

Diabetic Osteoporosis was Discussed Based on the Theories of Spleen and Kidney in Traditional Chinese Medicine

Mengmeng Chen¹, Zhen Li^{1,2,*}

¹*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, China*

²*Department of Endocrinology, Yulin Traditional Chinese Medicine Hospital, Yulin, shaanxi, China*

**Corresponding Author*

Abstract: Diabetic osteoporosis belongs to the category of osteopathy in traditional Chinese medicine, which can cause difficulty in walking in mild cases, increase the risk of fractures, and seriously affect the quality of life. This paper focuses on the internal connection of the internal organs in the disease, believing that spleen deficiency is the foundation of the disease, kidney deficiency is the root of the disease, and phlegm and blood stasis promote the progression of the course of the disease. There is a certain internal connection between deficiency of the spleen and kidney pattern, intertwined phlegm and blood stasis pattern and the pathological mechanism of the disease, and the spleen and kidney jointly affect the occurrence, development, and prognosis of the disease. Tonifying the spleen and kidney, circulating blood and transforming stasis, and removing turbidity are regarded as the treatment target to improve the clinical symptoms, and open up ideas for clinical application.

Keywords: Diabetic Osteoporosis; Osteoporosis; Theories Related to the Spleen and Kidney; Tonify the Kidneys and Strengthen the Spleen

1. Introduction

Diabetic osteoporosis (DOP) is a secondary complication of the skeletal system. Its clinical manifestations are mostly osteogenesis, bone fractures, balance impairment, and bone structure destruction [1]. At present, Osteoporosis (OP) and Diabetes mellitus (DM) are the two major chronic diseases in the world, and the prevalence of comorbidities is still rising. According to the study [2], between 2005 and 2014, the prevalence of comorbidity with OP in Type 2 diabetes patients increased from 3.13% to 6.10%, increasing the risk of fracture [3,4], and the mortality rate after fracture in DM

patients was significantly high [5]. Although the application of some drugs in clinical practice can reduce the incidence of DOP, their early symptoms are relatively mild [6], not easy to detect, and it is difficult to guide the use of drugs, and after long-term medication in the later stage of the disease, not only the therapeutic effect will be weakened, but also adverse reactions, low utilization rate, intolerance and other problems [7]. The mechanism of DOP is complex, affected by factors such as blood vessels, inflammation, hyperglycemia, insulin resistance (IR), and intestinal flora.

DOP did not have a name in traditional Chinese medicine (TCM) in ancient times. Modern scholars classify it as " bone flaccidity " and " bone impediment " according to the symptoms, which reflect the characteristics of the disease, bone mass reduction, and bone structure destruction [8]. In the past, the understanding of the pathology of this disease was mostly kidney deficiency, which was attributed to a single organ function. DOP is based on spleen and stomach damage, and kidney deficiency is the root. This article is based on the theory of the close relationship between the spleen and kidney in TCM, striving to provide theoretical support for the clinical application of the method of toning the kidney, strengthening the spleen, activating blood, and resolving turbidity.

2. The Connection between Spleen-kidney-related Theories and DOP

The theories of spleen and kidney-related originate from the theories of Zangxiang in TCM. It is a mutual influence relationship between the spleen and kidney, that is, they mutually aid in physiological functions, but pathologically, they transmit and induce the disease [9]. In terms of the attributes of the five elements, the spleen belongs to the earth, and

the kidney belongs to the water. The earth can restrain water, and the water can counter resist it. In terms of the functions of the internal organs, the spleen regulate the kidney and other organs. As stated in the Suwen that the spleen is associated with the element of the earth, and located in the center of the body. So it governs other four zang organs and nourishes and supplies them. In the five bodies, the spleen governs muscles and kidney governs the bones, bones and muscles interdepend and mutually benefit. Muscles and bones are inseparable, which are the specific manifestations related to the spleen and kidney, and jointly support the movement of the human body.

Su Wen said that if the five zang organs are damaged, they will transmit to organs they overcome, Spleen disease is transmitted to the kidney. Mostly the spleen and stomach are weak, and the yang qi cannot nourish and warm the spleen, so the kidney is short of nourishing, and bone marrow is insufficient, which all make the bone marrow empty and muscles weak. It shows that the spleen and kidney interaction jointly affect the occurrence and development of bone flaccidity.

The spleen and stomach are in harmony with their respective functions, and the qi and blood transported and transformed by spleen not only nourish the muscles of the whole body, but also complement the kidney essence to nourish the bone marrow. If the spleen is deficient, the muscles are weak, and the bones are not strong. The spleen and kidney are deficient, and bones and muscles dysfunction cause bone flaccidity. In a word, the spleen and kidney are closely related and indispensable in DOP.

3. The Connection between Spleen and Kidney-related Theories and the Pathogenesis of DOP

3.1 Spleen Deficiency is the Foundation of the Disease

Wasting and thirst disorders are followed by bone flaccidity, and the spleen and stomach are damaged first. Spleen qi ascends the nutrients, spleen yang warms and spleen yin moistening fluids of stomach, any link can hinder the function of the spleen's transportation and transformation. The food ingested enters the stomach and is transformed into refined substances, and the spleen transports the substances and water to nourish the whole

muscles and skeletons. When the spleen and stomach are damaged, which leads to the source of qi and blood produced by transportation and transformation is insufficient. If the muscles and bones are not nourished for a long time, the limbs will be impotent. On the other hand, it can cause water and dampness retention, and the body fluids and blood are not smoothly circulate, which will further hinder the transportation function of the spleen and stomach, and become blood stasis, forming a vicious circle of "deficiency-blood stasis". Bones are like the tree trunks, and muscles are like the walls of a building, they play an important role in the musculoskeletal system of the body. That is, muscles drive bone movement and have a protective and nourishing effect on bones, and bones are the attachment points of muscles, supporting the human body to stand. The spleen governs muscles and the kidney governs the bones in TCM, and research confirmed that the muscle content is positively related to bone density, while the TCM syndrome score of patients with spleen deficiency is negatively correlated with bone density [10]. With the aggravation of spleen deficiency, the bone density decreases relatively. Muscles and bones cannot be separated from the nourishment of the spleen. If the spleen is waxing, the qi and blood will be abundant, and the muscles will be strong and sturdy, thus increasing bone density and bone strength to promote the growth and development of bones [11]. All of these confirm the close relationship between muscles, bones, and the spleen and kidney. Pathogenic heat is one of the causes and pathogenesis of bone flaccidity. Spleen yin deficiency leads to fire hyperactivity, or prolonged blood stasis eventually transforms into heat, and they all consume fluids as well as further affect the bones or muscles. The spleen and stomach coordinate in receiving and transportation, so the deficiency of heat not only consumes the stomach fluids and hinders the functions of the stomach in governing receiving, holding, and decomposition, but also blocks the circulation of qi and blood, and finally makes the limbs weak and useless.

In a word, the spleen nourishes all the internal organs of the body, if the spleen and stomach are deficient, the five zang organs are not in harmony, the six fu organs are not in harmony, and the muscles and skeletons are lost in nourishing.

3.2 Kidney Deficiency is the Root of the Disease

Medical Invention said that the disease of hypodermation is damaged by the kidney, the second damage to the liver, the third damages are in the spleen. Kidney deficiency is the root cause of bone flaccidity, which means the loss of essence and the waning of yin or yang. The kidney stores essence and generates marrow, the essence and marrow is more enough, the bone is stronger and rigider, which explains that the essence has a certain effect on the strength of the bone. On the contrary, if the body is lack of kidney essence and marrow, it will lead to a decline in the ability of stem cell osteogenesis and differentiation, and inhibition of bone formation [12]. In conclusion, there bone changes increase the risk of fracture.

If the kidney essence is insufficient, the kidney yin and yang are also deficient, which in turn affects the transportation of nutrient substances in the spleen. After wasting and thirst disorders for a long time, the spleen heat is transmitted to the kidney, or fluids deficiency can't restrain the yang. It consumes the body fluids, so that fluid exhaustion leads to blood stasis, in turn, the stasis aggravate the deficiency of body, which make the bone marrow cavity empty and the bone is fragile. The Yilin Gaicuo says that" the Yuan-primordial qi is so empty that qi fails to circulates blood, blood will stay and stagnate". Kidney deficiency for a long time, when the impairment of yin affects yang, kidney's ability to warm and promote are diminishing, which manifests the Qi-blood disharmony, liquid deficiency, and phlegm and stasis further hinder the transmission of nutrients and accelerate the course of the disease. Danxi Xinfa says" wasting of the kidney, kidney deficiency firstly sufferers from it, the waist, knees, and the joints become sore and weak ", which clearly explains bone flaccidity is manifested as backache and bone pain. Modern traditional Chinese medicine research found that patients in the bone reduction group had a high frequency of symptoms such as waist and knee soreness, lumbago, tinnitus, hair loss, and tooth shaking, and diuresis, especially in OP group, among which the frequency of backache was the highest [13]. The waist is regardrd as the house of the the kidney, and the area covered by kidney essence, which further proves that the reduction of bone mass is closely related to

kidney deficiency. It can be seen that kidney deficiency occupies an important position in bone flaccidity.

3.3 Deficiency of Spleen and Kidney, Phlegm and Blood Stasis Aggravate the Progression of the Diseases

The qi-blood disharmony plays an important factor in the flexibility of the skeletal system. Therefore, when the blood is harmonious, the meridians flow freely, so as the muscles and bones are strong and durable, and the movements of joints are smooth. It is well known that the spleen is regarded as the source of phlegm generation. Therefore, the spleen deficiency generates pathogenic dampness, which obstructs the movement of qi-blood, so that the Ying-nutrients and Wei-defence are blocked as well as blood stasis without circulating. Finally, these excess pathogens further block the transportation of nourient essences. Modern scholars believe that spleen deficiency with dampness pattern is similar to lipid metabolism disorder [14]. Abnormal lipid metabolism increases the expression of inflammatory factors, causes inflammation and oxidative stress (OS), and aggravates bone loss. The kidney governs water and fluids and qi reception, qi controls and circulates blood. So if qi transformation of the kidney is not good, and the transformation with transportation and egestion of qi, blood and bodily fluids will be abnormal, and the accumulation into phlegm and stagnation becomes stasis. Besides, the blood stasis combine with the phlegm turbidity blocks mutually the circulation of qi and blood, the exchange of bone and vascular nutrients is impaired, the trabecula becomes thinner, and the number is reduced, and the residual trabecular load is aggravated, micro-fractures occur, damage the blood vessels, and the veins are blocked, causing bone pain [15]. Blood stasis and phlegm turbidity also hinder the regeneration of new blood, aggravate the deficiency, and further lead to stasis.

In a word, the deficiency of spleen and kidney is the initial cause, followed by phlegm turbidity and blood stasis. With the continuous development of the disease, these pathological products continue to accumulate, which aggravates the decay of the spleen and kidney.

5. Spleen and Kidney-Related Theories and Pathological Mechanism of DOP

4.1 Gut Microbiota Disorders

Gut microbiota (GM) disorders mainly manifest as beneficial bacteria are reduced, and the number of potentially pathogenic enterococci increases, and the metabolism of short-chain fatty acids is impaired, resulting in bone loss [16]. Besides, it also affects glucose metabolism and its metabolites affect intestinal mucosal barrier permeability and inflammatory response [17]. It was found out that by altering the composition of intestinal microorganisms or reducing the release of lipopolysaccharides (LPS) can promote the growth and differentiation of osteoblasts through multiple pathways and significantly reduce IR [18]. In TCM, the spleen and the intestine are connected by meridians, which is " the origin of the granary". Its essence is integrated and participates in the generation of nutritive substances, the process of absorbing nutrients by the spleen biochemical qi and blood is similar to that of the villi of the small intestine. Therefore, spleen deficiency lead to the stomach governs receiving and holding are out of order, and the spleen is inability to properly digest food and transport, which need to promote the regeneration of qi and blood by strengthening the spleen and helping transport and transform, so that the muscles and bones as well as other tissues and organs can be nourished. In addition, the spleen's main guard is also similar to the intestinal immune function. It is said in Lei Jing that "The spleen mainly transports the Qi and Blood to grow muscles, and the five zang organs and six fu organs depend on it to nourish, so the spleen is the main guard. Wei qi is the protective screen of resisting external pathogens. That is why it is said in Su Wen that" the wei-defensive qi guard, so it nourish the flesh, fills the skin, and protect the subcutaneous tissue from pathogenic qi." The spleen's main health depends on the nutritive substances produced by the water and food, which nourishes the muscles, the pore is closed, and the external pathogen is difficult to invade, the other is to remove the internal pathogenic factors that caused by seven emotions causing internal damage(such as phlegm, pathogenic dampness, etc.). On the contrary, if the spleen is weak, the outside of the guard will be lost. In addition, the transportation of the spleen will be disturbed by it, and the internal and external causes, and phlegm and pathogenic dampness

will be born. As an important immune organ of the human body, the intestine's mucous membranes, lymphocytes, macrophages, etc., building a complete barrier to prevent harmful substances from invading the human body, which is the embodiment of the microscopic perspective of the body [19].

From the theory of zang-xiang in TCM, the kidney governs water and fluids, small intestine governs thick body fluid and large intestine governs the thin body fluids. They participate in the metabolism of water and fluids. All in all, the kidney and the intestine are closely related to the function. Pathologically, the kidney of body fluids are insufficient, the intestine is dry, and the large constipation cannot be knotted. It can be seen that the kidneys are affected by pathogenic qi, which affects the function of the intestines. Microscopy, modern scholars have found that [20] intestines and kidneys have a two-way regulatory effect. Gut microbiota disorders and metabolites activate the renin-angiotensin-aldosterone system (RAAS) and damage kidney cells, in turn, kidney diseases can also cause intestinal microecological disorders, reduce the number of beneficial bacteria, inhibit the molecular expression of bone metabolic signals, and lead to a decrease in bone mass. The study found that there were differences in the composition of intestinal flora, portal, and genus levels between patients with different traditional Chinese medicine pattern. Among them, the spleen and kidney yang deficiency pattern group, the liver and kidney yin deficiency pattern group, and the kidney deficiency induced blood stasis pattern group had better bacterial abundance than other groups [21]. In a word, the stability of GM is inseparable from the establishment of the spleen and kidney organs.

4.2 Endocrine and Metabolic Disorders

DOP is not only involved in glycolipid metabolism, but also involves the hypothalamus, gonadotropin, thyroid hormone, estrogen, leptin, etc [22]. The qi and blood network formed by the liver-spleen-kidney is highly compatible with the endocrine system through the interconnection of meridians, the five elements mutually generate, mutually restrain, and mutually control and transform, as well as the coordination of functions. Among them, the spleen transport and transform function correspond to insulin metabolism and estrogen

metabolism, and the kidney stores essence corresponds to the hypothalamic-pituitary-gonadal axis and its regulation of growth hormone, which affects bone metabolism [23].

Under the condition of DM, the integrity of new bone formation and bone microstructure will be changed, Which result in an increased risk of vulnerability fracture and insufficient bone regeneration after injury. Hyperglycemia and blood sugar fluctuations directly inhibit osteoblast differentiation or affect bone remodeling through oxidative stress, advanced Glycation End-products (AGEs), and pro-inflammatory factor cells [24]. A fundamental research shows that insulin directly stimulates the mitosis of osteoblasts and inhibits cell apoptosis, it may also have a synergistic effect with other anabolic factors in the bone (such as parathyroid hormone) [25]. With the growth of age, the bone marrow gradually becomes fat, the bone marrow cavity space shrinks, and the activity of osteoblasts is inhibited, thus reducing bone mass and increasing the risk of fracture [26,27]. Fat accumulation and the increase in the number of aging cells in the bone marrow, which in turn promotes the activity of osteoclasts by increasing the production and secretion of cytokines such as IL-6 [28]. Besides, it also aggravates IR and the functional damage of pancreatic islet β -cells, and further lead to a glycolipid metabolism disorder [29]. The spleen is deficient and does not ascends the nutrients, and the essence, qi, blood, and body fluids cannot circulates. The stagnant liquid accumulates into pathogenic dampness turbidity, phlegm, and fluid retention. In addition, the pathogenic dampness and static blood is knotted with each other, damaging the five zang organs and the outer aspect of the five zang organs. Insulin deficiency or utilization disorders, and the blood sugar concentration rises, which damage the vascular endothelium, thus promote lipid enrichment and the activation of the coagulation system to form plaques. In the long run, it has caused multiple organs, multi-tissue damage, and increases the risk of cardiovascular and cerebrovascular adverse events. In TCM, kidney essence promotes the growth, development, and reproduction of the body. In mordern medicine, the essence of kidney deficiency is akin to the disorder of the hypothalamic-pituitary-gonadal axis, which

leads to a decrease in the level of sex hormones, the enhancement of osteoclercle activity, and aggravates bone loss. Spleen and kidney deficiency is the root of the disease, which induces various hormone secretion disorders in the body and affects bone metabolism.

4.3 Mitochondrial Dysfunction

Mitochondria are the " power source" of cellular activity, providing energy for bone cell differentiation and for muscle contraction and relaxation. Mitochondrial dysfunction is closely associated with spleen and kidney deficiency, thereby affecting the renewal and metabolism of bone cells.

The process of producing ATP through glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation in the whole body and in mitochondria is similar to the spleen governs transportation and transformation and ascends the nutrient [30]. Under normal physiological conditions of the human body, mitochondrial oxidation and antioxidant balance, and autophagy are stable, so that osteogenesis and bone breakage are in a dynamic balance, thus stabilizing the bone state. On the contrary, mitochondrial oxidation damage and cell energy loss occur, which largely determine the occurrence of OP. Moreover, hyperglycemia promotes the apoptosis of mesenchymal stem cells (MSCs) by enhancing ROS in mitochondria, reducing the potential of mitochondrial membrane, and upregulating the expression of cysteine-3/9 and cytochrome C [31], it also inhibits the MSC edgehog signaling pathway leading to bone defects, and osteogenic differentiation is inhibited [32]. The genetic material in mitochondria is similar to kidney essence. A part of innate essence of the kidney originates from the mother and father, which determines the growth, development, and rise and decline of bones. From the 14 years old or 16 years old to 56 years old or 64 years old, the kidney essence turns from the waxing to waning, and the five zang organs also decline. In this process of aging, mitochondria also aging, various metabolic homeostasis changes occur, the removal of damaged organelles, proteins, and other metabolites slows down, and the accumulation of oxidative bases, and the function of muscles and bones also declines [33]. Research shows that tonify the spleen and kidney can delay the aging process by enhancing autophagy and reducing damage.

Wen and others use the method of tonifying the kidney and strengthening the spleen to regulate the PINK1 / Parkin signal pathway to enhance mitochondrial autophagy [34]. There is, in addition, strengthening the spleen can also alleviate the degree of IR and thus improve the muscle content, so as to enhance bone mechanical stress to improve bone metabolism disorders and bone microstructure damage. In summary, the spleen, kidney, and mitochondria often coincide in function, and the method of tonifying the kidney and strengthening the spleen improves the energy metabolism of mitochondria and maintains its internal environmental homeostasis in many aspects.

4.4 Inflammation and Oxidative Stress

Chronic low-degree inflammation and oxidative stress affect the differentiation, proliferation, and apoptosis of bone cells, or participate in the process of bone reconstruction through glycolipid metabolism indirectly. The study found that especially in the early stage of DOP, the level of inflammatory mediators such as macrophages, tumor necrosis factor α (TNF- α), and interleukins are elevated [35]. Among them, pro-inflammatory macrophages M1 induce osteoclastogenesis, which leads to bone loss, while macrophages M2 polarize to enhance muscle regeneration, promoting muscle fiber regeneration and immune cell clearance in the body [36], and the latter will also inhibit osteoclast differentiation, proliferation, and activity, and play an anti-osteogenesis role [37]. Li Can and other studies further show that the hyperglycemic environment not only promotes osteoclastic differentiation, leading to bone matrix calcification and bone density and bone strength decline [38], it can also promote the formation of AGEs and ROS, increase the expression of pro-inflammatory factors, and thus aggravate the body's inflammatory response [39]. In a word, high blood sugar and inflammation affect each other to promote osteoblast dysfunction.

Spleen and kidney deficiency, qi stagnation and blood stasis pattern in TCM are related to inflammation and oxidative stress. Research shows that spleen deficiency is related to the increase of superoxide dismutase (SOD) [40]. The concentration of SOD affects the physiological concentration of superoxide free radicals, thus affecting the body's immune defense, energy metabolism, and other internal

regulation. Kidney deficiency and marrow and essence exhaustion, the bone differentiation ability of stem cells declines, and bone formation is inhibited, for a long time, phlegm and static blood endogenes, and the level of micro-environmental inflammation increases, which accelerates the occurrence of bone flaccidity. A cell experiment confirmed that nourish and supplement kidney yin can reduce ROS levels, inhibit protein expression and oxidative stress, significantly increase bone density, trabecular number, and trabecular thickness in mice, and improve osteoporosis [41]. After the treatment of DOP with the kidney tonic prescription Liuwei Dihuang Pill [42], the antioxidant index SOD increased, the content of propylene aldehyde (MDA) decreased, and bone metabolic markers such as osteocalcin and type I β -collagen degradation increased. In the later stage of the disease, the spleen and kidney are weak, and the phlegm and stasis are interconnected. Taohong Siwu soup circulate blood and transform stasis to regulate the signal pathway, reducing the expression of inflammatory factors TNF- α and IL-6 and cell apoptosis [43]. It can be seen that the method of tonifying the kidney, strengthening the spleen, and circulate blood can be anti-inflammatory, anti-oxidation and improve bone density.

5. Treatments of DOP based on the Theories of Spleen and Kidney Correlation

5.1 Tonifying for the Spleen and Kidney, Nourishing the Musculoskeleton

Spleen deficiency is the basis, and kidney deficiency is the key. Reinforcing the spleen and tonifying the kidney is not limited to simple tonic, but combined with different stages of symptoms, causative factors, and pathogenesis to treat them.

Reinforcing the spleen has the meaning of tonifying the spleen qi, nourishing the spleen yin, warming and tonifying the spleen yang, transporting the spleen, and stimulate the spleen. What matters most method of reinforcing the spleen is to tonifying the spleen qi. For example, mongolian milkvetch root is the strength of tonifying qi, specializing in the spleen qi, and there are also rhizoma atractylodis, codonopsis pilosula, radix pseudostellariae etc. Qi and blood are deficient, and dual deficiency of yin and yang. Add pueraria, yam, and polygonatum to nourish yin and generate body fluids to help

the spleen to transport and transform. In addition, cinnamon, rhizoma zingiberis, and other warm and help the spleen yang to remove pathogenic factors. Transporting and transforming the spleen mean that the spleen qi is capable of ascends the nutrients as well as transform the nutrients, so that the five zang organs and six fu organs are nourished, and the moisture and turbidity is removed by itself. Use more Chinese medicines of swordlike atractylodes rhizome, mangnolia officinalis, cabin potchouli herb, and elettaria cardamomum. If you find the disease of the liver, you will know that the disease of the liver runs to the spleen. If the liver qi is too waxing or stagnant it will hurt the spleen, which will affect the function of the spleen governs transportation and transformation. The method of stimulating the spleen is to restore ascend, descend, enter and exit of the qi movement, it is used to soothe the liver and regulate qi with costusroot, Chinese thorawax root, nutgrass galingale rhizome etc. In modern pharmacological research, the active ingredients of TCM tonify spleen qi such as monglian milkvetch root and common yan rhizome can also effectively regulate the level of serum bone metabolism in addition to lowering blood sugar, tonifying the spleen and nourishing blood, strengthening the spleen and tonifying qi, strengthening the spleen and transform dampnes, and other treatment methods can regulate bone metabolism by improving GM, anti-inflammatory and antioxidant, regulating mitochondrial autophagy [44].

Kidney deficiency is the key to the progression of the disease. In view of TCM, the OP evolves with the pattern of " kidney yin deficiency - essence deficiency - kidney yang deficiency - marrow empty - bone withering ", consequently, the treatment methods are primarily based on tonifying kidney yin, warming and tonifying kidney yang, and tonifying essence and marrow. Moreover, a variety of active ingredients of kidney tonic herbs, such as adhesive remannia root tuber, glossy privet fruit, short-horned peimedium herb, and fortune's drynaria rhizome etc, which have shown a positive effect on improving bone density. It has been clinically confirmed that nourishing yin and tonifying the kidney, warming the kidney yang, and tonifying essence and marrow methods promote osteoblasts and inhibit osteoclasts, reduce ROS levels, and delay the decline of bone mass and

function [45]. Besides, these teatments can relieve lower backache, improve clinical symptoms such as lower limb atrophy, fatigue, and difficulty walking and dizziness, so as to promote the quality of life and improve muscle function [46,47]. Furthermore, the use of Western medicine combined with gentle moxibustion to stimulate the acupoints such as Pishu point, Shenshu point, Zu Sanli point, Mingmen point, and Yao Yangguan point, aslo the pain score of the two groups of patients decreased, the experimental group had a lower score than that of the control group, and the quality of life score increased. The collaboractive treatments effectively alleviate the symptoms and improved the patient's compliance [48]. In a word, benefiting the spleen and tonifying the kidney can achieve the dual benefits of blood sugar control and bone health improvement, and there are few adverse reactions.

5.2 Treating both the Tip and Root, and Slow down the Progression of the Disease

Deficiency of the spleen and kidney is the root, blood stasis and other excess pathogens are tip, so tonifying kidney, strengthening spleen, and circulating the blood stasis throughout the entire process. In data mining, it was found that in the distribution rule of DOP traditional Chinese medicine pattern tybes, syndrome of deficiency pattern with excess pattern includes kidney deficiency and stasis pattern, qi and yin deficiency and blood stasis pattern, and spleen and kidney deficiency and stasis pattern [49]. With the progression of the disease, the degree of damage to the spleen and kidney organs and the state of stasis and turbidity also change. In the early stage, it is mainly spleen deficiency, and kidney deficiency is not obvious. The treatment should strengthen the spleen and circulate the blood. Based on common achyranthes, Chinese taxillus herb, fortune's drynaria rhizome, and other kidney-tonifying medicines, add monglian milkvetch root, Chinese angelica, szechwan lovage rhizome, Dan-shen root, and other beneficial qi and transform stasis and unblock collaterals to improve stasis. In the Xiaoke disease, yin deficiency is the underlying root pathogenesis. Over time, the liquid is secretly consumed, and the refining liquid becomes stasis. It is tonified qi and circulated the blood so that qi and blood can reach the bone marrow. If the essence is

exhausting, the blood will dried-up, and the vein will be shrunken. Research found that use tonify kidney essence and transform stasis methods to treat DOP patients, who the blood red blood cell aggregation index and whole blood viscosity will be significantly reduced, urine calcium and urine phosphorus will be significantly reduced, and the bone density index will increase, so that blood stasis will be removed and new blood will be born [50]. There are also representative Liuwei Dihuang soup, Zuogui pill is the adhesive rehmannia root tuber in the recipe, yam and common macrocarpium fruit are the monarch medicines, which tonifies the liver, spleen, and kidney, and benefits qi and tonifies blood to promote the movement of qi and blood in the whole body to nourish the tendons, bones, and muscles. If the stomach fluids is not enough, thirsty, hungry, with dwarf lilytuf root tuber, snakegourd root, common anemarrhena nourishing yin and generating fluids. If the deficiency heat of the kidney ascends and affects the house of the original spirit, it will feel dizzy, and difficult to urinate. So add common lophatherum herb, oriental waterplantain tuber, which utilizes these herbs of characteristics of sweet and cook properties to clear the heat and does not hurt the yin. In a word, it can effectively ease symptoms, stabilize muscles and bones, and delay the progression of the disease by nourishing and tonifying the liver and kidney, supplying kidney essence and transforming stasis. In the middle and late stages of the disease, the more deficiency and stasis of the kidney, the more serious it is, which consumes qi and yang. On the basis of nourishing yin and tonifying the kidney, add Chinese dodder seed, desertliving cistanche herb, medicinal morinda root, and monkshood daughter root etc to seek yang from the yin, and cultivate the original yang of the kidney to dispel the turbidity of phlegm and stasis. Teng Jiawen and others used Jiawei Yougui Pill to treat DOP with Gukang Capsule, which reinforce healthy qi and remove pathogenic factors simultaneously to circulate blood and transform stasis [51]. After above treatments, the levels of FPG, 2h PBG, and HbA1c were reduced, also the bone density of L1 to 4, femoral neck, and total hip were higher than before treatment, and the experimental group was higher than that of the control group. In the later stage of DOP, essence is depleted, the blood of the meridians is astringent, the camp

guard does not run smoothly, and the symptoms of bone flaccidity are aggravated. With centipede, scorpion, cicada slough, and other insect herb, use their characteristics of being good at moving and removing for evil, go deep into the meridians and collaterals, dispel the accumulation of blood clots, and ease pain symptoms. Blood stasis becomes an epilemosis over time, and take a small dose of leech and tabaus cleg in the Dahaung Zhechong pill to eliminate the stasis. In addition, if the phlegm pattern is much more obvious, add Indian mustard seed, taterinow steetflag rhizome, Sanchi, Yanhusuo, szechwan lovage rhizome, common turmeric rhizome etc. Long-term blood stasis becomes toxin, and transformed heat. It adds weep forsythia fruit that clears heat and removes toxins, and induces herbs to reach directly the disease.

In summary, tonifying the kidney and circulating stasis are carried out throughout, and the treatments are based on pattern identification according to the evolution of qi and blood, yin and yang, and kidney essence.

6. Brief Summary

Diabetic osteoporosis is caused by spleen deficiency and kidney deficiency. When the spleen and kidney are deficient, which lead to generate excess pathogens such as the phlegm, stasis blood, and toxic pathogens block the meridians and attach and kill yang qi. In the end, these factors constantly damage muscle and bone. The treatment methods are based on the principle of tonifying the kidney, strengthening the spleen, and circulate the blood. Specific ways for benefiting the spleen change with the deficiency of the spleen qi, spleen yang, and spleen yin, which contain nourish and supplement the spleen yin, warming the spleen yang ect. The methods of tonifying the kidney contain kidney yin, warming the kidney yang, and essence and marrow, so as to restore qi and blood to nourish the body. The methods of tonifying the kidney and circulating the blood is to treat DOP in layers. In the early stage, it is used to strengthen the spleen and the kidney and circulate the blood. In the middle stage, it nourishes and supplement the liver and kidney, tonifies the essence and slows down the progression of the disease. In the middle and late stage, it is used to nourish yin and tonify yang to remove foul turbidity. In the late stage, it needs reinforce healthy qi to strengthen the

body, dispel stasis without hurting the healthy qi. In a word, the methods of benefiting the spleen and tonifying the kidney and circulating the blood are not isolated, and can be applied flexibly to take into account the changes of symptom and pattern.

References

- [1] Nirwan N, Vohora D. Linagliptin in Combination With Metformin Ameliorates Diabetic Osteoporosis Through Modulating BMP-2 And Sclerostin in the High-Fat Diet Fed C57BL/6 Mice. *Front Endocrinol (Lausanne)*. July 19, 2022; 13:944323.
- [2] Xu Y, Wu Q. Trends in osteoporosis and mean bone density among type 2 diabetes patients in the US from 2005 to 2014. *Sci Rep*. February 12, 2021; 11(1):3693.
- [3] Ferrari SL, Abrahamsen B, Napoli N, Akesson K, Chandran M, Eastell R, El-Hajj Fuleihan G, Josse R, Kendler DL, Kraenzlin M, Suzuki A, Pierroz DD, Schwartz AV, Leslie WD; Bone and Diabetes Working Group of IOF. Diagnosis and management of bone fragility in diabetes: an emerging challenge. *Osteoporos Int*. 2018 Dec; 29(12):2585-2596.
- [4] Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Kostner A, Womack CR, Palermo L, Black DM; Study of Osteoporotic Fractures (SOF) Research Arch Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA* 2011 Jun 1; 305(21):2184-92.
- [5] Martinez-Laguna D, Nogues X, Abrahamsen B, Reyes C, Carbonell-Abella C, Diez-Perez A, Prieto-Alhambra D. Excess of all-cause mortality after a fracture in type 2 diabetic patients: a population-based cohort study. *Osteoporos Int*. 2017 Sep; 28(9):2573-2581.
- [6] Wang Xinghong, He Shuming, Yin Shipeng, etc. Based on the theory of "kidney essence main bone", the experience of treating diabetic osteoporosis with Dunhuang medicine Datong kidney soup. *Traditional Chinese Medicine Research*, 2021, 34(05):75-77.
- [7] Khosla S, Shane E. A Crisis in the Treatment of Osteoporosis. *J Bone Miner Res*. 2016 Aug; 31(8):1485-7.
- [8] Xiang Yi, Zheng Feng, Wang Xian. Brief analysis of the name of osteoporosis in traditional Chinese medicine. *Inner Mongolia Traditional Chinese Medicine*, 2019, 38(01):92.
- [9] Liu Chengli, Qiu Shijun, Liu Xiaobin. Discussion on the connotation of the theory related to spleen and kidney in traditional Chinese medicine. *Journal of Guangzhou University of Traditional Chinese Medicine*, 2009, 26(05):491-494.
- [10] Gao Ziren, Li Yuehua, Xu Yapei. Research on the relationship between spleen deficiency syndrome and osteoporosis in traditional Chinese medicine based on grip strength, muscle content, and BMI. *Fujian Traditional Chinese Medicine*, 2018, 49(05):54-56.
- [11] Liu Nana, Wang Yanyan, Bu Hanming, etc. From the perspective of spleen and kidney deficiency - bone and flesh separation to explore muscle deficiency - traditional Chinese medicine treatment of osteoporosis. *Chinese folk therapy*, 2025, 33(19):10-13.
- [12] Chen Guifeng, Shang Qi, Shen Gengyang, etc. The theoretical basis of traditional Chinese medicine reveals the microenvironment of osteoporosis inflammation from "renal main bone marrow". *Chinese Journal of Traditional Chinese Medicine*, 2022, 37(12):6906-6909.
- [13] Zeng Xiangrong, Zhao Wei, Wang Rongtian, etc. Preliminary analysis of traditional Chinese medicine symptom identification tools for people at high risk of osteoporosis. *Chinese Journal of Osteoporosis*, 2022, 28(10):1501-1506.
- [14] Wang Xiaoyi, Wang Haiqi, Liu Yutong, etc. Discussion on the mechanism related to the regulation of lipid metabolism in the treatment of osteoporosis with spleen-strengthening and moisturizing drugs. *Chinese Journal of Osteoporosis*, 2023, 29(12):1819-1825.
- [15] Huang Zhen, Li Wei, Ye Baisheng, etc. The relationship between cell death and osteoporosis is analyzed by the theory of "virtual stasis poison". *Chinese Journal of Osteoporosis*, 2025, 31(02):278-282.
- [16] Huang KC, Lin CY, Chuang PY, Yang TY, Tsai YH, Li YY, Chang SF. Microbiota diversity and its influence on diabetic

- osteoporosis development. *Biochem Biophys Res Commun.* 2025 Nov 19; 790:152884.
- [17] Han Mei, Zhang Gang, Zhao Jin, etc. Progress on the role and mechanism of intestinal flora in the development of diabetic nephropathy. *Journal of Capital Medical University*, 2025, 46(04):742-748.
- [18] Zhang, Y., Zhu, Y., Li, M., Zhang, M., Shou, D., & Tong, P. A promising approach to diabetic osteoporosis: oxymatrine's effects on gut microbiota and osteoblasts. *Nutrition & diabetes*, 15(1), 19.
- [19] Wang Guijie, Wu Yukun, Yu Zongliang, etc. Discuss the intestinal immune mechanism and clinical identification and treatment of Hashimoto's thyroiditis based on "wood depression and soil". *Chinese Journal of Traditional Chinese Medicine Information*, 2025, 32(11):172-176.
- [20] Su Jiliang, Xie Xingwen, Li Dingpeng, etc. Based on the liver, spleen, and kidney organs of traditional Chinese medicine, to explore the relationship between intestinal microecology and osteoporosis. *Chinese Journal of Traditional Chinese Medicine Information*, 2020, 27(07):16-18.
- [21] Zhou Zhicheng, Tian Han, Zhuang Xurui, etc. Differential analysis of intestinal flora in patients with osteoporosis of different traditional Chinese medicine syndromes. *Journal of Guangzhou University of Traditional Chinese Medicine*, 2024, 41(09):2289-2295.
- [22] Zhang Xinmei, Liu Nana, Bu Hanming, etc. Research progress on the immunotherapy of diabetic osteoporosis in traditional Chinese medicine. *Hebei Traditional Chinese Medicine*, 2025, 47(03):499-504+510.
- [23] Xiao Xiaoqiao, Zhao Shuke, Hao Linglun, etc. Based on the "liver-spleen-kidney" axis, explore the mechanism of endocrine system regulation and clinical application. *Journal of Traditional Chinese Medicine*, 1-7[2026-01-07].
- [24] Tabara, Y., Ikezoe, T., Yamanaka, M., Setoh, K., Segawa, H., Kawaguchi, T., Kosugi, S., Nakayama, T., Ichihashi, N., Tsuboyama, T., Matsuda, F., & Nagahama Study Group (2019). Advanced Glycation End Product Accumulation Is Associated With Low Skeletal Muscle Mass, Weak Muscle Strength, and Reduced Bone Density: The Nagahama Study. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 74(9), 1446–1453.
- [25] Thrailkill KM, Lumpkin CK Jr, Bunn RC, Kemp SF, Fowlkes JL. Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. *Am J Physiol Endocrinol Metab.* 2005 Nov; 289(5):E735-45.
- [26] Cheng Dongliang, Feng Hongmei, Wen Ge, etc. The value of the magnetic resonance fat quantification technique IDEAL-IQ to evaluate the severity of lumbar osteoporosis. *Chinese Journal of CT and MRI*, 2023, 21(05):157-159.
- [27] Yang Yueying, Zheng Dong, Cui Jie, etc. MRI multi-sequence scanning combined with serum Cathe K and DKK-1 to predict the risk of fracture in patients with type 2 diabetic osteoporosis. *Chinese Journal of CT and MRI*, 2025, 23(10):186-189.
- [28] Yao Qianing, Xie Xingwen, Wang Chunxiao, etc. The relationship between lipid metabolism disorders and osteoporosis and the research progress of traditional Chinese medicine intervention. *Chinese Journal of Osteoporosis*, 2023, 29(10):1496-1502.
- [29] Ma Lingyun, Liu Defeng, Song Jiatong, et al. The relationship between peripheral hematitis factor expression and bone metabolism and bone density loss in patients with type 2 diabetes combined with osteoporosis. *Progress of Modern Biomedical*, 2024, 24(08):1560-1565.
- [30] Hu Qi, Song Yafang, Sun Ying. Discussion on the correlation between "spleen governs muscle" and energy metabolism in mitochondrial biosynthesis in traditional Chinese medicine. *Shizhen Traditional Chinese Medicine*, 2014, 25(04):1018-1020.
- [31] Li C, Gong H, Shi P, Liu S, Zhang Q. Different Forms of Regulated Cell Death in Type-2-Diabetes-Mellitus-Related Osteoporosis: A Focus on Mechanisms and Therapeutic Strategies. *Int J Mol Sci.* 2025 May 6; 26(9):4417.
- [32] Zhang Cheng, Bao Lirong, Yang Yutao, etc. The effect of M2 macrophage exocrine on osteoblastic differentiation of bone marrow mesenchymal stem cells in mice under high sugar and high insulin conditions. *Journal of Sichuan University (Medical Edition)*, 2022, 53(01):63-70.

- [33] Huang Jiachun, Huang Hongxing, Wan Lei, etc. Theoretical analysis of spleen and kidney-muscle and bone-mitochondrial. *Chinese Journal of Osteoporosis*, 2021, 27(12):1844-1847.
- [34] Wen Xiaochen, Liu Ruoshi, Zhu Ke, etc. The method of toning the kidney and strengthening the spleen regulates the autophagy-related PINK1/Parkin signaling pathway to treat diabetic osteoporosis. *Chinese Journal of Basic Medicine of Traditional Chinese Medicine*, 2025, 31(04):649-654.
- [35] Xing SJ, Gao YF, Liu L, Sui BD, Da NN, Liu JY, Wang H, Yuan Y, Qin Y, Liu PS, Ying SQ, Zhang K, Liu JX, Chen J, Liu YH, Xie X, Jin Y, Zhang S, Zheng CX. Integrated Phenotypic and Transcriptomic Analyses of Osteoporosis in Type 2 Diabetic Mice. *Int J Med Sci*. 2025 Mar 10; 22(8):1773-1790.
- [36] Raimondo, T. M., and Mooney, D. J. Functional muscle recovery with nanoparticle-directed M2 macrophage polarization in mice. *Proceedings of the National Academy of Sciences of the United States of America*, 115(42), 10648–1065.
- [37] Saxena, Y., Routh, S., & Mukhopadhyaya, A. Immunoporosis: Role of Innate Immune Cells in Osteoporosis. *Frontiers in immunology*, 12, 687037.
- [38] Li Can, Chen Heng, Wang Liwei. Discussion on the correlation and clinical significance of blood sugar variability and bone metabolism in patients with type 2 diabetes. *Chinese Journal of Clinicians*, 2025, 53(10):1314-1317.
- [39] Liu T, Wang Y, Qian B, Li P. Potential Metabolic Pathways Involved in Osteoporosis and Evaluation of Fracture Risk in Individuals With diabetes. *Biomed Res Int*. May 23, 2024; 2024:6640796.
- [40] Luo Luyi, Liu Zengyin. Changes in the activity of copper-zinc superoxide dismutase and its significance. *Liaoning Journal of Traditional Chinese Medicine*, 1986, (10):10-11.
- [41] Jiang Bo, Mou Yanjie, Sun Qinguo, etc. The nourishing yin and tonic kidney recipe regulates the Nrf2/HO-1 pathway to inhibit the oxidative stress of diabetic osteoporotic rats. *Chinese Journal of Gerontology*, 2025, 45(12):2947-2951.
- [42] An Juan, Kuang Haoming, Li Zhenyu, etc. Evaluation of the efficacy of Liuwei Dihuang Pill in the treatment of type 2 diabetic osteoporosis. *Journal of Hunan University of Traditional Chinese Medicine*, 2022, 42(07):1216-1220.
- [43] Zhao Guoxiu, Wei Xinxin, Lan Qing, etc. Based on the theory of "kidney essence-bone metabolism", Taohong Siwu soup improves the multi-target coordination mechanism of diabetic osteoporosis by regulating the RANKL/OPG axis. *Western Medicine*, 2025, 37(10):1425-1430+1437.
- [44] Jiang B, Mou YJ, Zhang XM, Lu K, Xie P, Rao YL, Cong ZW, Sun QG. Ziyin Bushen Fang improves Diabetic Osteoporosis by Inhibiting Autophagy and Oxidative Stress in vitro and in vivo. *Comb Chem High Throughput Screen*. 2024; 27(5):786-796.
- [45] Xu Yingkai, Jiang Jianfeng, Wang Lei. Mechanism of action of warm kidney circulation on rats with osteoporosis secondary to diabetic nephropathy. *Guangdong Medicine*, 2025, 46(05):672-680.
- [46] Li Chao, Zhang Xian, Ma Yong, etc. Randomized controlled clinical trial of marrow tonic for the treatment of osteoporosis and renal yang deficiency syndrome. *Traditional Chinese Medicine Bone*, 2024, 36(12):24-31+54.
- [47] Duan Junhong, Liang Guiting. The effect of cordyceps tonic kidney capsule on bone transformation markers in patients with diabetic osteoporosis. *Journal of Hainan Medical College*, 2021, 27(12):898-901+909.
- [48] Yang Guofang, Fang Chaohui, Wang Jing, etc. Clinical effect of mild moxibustion combined with acupuncture on diabetic osteoporosis. *Journal of Practical Clinical Medicine*, 2021, 25(02):59-62.
- [49] Jiang Mengchun. Based on data mining, we will explore the distribution characteristics and drug laws of traditional Chinese medicine syndrome in diabetes combined with osteoporosis. *Guangxi University of Traditional Chinese Medicine*, 2023.
- [50] Zhang Enci. Clinical research on the treatment of type 2 diabetic osteoporosis with kidney filling and stasis. *Nanjing University of Traditional Chinese Medicine*, 2017.
- [51] Teng Jiawen, Chen Wenming, Li Baofeng.

Clinical research on the treatment of
diabetic osteoporosis with flavored Yougui
Pill and Bone Kang Capsule. Liaoning

Journal of Traditional Chinese Medicine,
1-10[2025-10-24]