REVIEW ARTICLE

Overview and Comparison of Chinese and Western Medical Treatments for Osteoporosis

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ABSTRACT

Objectives • Traditional Chinese medicine (TCM) can achieve similar effects to Western medicine in increasing bone mineral density, improving the destruction of bone micro-structure, inhibiting bone resorption, etc. However, there exist great differences between TCM and Western medicine in terms of theoretical basis and treatment methods. Therefore, to gain insights into their differences in treating osteoporosis (OP), we compared the disease name, etiology, pathogenesis, and clinical effectiveness to explore the potential benefits of combining the two approaches.

Methods Overview • The method of literature review is used in the study. We firstly use academic databases such as PubMed and CNKI to search relevant literature on the understanding of OP in TCM and Western medicine in the past 10 years, then exclude the literature that is not relevant to the study topic or does not meet the study purpose, and finally compare and summarize the findings, views and conclusions of the literature.

Key Findings or Insights • In the study, we find that the integrated approach of TCM and Western medicine can provide a gentler and more individualized treatment for patients with OP. By combining the conditioning means of Chinese herbs, compound prescription, acupuncture, moxibustion and Tuina can make up for the adverse reactions and side effects of Western medicine. Besides, TCM can make use of the clinical trials and animal experiments of Western medicine to prove the effectiveness of TCM theories and promote the clinical application.

Practical Implications • By exploring the differences between TCM and Western medicine and the potential benefits of their combination, this study can provide a theoretical basis for the individualized treatment of OP. Especially for the patients with postmenopausal OP, senile OP, long-term hormone use, hyperthyroidism and other secondary OP, this study can provide a more comprehensive rehabilitation guidance, prevent the recurrence of these diseases, and improve the quality of patients' life.

Recommendations or Future Directions • It is suggested that further clinical trials should be conducted to evaluate the effectiveness of the integrated treatment. (*Altern Ther Health Med.* 2024;30(6):170-180).

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INTRODUCTION

As a global public health problem, osteoporosis (OP) has typical characteristics of low bone mass and degradation of bone microstructure.[1] Fracture is the main cause of disability and death in elderly patients. According to epidemiological survey data, there are significant differences in the prevalence of OP among different countries and regions, such as 4.1% in the Netherlands, 52.0% in Turkey, 8.0% in Oceania and 26.9% in Africa, and the prevalence of developing countries with 22.1% is generally higher than that of developed countries with 14.5%.[2] At present, there is still no more comprehensive treatment strategy to prevent and treat OP.

Due to the multifaceted pathogenesis of OP, including imbalanced bone formation and resorption, hormonal imbalances, and the interaction between genetic and environmental factors. Western medicine has developed many synthetic drugs based on these mechanisms, including replacement therapies of diphosphonate, calcitonin and estrogen.[3] However, these drugs may cause related jaw bone necrosis and atypical bone necrosis,[4,5] as well as induce endometrial cancer.[6] Compared with them, natural drugs or physical therapy have a lower probability of side effects and have gradually been accepted and recognized by doctors and patients. Especially in China, many studies have clearly

proved that natural extracts of Chinese herbs,[7] acupuncture and moxibustion have significant therapeutic effects on OP.[8] They all belong to the natural therapies of traditional Chinese medicine (TCM). TCM natural therapies emphasize promoting the body's self-healing ability through natural methods.[9] For example, acupuncture involves inserting fine needles into specific acupoints to regulate energy flow in the body.[10,11] It is believed to regulate the balance of Yin and Yang in the body, alleviate pain, improve digestive function, and regulate endocrine function. Similarly, Tuina (TCM massage) can stimulate and adjust the body's meridians and acupoints to promote the circulation of Qi and blood, and balance the body, thereby improving the function of circulatory system and enhancing immunity.[12] Drugs made from various natural herbaceous plants are also believed to balance energy and repair body functions, playing a positive role in the management and prevention of chronic diseases such as OP.[13,14] However, there are currently some shortcomings in the scientific research of TCM, such as the lack of high-quality evidence to support the effectiveness and safety of TCM treatment methods, and the lack of unified diagnostic and treatment standards that makes it difficult to compare and replicate the results of TCM researches.[15,16]

This makes us ponder whether the treatment methods of Western medicine, accompanied by a series of side effects and unable to meet the needs of all patients (such as bone pain and joint pain), can be alleviated by Chinese herbs, acupuncture, moxibustion and Tuina, and whether Western medicine can be used to prove the effectiveness and safety of TCM treatment methods that lack high-quality evidence support, and to explore the application and development of TCM. The integration of TCM and Western medicine can not only improve the effectiveness of treatment and the quality of patients' life, but also provide a new set of rehabilitation guideline, which is highly likely a potential trend for future clinical treatment. Therefore, in this study, we mainly conduct a comparative review of the treatment methods of TCM and Western medicine for OP from the perspectives of disease name, etiology, pathogenesis, and clinical effectiveness. Through the comparison, we can identify the gaps and potential advantages of each medicine, and propose new ideas and strategies, so as to better address these gaps, and provide patients and doctors with more comprehensive treatment choices.

RECOGNITION OF OP DISEASE NAME

Historical understanding of Western medicine

Western medicine mainly refines and summarizes the related concepts from the perspective of pathological morphology. OP was first explicitly proposed by Albright in the 1950s. He believed that the occurrence of OP was mainly due to increased bone resorption and decreased bone formation. In 1996, the World Health Organization (WHO) gave a more refined definition: OP refers to a systemic bone disease with reduced bone mass, increased bone fragility, and susceptibility to fracture. The pain of the lower back and limbs is the most typical and common clinical manifestation of OP. In addition, shortened body length hunched back, and even thoracic deformities such as kyphoscoliosis and chicken chest are also important clinical signs.

Historical understanding of TCM

TCM focuses much on the summary of the different manifestations of OP at various stages. Since there is no clear record of the name of OP in ancient Chinese classics. Based on the clinical manifestations of OP, it is found that the records of 'Guwei or bone flaccidity', 'Guku or bone withering', 'Guji or bone exhaustion' and 'Gubi or bone obstruction' in TCM classics are quite similar to the OP defined in Western medicine. For example, *Huangdi's Inner Canon,* hereafter referred to as the *Canon*, the earliest medical classic in China, said that 'heat in kidney-Qi causes inflexibility of the waist and spine as well as dryness of bones and exhaustion of marrow, consequently leading to bone flaccidity', 'exhaustion of the Kidney Meridian of Foot Shaoyin makes the bones withered' and 'the disease in the bone marked by the heaviness of the bones that cannot be lifted, aching pain of the bone marrow and chills is called bone obstruction.' *Important Prescriptions Worth a Thousand Gold for Emergency*, written by Sun Si-Miao of the Song Dynasty (960--1279 CE), said that 'if kidney disease shows the manifestations of exhausted bone, tooth pain, hand and foot pain, inability to stand for a long time, unfavorable flexion and extension..... it is called bone exhaustion.' Therefore, it can be seen that the cognition of OP in TCM is no less than that of Western medicine.

RECOGNITION OF THE ETIOLOGY OF OP

Aging and endocrine abnormalities

Understanding of Western medicine. Western medicine often classifies OP according to disease cause. If the occurrence of OP is due to chronic bone loss caused by bone metabolism disorder, and there is no obvious underlying cause, it is called primary OP. If bone loss is caused by other diseases, drugs, or factors, it is called secondary OP. Primary OP is the most common in clinical practice, and usually occurs in the middle and old age, especially in women after menopause. Aging and endocrine abnormalities are the main causes of its occurrence. Under normal conditions, the human skeleton is a dynamic and constantly updated tissue. This kind of dynamic balance is realized by the continuous reduction of osteoclasts (the process of bone formation) and the gradual replacement of osteoblasts (the process of bone resorption). After birth, the human body is in the stage of bone mass accumulation, where bone formation is greater than bone absorption. By the age of 30, bone mass will reach a peak and maintain a relative balance. Then, this balance will be easily affected by aging and unhealthy lifestyles. After the age of 65 to 70, both sexes will experience degenerative bone loss. Women around the age of 50, they are at increased risk of developing OP due to reduced estrogen secretion and severe bone loss. The same is true for androgen. It can

develop male muscles, promote the calcitonin secretion of calcium load, and indirectly promote the growth of bone. In addition, secondary OP is also closely related to endocrine and metabolic disorders[17] such as hypogonadism, hyperthyroidism, parathyroidism, Cushing's syndrome, type-1 diabetes, or systemic diseases.

Understanding of TCM. Although TCM does not follow this classification method and divides diseases according to symptoms and manifestations, it also recognizes the influence of aging and endocrine abnormalities on the occurrence of OP. For example, the *Canon* also described the metabolism of bones. 'For a woman, her kidney-Qi becomes prosperous and her teeth begin to change at the age of seven..... At the age of fourteen, menstruation begins to appear..... At the age of twenty-one, her wisdom teeth begin to grow, and her body has fully developed..... At the age of twenty-eight, her musculature and bone become strong..... At the age of thirty-five, her face begins to wither, and her hair starts to lose..... At the age of forty-two, her countenance becomes wane, and her hair begins to turn white..... At the age of forty-nine, as both the Conception Vessel and Thoroughfare Vessel become deficient and menstruation stops, she becomes physically feeble and is no longer able to conceive a baby.' We can see that the *Canon* uses 'seven' as the rhythmic unit to discuss the growth process of the whole body bone. As for men, the rhythmic unit is 'eight'. Besides, it is emphasized that the age of forty-nine for women and the age of sixty-four for men are critical periods of physical and skeletal weakness, which is precisely the state of bone loss that occurs in Western medicine due to aging and decreased hormone levels.

Congenital genetic factors and acquired nutritional imbalance

Understanding of TCM. Both TCM and Western medicine have recognized the existence of congenital genetic factors and acquired nutritional imbalances that are collectively referred to as innate and acquired factors in TCM. As the ancestor of TCM, the *Canon* proposed the basic theories of 'the kidney governing bones' and 'the spleen governing muscles'. TCM practitioners of later generations inherited these theories and believed that the kidney and spleen were, respectively the innate and acquired foundations, jointly promoting the growth and development of the human body. The spleen and kidney deficiency and kidney essence deficiency will lead to skeletal dysplasia. Therefore, TCM regards 'kidney deficiency' and 'spleen deficiency' caused by congenital inheritance, improper diet, overstrain, aging, physical decline and emotional factors as important risk factors affecting the occurrence of OP.

Understanding of Western medicine. It is undeniable that TCM and Western medicine share a similar understanding of the causes of OP. According to the research of whole gene association analysis conducted by Western medicine, the candidate genes related to OP include (1) genes that regulate calcium balance hormones and their receptors; (2) genes of cytokines, growth factors, and their receptors;[18] (3) genes of bone matrix proteins;[19] (4) genes of sexual hormones and their receptors;[20] (5) other genes. The most attractive genes are vitamin-D receptor (VDR),[21] type-I collagen al (COL1A1),[22] estrogen receptor 1/2 (ER1/2),[23] osteoprotegerin/ receptor activator NF-kappa B ligand / Receptor activator of NF- kappa B (OPG/RANKL/RANK)[24] and Wnt signaling pathway-related signal molecule genes.[25] However, research results go beyond these, and most genetic factors have not yet been identified. In addition, nutritional imbalance is also an important factor. Elderly people often have impaired intestinal absorption and insufficient absorption of calcium salts and other nutrients, resulting in a negative calcium balance that hinders bone formation.[26]

RECOGNITION OF THE PATHOGENESIS OF OP

Recognition of the pathogenesis of Western medicine

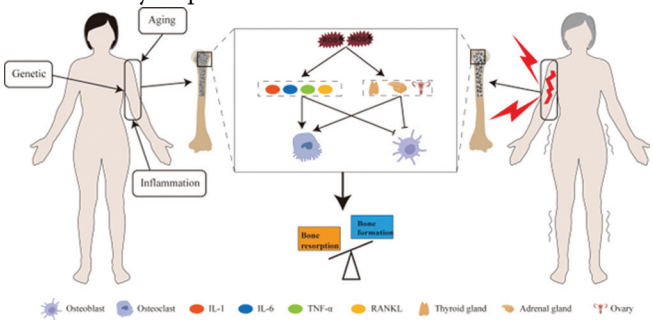
Estrogen decline. Now, let's explore the pathogenesis from the perspective of Western medicine. In the past 60 years, scholars have been conducting a series of studies on endocrine changes, including changes in estrogen, androgen, progesterone, and calcitonin. They give a special focus on the decline of estrogen levels and believe that the decrease in the sensitivity of bone to mechanical stimulation is related to estrogen decline.[26] This is because the estrogen levels will decrease after menopause, which can weaken the inhibitory effect of estrogen on osteoclasts, leading to excessive activity of osteoclasts and enhanced bone resorption. When bone formation mediated by osteocytes is insufficient to compensate for excessive bone resorption, the overactivity and unbalance of bone remodeling will make trabecular bone diminish, or even fracture, cortical bone porosity increase, and bone strength decrease. The bone shows pathological changes that are similar to those of disuse bone loss. However, with the deepening of research, it is found that estrogen decline is the most important pathogenesis of postmenopausal OP.

Oxidative stress and inflammatory reaction. Because oxidative stress and inflammatory reaction are the common pathogenesis of many diseases (including arteriosclerosis, aging, and cancer), scholars realize that they may also affect bone mass loss,[27] and have obtained relevant data support. For example, the meta-analysis conducted by Zhao et al.[28] showed that significant increases in levels of oxidative stress index (OSI), malondialdehyde (MDA), advanced oxidation protein product (AOPP), and vitamin-B12 could be detected in patients with OP. At the same time, the levels of total antioxidant status (TAS), total antioxidant capacity (T-AOC), catalase (CAT), glutathione peroxidase (GPx), uric acid (UA), and folic acid (FA) decreased. Oxidative stress refers to an imbalance in the body's redox homeostasis (oxidation reaction exceeding antioxidant capacity) that causes oxidative damage to cells. The fundamental reason lies in the excessive production of reactive oxygen species (ROS).[29] On the one hand, excessively increased ROS can promote the production and activation of osteoclasts by stimulating the activation of

NF- κ B ligand receptor RANKL and the expression of tumor necrosis factor (TNF-α). On the other hand, inflammatory reactions and oxidative stress often interweave. Inflammatory reactions can also increase the risk of bone loss and fracture. Certain stimuli in the body can strengthen the adaptive immune function, thereby upregulating TNF-α produced by activated T-cells and promoting osteoclast formation and bone resorption. Obviously, there are a large number of inflammatory factors and inflammatory signaling pathways involved in the process of OP, but the specific mechanism remains to be explored.

Oxidative stress and inflammatory reaction play important roles in the pathogenesis of OP. Oxidative stress is a state caused by the imbalance of the intracellular and extracellular environment due to the excess of reactive oxygen species and free radicals produced in the body. Oxidative stress can activate inflammatory reactions by promoting the release of inflammatory mediators and the aggregation of inflammatory cells, and the inflammatory reaction further increases the degree of oxidative stress, which is a vicious cycle. Therefore, oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants. Excessive ROS can damage bone cells, including osteoblasts and osteoclasts, leading to impaired bone formation and increased bone resorption.[30] This kind of imbalance can lead to the occurrence of OP. Besides, clinical observation shows that patients with OP have chronic low-grade inflammation. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) promote bone loss by stimulating osteoclast activity, inhibiting osteoblast function, and inducing cell apoptosis. The sustained inflammatory reaction leads to an imbalance between bone formation and absorption, leading to a decrease in bone density and an increased risk of fracture. In addition, oxidative stress itself can directly or indirectly affect the function of endocrine system. ROS can damage endocrine glands, such as the thyroid, adrenal, and gonads, thereby affecting hormone synthesis and secretion. These endocrine changes can directly or indirectly affect bone metabolism, calcium phosphorus balance, and bone morphology development, thus playing an important role in the occurrence and development of OP.[31] However, the formation of OP is multifaceted. The specific mechanism by which the mutual promotion of oxidative stress and inflammatory reaction can exacerbate the damage and destruction of bone tissue still needs to be explored. (Figure 1)

Figure 1. Relationship between OP and oxidative stress and inflammatory response



Recognition of the pathogenesis of TCM

Before understanding the pathogenesis of OP, we first understand the important principles of TCM, such as Yin and Yang, Qi and blood, the eight principles, and Zang-Fu viscera. They are interrelated and inseparable from each other. Yin and Yang refer to two relative and interdependent aspects of all things in the universe.[32,33] In the state of Yin-Yang balance, the human body is healthy, while in the state of Yin-Yang imbalance, diseases will occur, and the circulation of Qi and blood as well as the function of Zang-Fu viscera will be affected. Qi and blood are important material basis for maintaining human life activities.[34] Zang-Fu viscera are a general term of the internal organ system of the human body, which are the main places for the circulation of Qi and blood. Whether Qi and blood are plentiful and smooth or not directly affect the functional status of Zang-Fu viscera, and vice versa. The eight principles contain four opposing concepts, namely cold and heat, deficiency and excess, exterior and interior, and Yin and Yang, used to describe the nature, changes, and development laws of diseases.[35] These manifestations are closely related to the imbalance of Yin and Yang, and the abnormality of visceral functions. For example, the deficiency syndrome is often accompanied by the loss of Qi and blood, imbalance of Yin and yang, and other conditions. The external syndrome caused by exogenous wind and cold often involves abnormal reactions of the exterior of the lungs. Therefore, when analyzing the pathogenesis of OP, it is necessary to comprehensively consider the relationship between Yin and Yang, Qi and blood, and the eight principles. If we only focus on the state of Qi and blood, and neglect the balance of Yin and Yang, we may not be able to accurately determine whether the condition belongs to Qi deficiency or Yang deficiency, leading to the selection of the wrong medication or treatment method. In the next, we will take Zang-Fu viscera as key links to make a detailed explanation of the pathogenesis of OP.

Kidney deficiency. Kidney deficiency is the main pathogenesis of OP. TCM has long believed that the kidneys control bones, which has been proved by modern clinical trials.[36] Researches have shown that patients with kidney deficiency have pathological changes in bone mineral density (BMD) lowering. Kidney deficiency can affect the metabolism of calcium and phosphorus, leading to a decrease in BMD and the occurrence of OP.[37] The kidneys are considered as the main reserve viscera for human's vital essence. The adequacy of kidney essence plays an important role in the growth, repair, and metabolism of bone tissues. If kidney essence is insufficient to nourish the bone marrow, it will lead to the acceleration of bone loss, and show manifestations such as joint pain, limited joint movement, etc. What's more, kidney essence includes kidney Yang and kidney Yin. The former is responsible for providing power to maintain bone stability and ensure growth, while the latter is responsible for

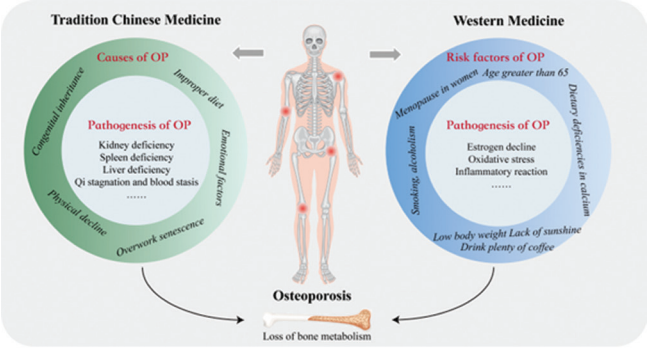
nourishing bones, ensuring bone metabolism and repair ability. Therefore, the main manifestations of kidney Yang deficiency are soreness, weakness, and coldness in the waist and knees, and kidney Yin deficiency leads to bone degeneration and affects bone regeneration. Besides, the kidneys are the root of the five Zang-viscera, whose pathological changes will affect the liver and the spleen, resulting in changes in syndrome types such as liver-kidney Yin deficiency and spleen-kidney Yang deficiency.[38] Therefore, when treating OP, TCM practitioners should first determine whether the main viscera that affect the pathological changes of OP are the kidneys or other viscera, and then analyze in depth whether it is due to the insufficiency of kidney essence, kidney Yang, or kidney Yin, and ultimately provide targeted guidance for treatment.

Spleen deficiency. Due to the mutual nourishment and promotion between the kidney and spleen, spleen deficiency is also an acquired cause of OP.[39] In TCM, the spleen is regarded as the 'acquired foundation' and is mainly responsible for the transformation of water-grain essence, which is an important generation source of Qi and blood. The kidney is regarded as the 'innate foundation,' containing the essence from parents and responsible for the development of bones throughout the entire life cycle. Therefore, the elderly with spleen deficiency can not transport the water-grain essence, and the bones will lose nutrition. In addition, the spleen also has the function of controlling muscles and limbs. This has been explained in multiple parts of the *Canon*. For example, 'the genuine-Qi of the Zang-viscera nourishes the spleen and the spleen stores Qi for the muscles', 'the spleen governs muscles', and 'why spleen disease affects the normal movement of the four limbs'. Spleen deficiency will lead to the failure of the generation of blood and Qi, and the limbs become flaccid and useless. Modern medicine also believes that the weakness of the spleen and stomach leads to the decline of digestion and absorption function, affecting the absorption and utilization of nutrients, and then affecting the nourishment of the bone marrow. For example, the physiological function and pathological manifestation of the spleen are similar to those of gastrointestinal motility,[40] intestinal flora,[41] and neuroendocrine-immune network system.[42] They can directly or indirectly affect bone metabolism, thereby inducing the occurrence of OP. For example, Dong et al.[43] found that the expression of adenosine monophosphate-activated protein kinase (AMPK), p-AMPK, ULK1, p-ULK1, LC3 - I and LC3 - II in skeletal muscle and the content of adenosine triphosphate (ATP) in the spleen of the patients with spleen were significantly lower than those of normal group. Therefore, it is also a common treatment method to evaluate OP from the spleen.

Liver deficiency. The liver governs sinews, and shares the same origin with the kidney. If the liver Qi stagnates, the circulation and supply of blood will be obstructed, and the bone metabolism of OP will also be affected. TCM believes that 'sinew' refers to a tough and strong tissue that connects muscles, bones, and joints The physiological function of the liver is to store blood and regulate sinews. If the liver Qi is deficient, the liver blood cannot nourish sinews, which in turn make bones fail to be nourished. Symptoms such as slow movement, fatigue, and inability to stand for a long time may occur. Besides, the liver and kidney share a common origin, that is, the essence of reproduction, and they all need to be replenished with the essence synthesized by the innate and acquired essence stored in the kidney. Therefore, the Qi-transformation function of kidney essence can assist in the generation and transformation of liver blood; at the same time, the nourishment function of liver blood also helps to replenish kidney essence and Qi. Modern medical research has confirmed that OP is a common complication of chronic liver disease, whose pathogenesis is complex. For example, cholestatic substances such as bilirubin and bile acid have adverse effects on the survival of osteoblasts, and low-grade inflammation may affect bone metabolism. As a key regulator involved in regulating the Wnt/β-catenin signaling pathway of bone formation, sclerosin may cause the reduction of bone formation.[43-45] It is evident that liver deficiency plays a crucial role in the pathogenesis of OP. Liver deficiency is most common in middle-aged women who are in menstrual, pregnant, childbirth, and suckling periods or suffer from several injuries to blood. Low blood volume in these circumstances leads to liver blood deficiency and hypofunction of the liver to store blood. The body does not have enough blood to nourish the organs and tissues, resulting in poor nourishment of sinews and unfavorable flexion and extension of the limbs.

Qi stagnation and blood stasis. Qi and blood are important material basis for maintaining the movement of muscles, bones and joints. This is clearly recorded in the *Canon*, that is, 'the meridians are the tunnels through which blood and Qi flow to nourish the interior and exterior parts of the body, moisten the sinews and bones as well as lubricate the joint.' Therefore, the pathogenesis of OP mainly has two types: Qi deficiency and blood stasis, as well as blood deficiency and liver depression. The former refers to that the obstruction of blood circulation due to the disorder of Qi movement leads to the failure to effectively transport nutrients to the bone marrow, and finally causes the occurrence of OP. The latter refers to that the emotional distress will lead to liver Qi stagnation, and then affect the circulation and supply of blood, resulting in bone loss. From the perspective of modern research, it may be related to energy metabolism disorder,[46] platelet mechanisms,[47] hemorheology,[48] microvascular circulation disorder.[49] As age increases, the smoothness, elasticity, tension and contractility of blood vessel walls, as well as the energy metabolism ability of the human body, will decrease.[50] Blood flow and its viscosity will be affected, and calcium and nutrients cannot fully nourish bone tissue and nerves, leading to pathological phenomena such as decreased osteogenesis, decreased bone mass, ultrastructural changes of bone trabeculae, increased intraosseous pressure, and bone pain.[51] All in all, Qi stagnation and blood stasis are important pathological factors in OP and important mechanisms that cause osteoporotic bone pain. (Figure 2)

Figure 2. Recognition of TCM and Western Medicine on the Pathogenesis of OP



Therefore, TCM usually follows the principles of 'holistic view' and 'treatment based on syndrome differentiation' when analyzing the pathogenesis of OP. The two principles embody the uniqueness of the concepts and treatment methods of TCM. In the process of disease analysis, TCM practitioners will first take into account the patient's medical history, clinical manifestations, pulse conditions, tongue pictures, and other information through inspecting, listening, smelling, inquiring, and palpating, in order to comprehensively understand the patient's physical condition. Then, they will divide the disease into different types (such as kidney Yang deficiency) based on various syndrome-differentiation methods, such as the eight-principle syndrome differentiation, Yin-Yang syndrome differentiation, and Qi-blood syndrome differentiation. Finally, according to the results of syndrome differentiation, a targeted treatment plan is formulated.

Treatment methods of OP

Treatment methods of Western medicine. The first clinical consideration in the face of most patients with OP is the use of anti-osteoporosis drugs. There are many types, including bone mineralizing drugs, drugs that inhibit bone resorption, estrogens, parathyroid hormones, and bone synthesis enhancers. They all have some prerequisites and precautions for use and need to be administered symptomatically.

For example, we know that bone remodeling and new bone formation cannot be achieved without adequate nutritional support from calcium and vitamin D. Therefore, the supplementation of calcium and vitamin D as a basic method must be combined with anti-osteoporosis drugs throughout the treatment of OP.[52] However, the correct dose and supplementation type of calcium and vitamin D need to be selected as intake levels vary somewhat between populations for patients with postmenopausal OP who no longer produce oestrogen at menopause. Estrogen replacement therapy is the preferred clinical treatment option, the mechanism of which is to provide estrogen that is no longer produced by the ovaries during menopause and to relieve postmenopausal symptoms. However, with estrogen only, potential risks such as endometrial cancer and breast cancer may follow. Therefore, when applying estrogen and progestin, it is possible to combine them with progestins or androgens, which can enhance the therapeutic effect and reduce the incidence of side effects.[53] For some postmenopausal chronic patients, the United States Preventive Services Task Force (USPSTF) recommends not using estrogens and progestins in combination for primary prevention and treatment of chronic diseases in the postmenopausal population. It is also not recommended to use estrogens alone for primary prevention of chronic diseases in postmenopausal women who have undergone hysterectomy.[54]

Calcitonin is often used in clinical practice for pain caused by OP. It is a calcium-regulating hormone secreted by the parafollicular cells of the thyroid gland, which causes a corresponding decrease in the release of calcium ions in the blood, thereby inhibiting the activity of osteoclasts, enhancing the ability of bone resorption and promoting the healing of fractures.[55,56] It can, therefore also reduce fractures caused by OP to a certain extent, but the dose and the, duration and method of use will depend on the patient's individual circumstances. At present, salmon Calcitonin (sCT) is the most commonly used. It was originally a peptide substance extracted from the body of salmon. Due to its short half-life in the body, frequent injection is required, and subcutaneous induration is prone to occur, resulting in poor patient compliance. Therefore, it is not commonly used compared to other drugs.[57] However, according to the latest research, some scholars have developed a composite separable microneedle (MNs) system composed of silk fibroin (SF) needle tips and hyaluronic acid (HA) matrix, which can be used for transdermal delivery of sCT to treat OP.[58] Compared to traditional needle injection therapy, it can better repair bone trabecula. This provides a new non-injection strategy for the treatment of OP.

In addition, the inability of bone formation to keep up with the speed of bone absorption can lead to bone loss. Some drugs developed based on the molecular mechanisms of bone resorption and bone formation, such as etidronate[59,60] and monoclonal antibodies, can exert their effects by inhibiting bone resorption. Monoclonal antibodies are of particular concern, and scholars have found through randomized clinical trials that these antibodies exhibit strong anti-fracture effects. However, after discontinuation, BMD will quickly return to baseline. The discontinuation of Dinosemide especially not only leads to rebound bone loss but vertebral fracture.[61] Besides, there are various new methods, including cytokine immunotherapy, gene therapy, and stem cell therapy, with definite short-term clinical efficacy, but certain adverse reactions caused by long-term use, which are still controversial, and need more data to further determine their efficacy.[62]

Treatment methods of TCM

Chinese herbs and compound prescriptions. In China, the prevention and treatment of OP with Chinese herbs and compound prescriptions have been documented since ancient times. For example, for OP with the manifestation of

Table 1. Therapy Methods of Chinese herbs and Compound Prescriptions

Medicines	Efficacy	Models	Potential action mechanism to treat OP		References
ZGP	Tonifying kidney-Yin	OP patients	Inhibited oxidative stress and inflammatory response; Regulate hormone levels; Improve ovarian function; Promote follicle development	Biased towards immunomodulation	Li[63], Mei[64]
YGP	Tonifying kidney-Yang	OP patients		Biased towards insulin regulation.	
QEP	Tonifying kidney-Qi	Mice models of postmenopausal osteoporosis by OVX	Increased expression of β-catenin		Shuai[65]
		Rat models of postmenopausal osteoporosis induced by OVX	Improved OP and inhibited ferroptosis via the PI3K/AKT pathway and ATM.		Hao[66]
Qianggu capsule	Tonifying the kidney and strengthening the bones	OP patients	Increased femoral neck BMD and femoral trochanteric BMD		Wei[67]
Paeoniflorin	Nourishing blood and soothing the liver	MC3T3-E1 cells	Promoted osteogenic differentiation of MC3T3-E1 cells by regulating the Wnt/β-catenin pathway		Guo et al.[69]
Quercetin, Kaempferol, Rutin	—	In vivo clinical and animal research	Bone formation is mainly affected by TGF-β-Smad signaling, fibroblast growth factor and Wnt/β-catenin signaling, and bone resorption is affected by RANKL signaling, NF-κB signaling and macrophage colony-stimulating factors		Shen. et al.[70]

kidney deficiency, Zuogui Pill (ZGP) and Yougui Pill (YGP) recorded in *Jingyue's Complete Work* from the Ming Dynasty (1368--1644 CE) are suitable. They are suitable respectively for OP with kidney Yin deficiency and kidney Yang deficiency and have been approved by the National Medical Products Administration (NMPA). Clinical study has proved that they could improve OP patient's bone mineral density (BMD), inhibit bone conversion and, regulate the coupling balance of bone formation and bone resorption, relieve kidney deficiency syndrome.[63] Of course, there are obvious similarities and differences in the specific action mechanisms between them. Mei et al.[64] found that they could treat OP by inhibiting oxidative stress and inflammatory response, regulating hormone levels, improving ovarian function, and promoting follicle development through network pharmacology, but ZGP was biased towards immunomodulation, and YGP was biased towards insulin regulation.

Qing'e Pill (QEP), which is known as a good prescription for tonifying the kidney, is also commonly used to improve the bone micro-structure of patients with OP. Some studies suggest that the underlying biological mechanism may be related to the increased expression of β-catenin.[65] It has also been found that QEP may be associated with the inhibition of ferroptosis of osteoblasts through the serine/threonine kinase (ATM) and PI3K/AKT pathways, as demonstrated by GO/KEGG enrichment analysis and experimental validation.[66]

In addition, a Chinese patent medicine, Qianggu capsule,[67] with osteopractic total flavone as the main active ingredient, is suitable for kidney Yang deficiency. It can increase femoral neck BMD and femoral trochanteric BMD, but at the same time, it has the side effects of constipation and dry mouth. In these compound prescriptions, Chinese herbs, such as epimedii herba, eucommia bark, and psoraleae fructus, are often the core herbal combinations.[68] It can be seen from the above literature that one conclusion can be drawn: Chinese herbs and compound prescriptions with the effect of 'tonifying the kidney and strengthening the bones' clearly correspond to the mechanism of anti-osteoporosis action in Western medicine.

However, the most effective prevention and treatment of OP by Chinese herbs and compound prescriptions are based on syndrome differentiation. Moreover, compound prescriptions are concerned with the compatibility of ingredients, and their chemical compositions are complex and diverse. Thus, it is difficult to make the specific action mechanism of Chinese herbs and compound prescriptions clear. At present, in addition to focusing on the kidney, Guo et al.[69] also investigated that paeoniflorin could promote osteogenic differentiation of MC3T3-E1 cells by regulating the Wnt/β-catenin pathway from the perspectives of blood stasis and the spleen. However, there are still relatively few studies on the Chinese herbs and compound prescriptions to treat OP that are related to the liver and spleen. By comparing the herbal properties (including medicinal properties, flavour, meridian affinity, and efficacy) of 20 Medicine Food Homology Plants, Shen. et al.[70] found that they all contained quercetin, rutin, and kaempferol, and all had anti-osteoporotic activity in vitro and in vivo, which could be used as daily food supplements. This indicates that the chemical components of Chinese herbs may be potential drugs to treat OP and have great research value, especially since the compound drugs are molecular mechanisms that carry out multiple targets. Mechanistic analysis of whether they exert synergistic or antagonistic effects on each other requires careful development of detailed experiments (Table 1).[71]

Acupuncture, moxibustion and Tuina. Acupuncture and Tuina are beneficial in protecting bones and relieving clinical symptoms of OP. For example, Tian et al.[72] reviewed 290 papers (including 115 reviews, 109 clinical observations and 66 preclinical studies) and concluded that the top ten most commonly used acupuncture points were Shenshu (BL23), Zusanli (ST36), Pishu (BL20), Dazhu (BL11), Guanyuan (CV4), Mingmen (GV4), Sanyinjiao (SP6), Taixi (KI3), Ganshu (BL18) and Xuanzhong (GB39). The underlying action mechanism may be related to the regulation of the hypothalamic-pituitary-gonad (adrenal gland) axis, the activation of the Wnt/β-catenin and OPG/RANKL/RANK signaling pathways.[73,74] Fan et al.[75] also conducted a clinical study and found that most of the acupoints used in most studies are associated with the liver, spleen and kidney.[76] Of these, BL23 in the Bladder Meridian of Foot Taiyin was the most commonly stimulated. It activates the Yuan-primordial Qi of the kidney and makes the kidney nourished.

In addition, ST36 in the Stomach Meridian of Food Yangming is often applied. It regulates the spleen and kidney, invigorates Qi, and generates blood. Li et al.[77] treated

Table 2. Acupuncture, Moxibustion and Tuina

Treatment methods	Commonly used acupuncture points	Models	Possible mechanisms	References
Acupuncture	BL23, ST36, BL20 BL11, CV4, GV4, SP6, KI3, BL18, and GB39	—	Regulate the hypothalamic-pituitary-gonad (adrenal gland) axis, and activate the Wnt/β-catenin and OPG/RANKL/RANK signaling pathways	Tian et al.[72]
	ST36, BL23, and BL11	OVX- rats	Improve BMD, bone mineral content, trabecular structural parameters, femoral biomechanical properties, and femoral histomorphology; Modulate serum levels of estradiol, CRH, ACTH and CORT, and exerts endocrine regulatory effects	Li et al.[77]
Moxibustion	birdpecking and revolving moxibustion on twelve back-Shu points	OVX- rats	Reduce BALP, urinary hydroxyproline and femoral bone morphological indicators, thereby preventing bone metabolic decline and slowing down bone morphological degradation	Zhang et al.[81]
	CV4, SP6	OVX- rats	Increase BMD and bone strength, and the therapeutic mechanism may be related to increasing serum E2 concentration, reducing serum ALP concentration, and upregulating the expression of ERα in MSCs.	Yao et al.[82]
Tuina	BL23, SP6	OVA-rabbits	With peripheral nerve signals being transmitted to the brain, leading to the activation of neural pathways and the secretion of associated endocrine mediators	He[84]

ovariectomized rats with acupuncture for 12 weeks by taking the acupoints of ST36, BL23 and BL11, and found that the treated ovariectomized rats showed improvements in BMD, bone mineral content, trabecular structural parameters, femoral biomechanical properties, and femoral histomorphology. It also modulates serum levels of estradiol, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and corticosterone (CORT), and exerts endocrine regulatory effects. In addition, like acupuncture, moxibustion and Tuina have an important therapeutic and preventive role in relieving spasm and pain, unblocking the meridians, promoting blood circulation and nourishing nerve function,[78-80] and can be used as a complementary tool to OP treatment. Zhang et al.[81] showed that birdpecking and revolving moxibustion on twelve back-Shu points could effectively reduce OP rat BALP, urinary hydroxyproline and femoral bone morphological indicators, thereby preventing bone metabolic decline and slowing bone morphological degradation down. Yao et al.[82] also found that CV4 and SP6 in moxibustion could effectively increase BMD and bone strength in ovarian rats, and the therapeutic mechanism might be related to increasing serum estradiol (E2) concentration, reducing serum alkaline phosphatase (ALP) concentration, and upregulating the expression of ERα in bone marrow mesenchymal stem cells (MSCs). Dong et al.[83] were the first to evaluate the efficacy and safety of Tuina in the treatment of OP, including pain relief, adverse events, improved spinal motor function, and improved self-care and daily living. Tuina was found to be safe and effective. However, strong evidence may still come from prospective and well-designed clinical trials and animal studies to elucidate the potential role of acupuncture and Tuina in protecting against bone loss. Furthermore, a major development in the history of modern acupuncture is the discovery of the action mechanism of central nervous system. In particular, the two acupoints BL23 and SP6 both serve to tonify the kidney and fill the essence that can be transformed into bone marrow to nourish bones, the process of which is also likely to be related to peripheral nerve signals being transmitted to the brain, leading to the activation of neural pathways and the secretion of related endocrine mediators.[84] This, of course, requires further research. Moreover, acupoints BL20, BL23 and SP6 are often used clinically to treat renal, gastric and intestinal disorders, demonstrating the heterogeneous nature of TCM and showing promise as a potentially effective treatment for bone loss (Table 2). However, the clinical evidence on the treatment of OP by acupuncture is still lacking. The relevant research is still in the preliminary stage, and there are limitations in sample size and study quality.

LIMITATIONS OF TCM AND WESTERN MEDICINE IN THE TREATMENT OF OP AND FUTURE RESEARCH NEEDS

Limitations of TCM and Western medicine

Western medicine mainly focuses on the etiology treatment, but there are still some limitations on fracture rehabilitation and bone reconstruction after OP. Besides, Western drugs can increase bone density very quickly, but some of them may cause adverse reactions, and long-term use of them may lead to drug tolerance. Both the advantages and disadvantages of TCM are obvious. Its advantages mainly lie in its long history of medication, precise efficacy, wide application, high safety, and slight side effects. However, the properties of Chinese herbs are influenced by many uncontrollable factors, such as natural environment,[85] dosage,[86] compatibility,[87] and processing.[88] This will cause the effective ingredients of prescriptions to be inconsistent every time applied and the overall efficacy to be unstable. Secondly, classic prescriptions recorded in ancient literature have a long history, and their meanings may evolve. Thus, it is impossible to fully reach the treatment level that the classic prescriptions could reach in ancient times. Thirdly, TCM is based on the principles of 'holistic view' and 'treatment based on syndrome differentiation',[89] and the diagnosis and treatment of diseases should go through five processes -- inspecting, listening, smelling, inquiring, and palpating, and then determine the symptoms of the disease. However, the diagnostic process lacks clear quantitative indicators related to microbiology and fails to unify the syndrome stages of the disease fully. Fourthly, acupuncture treatment is based on the theory of meridians and collaterals, but the nature of meridians and collaterals has not been accurately determined until now. These problems have hindered the application and promotion of TCM in the prevention and treatment of OP. Therefore, although both TCM and Western medicine have certain efficacy in supporting bone health, the treatment effect of TCM, in general, is slow and requires long-term adherence, and the long-term use of Western medicine may have adverse reactions and drug tolerance. For patients with OP that has developed to a severe degree, neither TCM nor Western medicine may be able to relieve the symptoms of OP quickly in the case of single use.

Integrated application of TCM and Western medicine

TCM and Western medicine complement each other, and their integration is a potential therapeutic direction in the future.[90] In China, the integration of TCM and Western medicine for medical development has been advocated since 1958, when Chairman Mao Ze-Dong proposed the important instruction of 'Western medicine learning from Chinese Medicine', and continues to this day[91,92] The main advantages are as follows. Firstly, the etiology and pathogenesis of OP can be analyzed more comprehensively. The cellular-level concept of Western medicine and the overall concept of 'the kidney governing bone, the spleen governing muscle, and the liver governing sinews' in TCM jointly explain the occurrence and development of OP, and mutual references can help find the most suitable treatment plan. Secondly, it can generate synergistic effects. Chinese herbs can promote Western drugs to provide calcium and other nutrients more quickly and accelerate the growth of bone density by adjusting the internal environment and improving the circulation of Qi and blood. Ko et al.[93] found that ELP (epimedii herba, ligustri lucidi fructus, and psoraleae fructus) that tonifies the kidney in a 5: 4: 1 weight ratio synergistically enhanced the therapeutic effect of laroxifen and reduced its clinical dosage. Thirdly, it can relieve the pain and reduce adverse reactions. As physical therapies, acupuncture and moxibustion can reduce the risk of operation and relieve the pain in OP patients. Cai et al.[94] found that when patients with osteoporotic vertebral compression fractures receiving vertebroplasty, anaesthesia by acupuncture (Hegu (LI4), Neiguan (PC6), Jinmen (BL63), and Yintang (EX-HN3)) combined with lidocaine were selected, with acupuncture needles retained until the end of surgery had significantly less pain, less use of anesthetics, and less adverse effects. The operative time was shortened and patient subjective satisfaction was significantly improved. Li et al.[95] found that acupuncture combined with PKP/PVP was more effective than PKP/PVP in treating osteoporotic vertebral compression fractures, effectively relieving the patient's pain, increasing BMD, and improving life quality. In short, the combination of TCM and Western medicine is a very important treatment strategy. However, it should be conducted under the guidance of a professional doctor, and be adjusted according to individual conditions.

SUGGESTIONS ON TREATMENT STRATEGIES OF INTEGRATED TCM AND WESTERN MEDICINE

OP is a complex disease involving multiple factors, and its pathogenesis is very complicated. Therefore, in order to achieve a comprehensive treatment, it is necessary to comprehensively consider multiple aspects such as genetic factors, lifestyle, dietary habits and medication treatment, and adopt individualized treatment strategies. This requires doctors to have comprehensive and professional knowledge and to work closely with patients. Based on the above analysis, we provide a simple set of suggestions for the integrated treatment method of TCM and Western medicine.

Comprehensive Assessment: The inspecting, listening, smelling, inquiring, and palpating of TCM can be combined with Western medical imaging (such as X-ray, CT scanning, MRI, etc.) and laboratory. It is under this condition that a comprehensive examination of the patients' bone density, blood, etc. can be conducted to understand the severity and etiology of OP, and then determine the TCM syndrome types more scientifically.

Medication: Based on the treatment of OP with Western drugs (such as calcium, vitamin D, bisphosphate drugs, etc.), TCM can focus on adjusting the body's kidney deficiency, liver depression, and spleen deficiency to promote bone metabolism and growth, such as QEP for tonifying the kidney, Qianggu capsule for tonifying the kidney Yang, Chaihu Shugan powder for soothing liver stagnation, Guipi Tang for tonifying the spleen, and Siwu Tang for tonifying qi and promoting blood circulation. In addition, for patients with bone pain, additional methods such as Tuina, acupuncture, and moxibustion can be applied to alleviate the pain. The commonly used acupoints include ST36, CV4, KI3, etc.

Exercise Therapy: For elderly OP patients, it is recommended to use Baduanjin, Wuqinxi, and Taiji to regulate the balance of Yin and Yang, promote the flow of Qi and blood, and help the improvement of bone density and muscle strength.

Daily Diet and Prevention: The dietary structure should be adjusted according to personal physical differences. The food that benefits the bone health should also be added. For example, black sesame, walnuts, peanuts, black beans, and black fungus not only have the functions of tonifying kidney and strengthening bones in TCM, but also contain rich nutrients such as calcium, zinc, and protein.

Psychological Adjustment: Doctors of both specialties can consult together, and adjust the patients' psychology by combining their own advantages. For example, the combination of the acupuncture from TCM with the relaxation techniques of psychologists from Western medicine can help patients alleviate negative emotions, such as anxiety and depression.

CONCLUSION

Through the literature review, we believe that the integrated approach of TCM and Western medicine can make up for each other's limitations, which will be a potential trend in the future clinical treatment. The most prominent advantage is that the evaluation and diagnosis of OP will be more comprehensive. TCM uses the diagnostic methods of inspecting, listening, smelling, inquiring, and palpating to gather the information of tongue coating, pulse conditions and facial complexion, etc., and to evaluate the balance between Yin and Yang and five Zang-viscera of the OP patients in a syndrome-differentiation way. Western medicine focuses on modern examination techniques, such as blood tests and imaging. When the two are combined, doctors can get a multi-dimensional understanding on the patients' condition. Besides, the integrated approach can accurately position the needs of patients, and provide individualized treatment strategies for each patient. For example, some OP

patients may have bone pain, muscle pain, or atypical symptoms. In these cases, the treatment methods of acupuncture, moxibustion and Tuina in TCM can reduce the pain, and improve the quality of life. What's more, the treatment by Chinese herbs is mild, and emphasizes overall adjustment. The clinical use of Chinese herbs can significantly reduce the side effects of Western medicine. In this way, the unique needs and preferences of each patient are considered for individualized treatment, which greatly ensures the shared decision-making between healthcare providers and patients, and reduces doctor-patient disputes. However, the integrated approach requires the guidance and supervision of professional doctors to ensure the coordination and safety of the treatment plan. Moreover, the study of OP still needs further investigation in the future. For example, clearer quantitative indicators for TCM should be developed, rigorous clinical trials should be conducted, and new treatment methods based on the extraction techniques of plant vesicles.[96] We firmly believe that the combined treatment of TCM and Western medicine will become a trend in the future in order to better serve society.

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DATA AVAILABILITY

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Yawen Song: Conceptualization, Formal analysis, Visualization, Writing - original draft. Qin Lyu: Conceptualization, Methodology, Visualization, Writing - original draft. Yufan Zheng: Software, Data curation. Baozhao Ju: Conceptualization, Project administration, Writing - review & editing.

DECLARATION OF COMPETING INTEREST

There was no any commercial involvement in the conduct of the study. The authors declare that they have no competing interests.

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ETHICAL COMPLIANCE

Not applicable.

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