridians, qi, and blood, thus eliminating pain and restoring function. It was found [36] that acupuncture treatment for this disease is effective in improving symptoms and joint function and can reduce the inflammatory response of the knee joint, and its mechanism of action may be related to the expression of proteins related to the wnt/β-catenin signaling pathway.

3.2.7. Tui-Na therapy

Tui-Na therapy refers to the use of Tui-Na techniques to treat diseases. In the case of this disease, it refers to the use of techniques to loosen the soft tissues around the knee joint, such as kneading, pointing, plucking, pushing, etc., together with movement techniques such as flexion and extension, extraction and extension, which have the effects of unblocking the meridians, harmonizing qi and blood, and improving immunity. A Meta-analysis by Zhang Xu et al. [37] concluded that Tui-Na therapy could provide a certain degree of improvement in walking speed and joint mobility recovery after treatment, however, it did not have significant clinical efficacy in reducing pain. In contrast, a randomized controlled trial by Song Shilong et al. [38] showed that Tui-Na therapy was more effective in treating early to mid-stage KOA patients, improving the mobility of the affected knee joint, quadriceps muscle strength and fatigue tolerance. Currently, the treatment of KOA with Tui-Na therapy is limited to the release of the soft tissues around the knee joint and the improvement of the knee joint motion. The relatively single technique has certain limitations in clinical efficacy. In addition, the research on the mechanism of Tui-Na therapy for this disease is not deep enough and thorough enough to provide a more theoretical basis for the promotion of Tui-Na therapy, and further research is urgently needed.

3.2.8. Chinese herbal acupuncture point injection

Chinese herbal acupuncture point injection is to adjust the function of the body and treat the disease through the dual effect of acupuncture and drugs on the peri-knee acupuncture points. It has been found that herbal acupoint injection therapy is an effective treatment for early to mid-stage KOA with precise efficacy in reducing pain, improving knee function, and increasing knee extensor muscle strength [39]. (Figure 1)

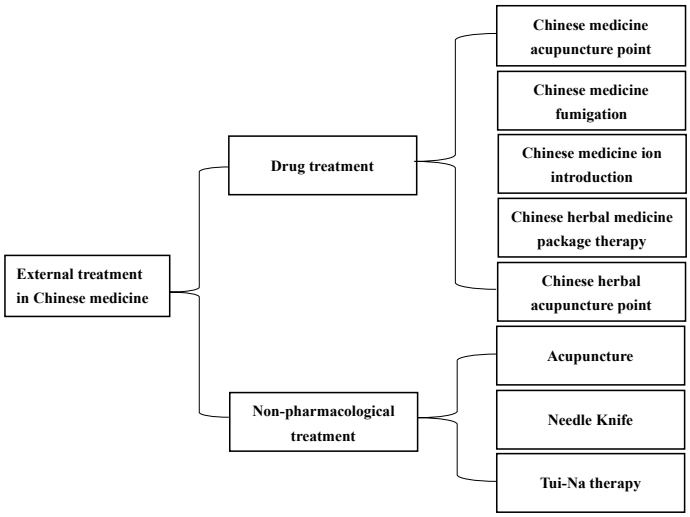

Figure 1: External treatment in Chinese medicine

The external treatment of Chinese medicine has certain advantages compared with the internal treatment of Chinese medicine because KOA combined with OP is a chronic disease, which has better compliance for some patients who have difficulty in adhering to long-term oral Chinese medicine or other therapies. Moreover, the external treatment of Chinese medicine can avoid gastrointestinal discomfort and potential liver and kidney function damage caused by internal medication, which is conducive to long-term treatment, so the external treatment of Chinese medicine is an effective and safe therapy.

3.3. Traditional Chinese medicine physiotherapy

It is the use of physical factors to exert local effects on the human body directly, or through the

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indirect effects of nerves and body fluids to cause the body to react, to adjust local blood circulation, promote the absorption of inflammation, and reduce swelling and analgesia, which has an important role in the treatment of KOA combined with OP. A study by Li Yun et al. [40] used computerized intermediate frequency, ultrashort wave and infrared local irradiation with exercise training, and after comparing the functional scores of the knee joint before and after treatment, it showed that the treatment group not only had better clinical effects but also had significantly better knee joint function than the control group, with a total effective rate of 93.8%. And a meta-analysis on the effect of KOA pain relief showed that laser therapy and exercise therapy were the most effective for pain relief in KOA patients [41].

3.4. Exercise

As representatives of Chinese traditional fitness qigong, Ba Duan Jin, Taijiquan, and Five Animal Play have been recommended in expert consensus as one of the methods of joint muscle exercise for KOA patients because of their advantages of safety, simplicity, and effectiveness [42]. Baduanjin is one of the most widely circulated and developed influences among the ancient Chinese guided arts. By practicing Baduanjin, on the one hand, it can promote blood flow throughout the body and nourish the musculofascia, on the other hand, it can also promote local blood circulation and accelerate the elimination of inflammatory substances, as well as loosen muscle spasms, adhesions and stuck neurovascular pressure by stretching the musculofascia, while balancing the biomechanics of the knee joint, thickening muscle fibers, strengthening atrophied muscles and improving joint stability. In a study by Dong Hong et al. [43], it was shown that the combination of general treatment with Baduanjin exercises for atrophied muscles and unfavorable joints could lead to better clinical results. Li Changhui et al. [44] randomly divided 180 KOA patients into three groups: Tui-Na + Isokinetic training + Five Animal Play, Tui-Na + Isokinetic training, and Tui-Na + Five Animal Play. All three groups were treated once every other day for 10 consecutive sessions, and the results showed that Tui-Na combined with Isokinetic training with Five Animal Play was a proven and optimized program to treat KOA, which could improve the flexion and extension muscle strength of the knee joint, thereby enhancing the joint It can improve the flexion and extension of the knee joint, thus enhancing the stability of the joint and reducing the recurrence rate.

3.5. Integrative therapy

Therefore, in the treatment of KOA combined with OP, the above treatment modalities are often dialectically combined to achieve the best therapeutic effect, including internal Chinese medicine combined with external Chinese medicine, internal Chinese medicine combined with acupuncture, acupuncture combined with Tui-Na, acupuncture combined with medicine, and Chinese medicine fumigation combined with gong practice different forms.

4. Summary

Western medicine treatment of the disease mainly uses non-steroidal anti-inflammatory drugs, joint cavity injection, functional exercise, physical therapy machines and other methods combined with anti-osteoporosis drugs for treatment, but these methods can only temporarily relieve the patient's pain, easy to relapse, and there are varying degrees of side effects. For patients with advanced disease, surgery is performed, but it can be complicated by other diseases after surgery, and the treatment is expensive and not suitable for older patients, although surgery is a form of treatment, it is not a cure. Chinese medicine treatment has outstanding features and obvious advantages for this disease, with rich treatment experience and various treatment methods, and there are fewer contraindications for Chinese medicine treatment of this disease, patients rarely have adverse reactions during the treatment process, and the symptoms improve significantly. At present, the treatment of this disease by TCM has developed from single means of treatment to a combination of multiple means, including the organic combination of different treatment modalities of TCM, and also covering some modalities of combining Chinese and Western medicine, thus providing more options for the treatment of KOA combined with OP, more conducive to individualized treatment, more conducive to the advantages of TCM, and at the same time reducing the pain and treatment costs of patients. However, the current clinical efficacy evaluation system for TCM treatment techniques is not yet complete and scientific and objective enough, so the establishment of a scientific and objective unified efficacy evaluation system is a need for future development. Further, the focus of future research should not only be on proving the effectiveness of TCM methods in treating this disease but also on further clarifying the mechanisms

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and pathways of action of various treatment methods through high-quality clinical and experimental studies.

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