

Overview of the Research Progress of Traditional Chinese Medicine in the Intervention of Kidney Deficiency and Blood Stasis Type Osteoporosis by Regulating the PI3K/Akt Signalling Pathway

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Abstract: Osteoporosis (OP), as a chronic and complex metabolic bone disease, is centred on disturbances in the bone microcirculatory system, which exacerbates bone loss and damage to the microstructure of bone tissue, resulting in increased bone fragility. Typical clinical manifestations include persistent low back pain, a significant increase in fracture risk, and marked changes in spinal morphology, all of which have a serious impact on patients' quality of life. The incidence of osteoporosis (OP) is showing a year-on-year increase as the proportion of the elderly population continues to rise globally. Despite the success of Western medicines in the treatment of OP, the ensuing adverse effects and uncertainty of efficacy remain to be addressed. This has prompted the medical community to actively explore safer and more effective treatments. The field of Traditional Chinese Medicine (TCM) has demonstrated unique advantages in the treatment of osteoporosis. Notably the PI3K/Akt signalling pathway, as a key mechanism regulating bone metabolism and blood circulation, has received extensive attention in recent years. According to Chinese medicine, the pathogenesis of OP is closely related to kidney deficiency and blood stasis. Therefore, from the molecular mechanism of PI3K/Akt signalling pathway, we will discuss how Chinese medicine can establish and maintain a relatively stable "bone balance" between osteoblasts and osteoclasts through the regulation of this key pathway, promote the growth of trabecular number and thickness, and at the same time, reduce the separation of trabeculae, so as to improve the bone balance of patients with OP due to kidney deficiency and blood stasis. This will improve the symptoms and quality of life of OP patients with kidney deficiency and blood stasis.

Keywords: Osteoporosis; Kidney deficiency and blood stasis; PI3K/Akt signalling pathway; Traditional Chinese medicine; Review.

1. Introduction

Osteoporosis (OP), a systemic metabolic bone disease, is characterised by a reduction in bone mass and a deterioration of the bone microstructure, which leads to an increase in bone fragility and a higher risk of fracture. The clinical manifestations are diverse, including low back pain, frequent fragility fractures, and spinal deformities [1]. The clinical manifestations are diverse, covering low back pain, frequent fragility fractures and spinal deformities. Epidemiological data show that the prevalence of OP is as high as 35.56% among residents aged 60 years and above in a community in Beijing. Given the increasing trend of aging in China, it is expected that the prevalence of OP will continue to climb in the future [2]. In view of the increasing trend of aging in China Given that osteoporosis has become one of the major causes of fractures and disability in the elderly worldwide, taking efficient measures to prevent and control osteoporotic fractures is of vital importance to improve the quality of life of the elderly [3]. Existing studies widely agree that the risk of fracture in OP patients is dozens of times higher than that in healthy people, which not only poses a serious threat to their physical health, but also creates not only a higher economic burden but also a heavier psychological pressure, which seriously reduces the quality of life of the patients. The root causes are closely related to the high prevalence of osteoporosis, the potential risk of death, and the high cost of medical care. However, there is a lack of consensus on how to optimally manage and prevent osteoporotic fractures through pharmacological means [4,5]. Chinese medicine can broadly

categorise them as diseases of tendon atrophy and bone erosion, such as "bone impotence", "bone paralysis", "bone withering" and "bone extremity". At present, most scholars to bone impotence, that it is closely related to the liver, spleen, kidney, and the root cause of this disease is "kidney deficiency". The medical Zong must read the scripture said: "kidney impotence, bone impotence [6]. "The Chinese medicine is that "the kidney is the main bone marrow" [7], the kidney indirectly or directly affects the physiological and pathological changes in the bone. Fully explains the bone mineral salt content and the theory of Chinese medicine in the kidney is closely related to the abundance or decline of [8] The PI3K/Akt pathway is an intracellular signal transduction pathway that responds to extracellular signals to promote metabolism, proliferation, cell survival, growth and angiogenesis [9,10] PI3K/Akt Pathway Studies have shown that skeletal blood circulation plays a central role in maintaining bone homeostasis and promoting bone repair. Therefore, maintaining the skeletal microcirculation in a relatively stable state enables osteoblasts and osteoclasts to reach a state of "bone balance", which is important for the prevention and treatment of osteoporosis (OP) [11-13]. This is important for the prevention and treatment of osteoporosis. Recent studies [14,15] It is further revealed that TCM plays a key role in regulating the activity of key factors such as nitric oxide (NO) and vascular endothelial growth factor (VEGF) in skeletal endothelial tissues by modulating the signalling pathways formed by phosphatidylinositol-3-kinase (PI3K) and serine/threonine protein kinase B (Akt). The PI3K/Akt signalling pathway has

become a hot topic in the treatment of osteoporosis. However, there is still a lack of comprehensive review on the regulation of PI-type osteoporosis by traditional Chinese medicine. Therefore, this article elucidates the mechanism of Chinese medicine intervention in kidney deficiency and blood stasis type osteoporosis based on the PI3K/Akt signalling pathway through modern pharmacological research and Chinese medicine theories in order to provide a new way of thinking for the treatment of osteoporosis.

2. Link between PI3K/Akt Pathway and Osteoporosis

2.1 Overview of the PI3K/Akt Pathway

The PI3K/Akt pathway plays a crucial role in the regulation of cell migration, proliferation, differentiation, apoptosis and inflammatory factor expression [14-15]. Derived from a multimeric family of heterodimeric lipid kinases, PI3K is subdivided into three classes. Among them, class IA PI3K is characterised by an activation mechanism that is mainly dependent on the action of receptor tyrosine kinases, including the p85-like regulatory subunit and the p110 catalytic subunit, which is the core of the pro-enzymatic reaction [16-17]; class IB PI3K is induced by G protein-coupled receptors and their regulatory subunits; while class II PI3K contains three proteins, PIK3C2A, PIK3C2B, and PIK3C2G; and, finally, PIK3C3, as a single member, belongs to class III PI3K. The activation pathways of the members of the PI3K family show a diversified pattern, and can be activated by a wide range of upstream receptors. In response to these stimuli, class I PI3K catalyses the conversion of PI (4,5) P2 to PIP3, a second messenger that is essential for subsequent signalling. Akt and PDK-1 are two serine/threonine kinases with PIP3-binding Pleckstrin homology (PH) structural domains, which are tightly coupled to the PI3K signalling pathway in a variety of cells [18-19]. Akt is an evolutionarily highly conserved serine/threonine protein kinase belonging to the AGC kinase subfamily. Its structure consists of an N-terminal PH domain, a short C-terminal tail containing a regulatory hydrophobic motif (HM), and a central kinase-catalytic domain forming the linkage [20]. The Akt protein family contains three homologous isoforms, Akt1, Akt2, and Akt3. When PIP3 levels rise, Akt is recruited to the cell membrane via the PH structural domain and is subsequently activated by PDK1 and mTORC2-mediated threonine phosphorylation and serine phosphorylation, respectively. These phosphorylation events occur precisely at the specific sites of each Akt isoform [21-22]. Akt affects cell proliferation, survival, genomic stability and metabolic pathways by regulating a series of downstream effector molecules such as FoxO, mTOR and GSK3 β [16]. Akt affects cell proliferation, survival, genomic stability and metabolic pathways by regulating a series of downstream effectors such as FoxO, mTOR and GSK3 β . This process not only demonstrates the complexity of the PI3K/Akt pathway, but also highlights its centrality in cell biology.

2.2 Role of the PI3K/Akt Pathway in Osteoporosis

The unique mechanism of PI3K/Akt pathway was revealed by using ovary-removed rats as research subjects [23] The results showed that osteopontin significantly increased the serum

levels of nitric oxide (NO) and vascular endothelial growth factor (VEGF) in rats with PMOP, a process that is thought to promote the reconstruction and neogenesis of the skeletal vascular network. In addition, osteopontin not only enhances osteoblast activity to support bone reconstruction, but also inhibits osteoclast activity, thereby favouring bone formation in the complex balance of bone metabolism. Phosphorylation of Akt, a unique mechanism of this signalling pathway, enhances Akt's ability to regulate angiogenic and remodelling-related factors, thereby driving the reconstructive and neoplastic processes of the vasculature. Specifically, by regulating nitric oxide (NO) signalling in vascular endothelial cells, it accelerates the release of highly potent vascular endothelial growth factor (VEGF), which promotes vascular growth and repair activities. This complex chain reaction reconfigures the blood circulation microenvironment within the skeleton, and also creates relatively favourable conditions for the active proliferation of osteoblasts and key aspects of bone formation in bone metabolism [24-25]. The present study shows that [26-27] Akt-deficient mice exhibit restricted bone growth and bone fragility in juvenile age, and reduced bone mass and increased fracture risk in adult age. However, when the PTEN gene on chromosome 10, a key negative regulator of the PI3K signalling pathway, was deleted, Akt signalling was activated and enhanced, leading to a significant increase in bone mass. From the perspective of cellular focal death [28] The PMOP model rats inhibited the activity of the PI3K/AKT signalling axis, exacerbated oxidative stress damage and induced mitochondrial dysfunction, a series of changes that prompted caspase-3 to cleave GSDME and generate GSDME-N fragments, which then triggered the process of osteoblasts' cellular juxtaposition, ultimately leading to a decrease in bone mass. However, when PI3K/AKT is activated, oxidative stress damage is effectively suppressed and mitochondrial dysfunction is ameliorated, thereby alleviating PMOP via the caspase-3/GSDME pyroptosis axis, a phenomenon that highlights the unique role of the PI3K/Akt signalling pathway in bone formation, which exquisitely maintains the bone metabolism balance between osteoblasts and osteoclasts. If this balance is disrupted, the development of osteoporosis (OP) may be triggered. Taken together, the PI3K/Akt signalling pathway is one of the key mechanisms for maintaining healthy bone homeostasis.

3. Modulation of PI3K/Akt Pathway by Traditional Chinese Medicine for the Treatment of Kidney Deficiency and Blood Stasis Type Osteoporosis

Numerous studies have revealed the remarkable efficacy of Chinese medicine in the treatment of osteoporosis (OP). Both herbal formulas and acupuncture therapies have attracted the attention of domestic and international academics. With the deepening of research, the mechanism of action of Chinese medicine in the treatment of OP is gradually clear. According to the theory of Chinese medicine, OP is a syndrome of "mixed deficiency and reality", and the principle of treatment should focus on "dialectical treatment, overall balance, and prevention and treatment at the same time". Clinically, for osteoporosis with kidney deficiency and blood stasis, kidney tonifying and blood activating tonic is often used as a

representative formula, aiming to tonify the kidney and activate blood circulation, resolve blood stasis and relieve pain. The treatment is based on patient's specific symptoms, and the prescription is selected to enhance bone health, slow down bone loss, reduce the risk of fracture and alleviate clinical symptoms, and ultimately improve the patient's symptoms, thereby improving his/her quality of life.

3.1 Chinese Medicine Monomers

Saponins (ASA) of Szechuan schizandra extract have shown significant effects in the treatment of osteoporosis (OP) [29]. Alkaline phosphatase (ALP) activity was found to be significantly increased in the ASA group compared to the blank control group. Meanwhile, ASA also increased the mRNA transcript levels of several key osteogenic genes, including ALP, osteoblast protein (OPN) and Runx2, suggesting that ASA can effectively activate the activity of osteoblasts. Further studies found that PI3K and P-AKT protein expression was increased after ASA action by immunoprotein blotting, while the PI3K inhibitor Wortmannin group showed a decreasing trend. In summary, the mechanism of ASA treatment of OP is achieved through PI3K/AKT signalling pathway transduction. On the other hand, another constituent in *S. aristolochiae*, DAP, induces AKT phosphorylation by stimulating the activity of vascular endothelial growth factor (VEGF) and indirectly induces the phosphorylation of eNOS downstream of PI3K/AKT to produce nitric oxide (NO), thus promoting angiogenesis and improving the blood supply capacity of bone tissues, and achieving the treatment of OP. blood supply capacity and achieve the effect of treating OP [30] The effect of *Rhodiola rosea* glycosides effectively down-regulated the serum levels of inflammatory factors IL-6 and TNF- α , simultaneously increased bone mineral salt content, and significantly improved a series of bone biomechanical parameters, such as the elastic modulus, ultimate load, and yield load of rat femur [31]. Western blot analysis showed that the expression of phosphorylated PI3K and AKT proteins increased in the *Rhodiola rosea* group compared with the model group and the PI3K/AKT pathway blocker LY29400 group, suggesting that it has therapeutic potential for inflammation-induced osteoporosis (OP) through activation of the PI3K/AKT signalling pathway. In addition, psoralen, the active ingredient in psoralen, also demonstrated significant therapeutic effects against a rat model of postmenopausal osteoporosis (OP) [32] The mechanism is through the activation of PI3, which is the most important component of osteoporosis. The mechanism is that by activating mTOR, the downstream effector protein of PI3K/AKT, osteocalcin and pre-collagen type I N-terminal peptide (P1NP) in the serum of rats can effectively increase the indicators of osteogenesis. At the same time, osteopontin also elevated the content of vascular endothelial growth factor (VEGF), which indicated that the blood supply of bone tissue was ensured accordingly. Resveratrol and puerarin show potential for the treatment of osteoporosis (OP) under oxidative stress [33] that inhibited osteoclast survival by effectively activating the PI3K/AKT downstream protein FOXO1. Similarly, tanshin can also effectively intervene in oxidative stress-induced OP [34], whose specific mechanism is related to the inhibition of PI3K/AKT downstream-related apoptotic proteins BAX, AIF, CYTO-C, etc., thus reducing cell death. Cortex *Eucommiae*,

Cortex Bone, and *Cuscuta* can also inhibit osteoclast differentiation via the PI3K/ AKT pathway [47], whose mechanism at the molecular level is related to the down-regulation of PI3K/ AKT expression to inhibit osteoclast differentiation and thus treat osteoporosis.

3.2 Chinese Medicine Compound Prescription

The treatment of kidney deficiency and blood stasis in OP with traditional Chinese medicine based on tonifying the liver and kidney, promoting qi and activating blood circulation has achieved remarkable therapeutic effects. However, the specific molecular mechanism has yet to be analysed in depth. Right Angelica Drink is composed of *Radix Rehmanniae Praeparata*, *Cornu Cervi Pantotrichum*, *Rhizoma Dioscoreae*, *Rhizoma Dioscoreae*, *Rhizoma Dioscoreae*, *Rhizoma Polygonati Odorati*, *Rhizoma Polygonati Odorati*, *Rhizoma Polygonati Odorati*, and *Rhizoma Polygonati*. In the late stage of postmenopausal osteoporosis (OP), when kidney yang deficiency is converted to yin and yang deficiency, Right Angelica Drink can improve the OP condition by replenishing both yin and yang and maintaining the balance of yin and yang. Experimentally, it was verified that the serum containing Right Angelica Drink activated the PI3K/AKT signalling pathway and inhibited the apoptosis of osteoblasts to achieve the treatment of osteoporosis [35]. The experiments illustrated that one of the mechanisms by which the drug-containing serum of Right Angelica Pill inhibited OC differentiation and bone resorption function was achieved by inhibiting the PI3K/AKT signalling pathway and its key factors [36]. It was found that the serum contained in the formula of tonifying the kidneys and activating blood had a significant effect on the proliferation of osteoblasts (OB) mediated by the PI3K/AKT pathway, and also activated the dual pathways of p38 MAPK and PI3K/AKT, which promoted the process of OB differentiation, which suggests that the p38 MAPK and the PI3K/AKT are the main mechanisms of the formula of tonifying the kidneys and activating blood in the treatment of OP.[37] This suggests that p38 MAPK and PI3K/AKT are the main mechanism of action of the formula in OP treatment. The study proved that the active ingredients of deer antler gelatin pill in the classic formula promoted the apoptotic process of osteoclasts (OC) mediated by the PI3K/AKT signalling pathway. and was accompanied by a rise in the expression of Bcl-2 protein, while the expression of Bax protein was inhibited, and the activation and cleavage of Caspase 3 was blocked [38]. Through the exploration of animal experiments, it was found that *Si Wu Tang* was able to directly or indirectly regulate the GPER (gastric peptide receptor for acid regulation) pathway through complex molecular levels. In turn, it precisely affects the expression of PI3K and p-AKT signalling molecules downstream of GPER, thus effectively promoting the proliferation process of osteoblasts (OB) [39]. The OB proliferation process can be effectively promoted. In an in-depth study of Henggu Bone Healing Agent [40] the active ingredients of Henggu Bone Healing Agent were found to precisely regulate the PI3K/AKT pathway to activate the proliferation of OB, and then treat postmenopausal OP. *Erxian Tang* mediated the IGF1/PI3K/AKT pathway to improve the bone loss in the OVX rat model by regulating the metabolism of lipids and fatty acids, which may be related to the mechanism of activating the IGF1/PI3K/AKT pathway.

Serum estrogen and stearoyl-CoA desaturase 1 (SCD1) were found to be up-regulated under the intervention of Erxian Tang, however, osteocalcin (OC), type I collagen proto-N-terminal peptide (PINP), type I collagen C-terminal telopeptide (CTX-1), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels were suppressed [41]. Qing'e Pill inhibits iron death and promotes osteoblast survival via the PI3K/AKT pathway [42]. The mechanism is that activation of the PI3K/AKT pathway shelters cells from iron death and induces osteogenic differentiation, such as Bmp2 and Runx2. Qing'e Pills have therapeutic effects in improving osteoporosis by promoting osteogenic protein expression and calcium-phosphate metabolism, and by inhibiting osteoclast function to promote osteogenesis. The extract of Ba Ji Tian Wan is effective in protecting against iron overload-induced osteoporosis by a mechanism related to the activation of the RAGE/PI3K/AKT signalling pathway [43]. Other traditional Chinese medicine formulas, such as the Kidney, Spleen and Blood Formula, and Bone Strengthening and Marrow Formula and Bone Strengthening and Pain Relieving Capsule, were able to protect against osteoporosis through PI3K/AKT signalling [44-46]. and other Chinese herbal medicine formulas, such as the Kidney, Spleen and Blood Strengthening Formula, the Bone and Marrow Strengthening Formula and the Bone Pain Relieving Capsule, are able to affect cell proliferation and apoptosis through the PI3K/AKT pathway.

3.3 Acupuncture

Acupuncture for the prevention and treatment of primary osteoporosis is based on the main meridians of the Duk Jing, the Foot Shaoyang Gallbladder Meridian, and the Foot Sun Bladder Meridian, and the commonly used acupoints are mainly concentrated in the trunk and lower limbs, among which Kidney Yu and Spleen Yu are the dorsal acupoints of the kidneys and the spleen, respectively, and they are the places for the spleen and kidneys to infuse their vital energy, so they are firstly chosen to carry out the treatment. The method of tonifying the kidney and strengthening the spleen was used to puncture the "Spleen Yu", "Vital Gate", "Great Loom" and "Guan Yuan" points and the bilateral "Foot Sanli" points. "The treatment of postmenopausal osteoporosis using the method of tonifying the kidney and strengthening the spleen by inserting acupuncture points of the spleen, the loom, the loom and the guanyuan, as well as bilateral acupoints of the foot and kidney, was found to increase the serum estradiol level in rats after three months of continuous treatment, and the level of serum estradiol increased by the method of tonifying the kidney and strengthening the spleen was close to that in the group of estrogens [48]. The results of this study are summarised in the following table. Acupuncture of "Guilai", "Qihai", "Liver Yu", "Kidney Yu", "Spleen Yu", "Sanyinjiao", "Qihai", "Guilai", "Hegu". "Taichong, Sanyinjiao and Gongsun can increase the level of E2 secretion and restore the ovary's hormone secretion to the normal level, and at the same time increase the number of mature follicles, primordial follicles and a large number of primary follicles. At the same time, it can promote the increase of mature follicles, the formation of primordial follicles and a large number of primary follicles. The mechanism of action of acupuncture in treating premature ovarian failure may be related to the up-regulation of the gene and protein expression levels of

PI3K/Akt/mTOR [49]. The mechanism of action of acupuncture in the treatment of premature ovarian failure may be related to the upregulation of PI3K/Akt/mTOR gene and protein expression levels. Electroacupuncture stimulation can up-regulate the phosphorylation level of PI3K/AKT in autologous transplanted ADSCs, which can promote their in vitro survival and osteogenic differentiation. Experiments have verified that the in vitro osteogenic differentiation of ADSCs requires the participation of the PI3K/AKT signalling pathway, and the inhibition of the phosphorylation level of PI3K/AKT will reduce the gene and protein expression of the osteogenic regulators (Runx2, Col1a1) associated with ADSCs. gene and protein expression of ADSCs-related osteogenic regulators (Runx2, Col1a1) [50]. The results show that acupuncture and electroacupuncture can improve the expression of genes and proteins of ADSCs. It can be seen that acupuncture and electroacupuncture can improve bone metabolism in rats with denuded osteoporosis model, and inhibit osteoclastogenesis by regulating the expression of PI3K/AKT signalling pathway and estrogen level, promote the proliferation and differentiation of osteoblasts, and correct the imbalance of bone metabolism to counteract bone loss, in order to treat postmenopausal osteoporosis.

4. Conclusion

OP (Osteoporosis) is figuratively called the "silent killer" of the skeletal system because it often develops unknowingly and is not detected until there are serious consequences such as bone fractures, which poses a great threat to the patient's health. Its pathogenesis is characterised by "multiple causes and one effect" and "multiple dimensions and one effect", i.e. multiple factors acting together to cause a single disease outcome, while the interactions of these factors are multi-dimensional, resulting in a prolonged and more difficult treatment cycle and multiple complications. In the face of this challenge, Chinese medicine has demonstrated its unique advantages. Based on the "holistic concept" and "diagnosis and treatment", Chinese medicine believes that the basic pathogenesis of OP is "deficiency at the root and stagnation in the blood", i.e., kidney deficiency is the root cause and blood stasis is the symptom. Nowadays, with the in-depth study of PI3K/Akt signalling pathway, many experiments have confirmed that Chinese medicine provides multi-targets and multi-faceted treatment for kidney deficiency and blood stasis osteoporosis by intervening in the PI3K/Akt signalling axis, which can inhibit osteoclasts' activity from the overall perspective, promote osteoblasts' proliferation and differentiation, regulate bone metabolism imbalance of osteoclasts and osteoblasts, and bring the bone metabolism microscopic environment to a dynamic balance, and then maintain the bone metabolism and bone health. dynamic balance, and then maintain the physiological homeostasis of bone. In recent years, Chinese medicine has made new breakthroughs in the treatment of osteoporosis, and the research on the pathway is becoming more and more perfect, which is conducive to the targeted treatment of Chinese medicine. Through the regulation of PI3K/AKT signalling pathway, TCM provides new ideas for the treatment of OP, enriches the connotation of TCM, keeps the right and innovation, and promotes the process of TCM to keep pace with the times. In this paper, we synthesise and summarise the research on the regulation of PI3K/Akt signalling pathway in

Chinese medicine for the treatment of osteoporosis in recent years: a total of 8 Chinese medicines with single active ingredients and 12 Chinese medicines with compound formulas are included. The single active ingredients of TCM are mainly flavonoids, polysaccharides, phenols, alkaloids, glycosides and terpenoids; the compound formulas are mainly formulas with the functions of tonifying the kidney, strengthening the spleen, activating blood circulation and eliminating blood stasis, which fit the TCM pathogenesis of osteoporosis with kidney deficiency and blood stasis. Currently, the research on osteoporosis treatment by Chinese medicine through the regulation of PI3K/AKT signaling pathway is mainly animal and cellular research, with fewer clinical studies. The initial purpose of the research on the pathological mechanism of osteoporosis is to understand the disease, and the ultimate goal is to guide the clinical treatment of the disease, so it is necessary to analyze the deeper mechanism of osteoporosis from a variety of aspects, and at the same time, improve the large-sample, multi-center, and standardized clinical research, so as to provide better clinical treatment for osteoporosis. Therefore, in the future, it is necessary to analyse the deeper disease mechanism of osteoporosis from more levels, and improve the large-sample, multi-centre, scientific and standardized clinical research at, so as to provide evidence-based basis for clinical treatment of osteoporosis. In conclusion, although there are still many deficiencies in the study of TCM regulation of PI3K/Akt signalling pathway in the treatment of osteoporosis, with the further improvement of the study, it is expected that the regulation of PI3K/Akt signalling pathway by TCM will provide new ideas for the potential treatment of osteoporosis and the development of new drugs.

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