Postprint: Distribution Patterns of TCM Syndrome Types and Muscle-Bone-Fat Relationships in Primary Osteoporosis Patients

Authors: Lin Yanping, Huang Jiachun, Guo Haiwei, Zhao Rui, Yang Haolin, Wan Lei, Zhu Genfu, Huang Hongxing, Huang Hongxing

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Abstract

Background: Osteoporosis (OP) is a systemic bone disease characterized by reduced bone mass, destruction of bone microarchitecture, increased bone fragility, and susceptibility to fracture. China has a large population of OP patients. With advancing age, not only is bone health compromised, but muscle strength also gradually declines. Currently, research on the dynamic balance among "muscle-bone-adipose" and its relationship with OP pathogenesis remains limited. Objective: To investigate the distribution patterns of traditional Chinese medicine (TCM) syndrome types in OP patients and their relationship with muscle-bone-adipose, and to explore the clinical characteristics of OP populations from the perspective of TCM syndrome differentiation, thereby facilitating better prevention of OP and further leveraging the advantages of TCM syndrome-based prevention and treatment of OP. Methods: From July 19, 2019, to January 31, 2022, primary OP patients were prospectively recruited at the Third Affiliated Hospital of Guangzhou University of Chinese Medicine. A total of 108 OP patients meeting the study criteria were enrolled, comprising 97 females and 11 males, aged 49–88 years with a mean age of (62.9$±$7.2) years. General clinical data were recorded. According to different TCM syndrome types, patients were divided into a liver-kidney yin deficiency group (n=39), a spleen-kidney yang deficiency group (n=53), and a qi stagnation and blood stasis group (n=16). Dual-energy X-ray absorptiometry (DXA) was employed to measure bone mineral density of the anteroposterior lumbar spine (L1–L4). Enzyme-linked immunosorbent assay was utilized to detect 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25-(OH)2D], fibroblast growth factor 23 (FGF-23), semaphorin 4D (SEMA4D), serum soluble receptor activator of nuclear factor- B ligand (sRANKL), among others. Results: Significant differences in bone mineral content and fat mass were observed among different TCM syndrome type groups ($P<0.05$). Specifically, bone mineral content in both the spleen-kidney yang deficiency and qi stagnation and blood stasis groups was higher than that in the liver-kidney yin deficiency group; fat mass in the spleen-kidney yang deficiency group was lower than that in the liver-kidney yin deficiency group, while fat mass in the qi stagnation and blood stasis group was higher than that in the spleen-kidney yang deficiency group ($P<0.05$). The incidence of severe OP was 48.72% (19/39) in the liver-kidney yin deficiency group, 37.74% (20/53) in the spleen-kidney yang deficiency group, and 12.50% (2/16) in the qi stagnation and blood stasis group. Comparison of severe OP incidence among the three groups revealed a statistically significant difference (2=6.32, P=0.04), with the OP rate in the liver-kidney yin deficiency group being higher than that in the qi stagnation and blood stasis group (P=0.01). Comparison of sRANKL among severe OP patients with different syndrome types showed statistically significant differences ($P<0.05$), with sRANKL in the spleen-kidney yang deficiency group being lower than that in the liver-kidney yin deficiency group ($P<0.05$). Bone mineral content was positively correlated with fat mass and muscle mass. Fat mass was positively correlated with muscle mass, 1,25-(OH)2D, FGF-23, SEMA4D, and sRANKL. 25(OH)D was positively correlated with 1,25-(OH)2D, FGF-23, SEMA4D, and sRANKL. 1,25-(OH)2D was positively correlated with FGF-23, SEMA4D, and sRANKL. FGF-23 was positively correlated with SEMA4D and sRANKL. SEMA4D was positively correlated with sRANKL ($P<0.05$). Conclusion: With increasing bodily age, deficiency of spleen and kidney leads to muscle weakness and fragile bones, manifesting as bone atrophy. Further fluid retention leads to phlegm and fat formation, disrupting the dynamic balance among muscle, bone, and adipose tissue in the body. Among OP patients with different syndrome types, there exist certain differences in muscle, bone, and muscle mass, wherein fat mass correlates with biochemical indicators of bone metabolism.

Full Text

Study on the Distribution of TCM Syndrome Types and the Relationship between Muscle-Bone-Lipid in Patients with Primary Osteoporosis

LIN Yanping[1], HUANG Jiachun[1], GUO Haiwei[1], ZHAO Rui[2], YANG Haolin[2], WAN Lei[1], ZHU Genfu[1], HUANG Hongxing[1]*

[1]The Third Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510240, China

[2]The Third Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou 510405, China

*Corresponding author: HUANG Hongxing, Chief Physician; E-mail: gzhhx@126.com

Abstract

Background: Osteoporosis (OP) is a systemic bone disease characterized by decreased bone mass, damaged bone tissue microstructure, increased bone fragility, and susceptibility to fractures. China has a large population affected by OP, and with advancing age, not only bone health but also muscle strength gradually declines. Currently, few studies have investigated the dynamic balance between "muscle-bone-fat" and the pathogenesis of OP.

Objective: This study aims to explore the distribution pattern of TCM syndrome types in OP patients and their relationship with muscle-bone-fat, and to analyze the clinical characteristics of OP populations from the perspective of TCM syndrome differentiation, in order to better prevent OP occurrence and further exert the advantages of TCM in the prevention and treatment of OP through syndrome-based approaches.

Methods: From July 19, 2019, to January 31, 2022, we prospectively recruited primary OP patients at the Third Affiliated Hospital of Guangzhou University of Chinese Medicine. A total of 108 patients meeting the study criteria were selected, including 97 females and 11 males, aged 49-88 years with an average age of (62.9$±7.2)*years.Generalclinicaldatawererecorded,andpatientsweredividedintothreegroupsaccordingtod*
39*casesintheliver − kidneyyindeficiencygroup*, 53*casesinthespleen −*
*kidneyyangdeficiencygroup, and*16*casesintheqistagnationandbloodstasisgroup.Bonemineraldensityofthean*
*L*4)*wasmeasuredusingdual−energyX−rayabsorptiometry*(*DXA*)*.Serumlevelsof*25−
hydroxyvitaminD[25(*OH*)*D*], 1, 25−*dihydroxyvitaminD*[1, 25−(*OH*)_{2}$D], fibroblast growth factor 23 (FGF-23), semaphorin 4D (SEMA4D), and soluble receptor activator of nuclear factor B ligand (sRANKL) were detected by enzyme-linked immunosorbent assay (ELISA).

Results: Statistically significant differences were found in bone mineral content and fat mass among different TCM syndrome type groups (P<0.05). The spleen-kidney yang deficiency group and qi stagnation and blood stasis group showed higher bone mineral content than the liver-kidney yin deficiency group. The spleen-kidney yang deficiency group had lower fat mass than the liver-kidney yin deficiency group, while the qi stagnation and blood stasis group had higher fat mass than the spleen-kidney yang deficiency group (P<0.05). The incidence of severe OP was 48.72% (19/39) in the liver-kidney yin deficiency group, 37.74% (20/53) in the spleen-kidney yang deficiency group, and 12.50% (2/16) in the qi stagnation and blood stasis group, with statistically significant differences among the three groups (^{2}=6.32, P=0.04). The liver-kidney yin deficiency group had a higher severe OP rate than the qi stagnation and blood stasis group (P=0.01). Significant differences in sRANKL levels were observed among different syndrome types in severe OP patients (P<0.05), with the spleen-kidney yang deficiency group showing lower sRANKL than the liver-kidney yin deficiency group (P<0.05). Correlation analysis revealed that bone mineral content was positively correlated with fat mass and muscle mass; fat mass was positively correlated with muscle mass, 1,25-$(OH)_2D$, FGF-23, SEMA4D, and sRANKL;

25(OH)D was positively correlated with 1,25-$(OH)_2D$, FGF-23, SEMA4D, and sRANKL; 1,25-$(OH)_2D$ was positively correlated with FGF-23, SEMA4D, and sRANKL; FGF-23 was positively correlated with SEMA4D and sRANKL; and SEMA4D was positively correlated with sRANKL ($P<0.05$).

Conclusion: With increasing age, spleen-kidney deficiency leads to muscle weakness and bone insufficiency, resulting in bone atrophy. Further internal water retention generates phlegm and fat, disrupting the dynamic balance between muscle-bone-fat in the body. In OP patients with different TCM syndrome types, there are certain differences in muscle, bone, and fat mass, and fat mass is correlated with bone metabolism biochemical indicators.

Keywords: Osteoporosis; TCM syndrome type; Bone mineral content; Adipose tissue; Bone-fat metabolism level

Introduction

Osteoporosis (OP) is a common skeletal disease characterized by reduced bone mass, damaged bone microarchitecture, increased bone fragility, and susceptibility to fractures. According to epidemiological surveys in China, the prevalence of OP among people over 50 years old is 19.2%, affecting 32.1% of women and 6.9% of men. Among those over 65, the prevalence reaches 32.0%, affecting 51.6% of women and 10.7% of men. Based on these data, the current number of OP patients in China is approximately 90 million, including about 70 million women. With advancing age and the onset of menopause in women, not only is skeletal health affected, but muscle strength also gradually declines. Increasing skeletal muscle mass can reduce the prevalence of sarcopenia and OP to a certain extent. The influence of adipose tissue on bone mineral density and bone strength remains controversial. As an endocrine organ, adipose tissue can promote bone resorption and inhibit bone formation, while also providing mechanical load and stimulating higher bone mass accumulation to prevent bone loss. The ratio of fat mass to muscle mass has a certain impact on bone mass, and adipose tissue can synthesize estrogen through aromatase, promoting bone formation and reducing bone resorption, which significantly affects bone mass and strength.

Our research group previously found that the dynamic balance between "muscle-bone-fat" may be related to the pathogenesis of OP. This study combines TCM syndrome differentiation to explore the distribution pattern of TCM syndrome types in OP patients and its relationship with muscle-bone-fat, analyzing the clinical characteristics of OP populations from the perspective of TCM syndrome differentiation to prevent OP occurrence and exert the advantages of TCM in the prevention and treatment of OP through syndrome-based approaches.

Methods

Study Subjects

From July 19, 2019, to January 31, 2022, we prospectively recruited OP patients at the Third Affiliated Hospital of Guangzhou University of Chinese Medicine. A total of 108 patients meeting the inclusion and exclusion criteria were selected, all of whom had resided in the Guangzhou area for at least 6 months. The cohort consisted of 97 females and 11 males, aged 49-88 years with an average age of (62.9$±$7.2) years. This study was approved by the Hospital Medical Ethics Committee (approval number: 2020034).

Inclusion Criteria

1. Female patients aged $ $49 years who had been postmenopausal for more than 1 year, and male patients aged $ $60 years
2. No prior systematic OP treatment with relatively obvious clinical symptoms
3. No severe heart, lung, liver, kidney function impairment or bone metabolism diseases
4. Understanding of the study and voluntary participation

Exclusion Criteria

1. Patients with secondary OP (endocrine diseases such as hyperthyroidism and diabetes; immune diseases such as rheumatoid arthritis and ankylosing spondylitis; hematological diseases such as multiple myeloma; digestive and kidney diseases affecting calcium and vitamin D absorption and metabolism; neuromuscular diseases; OP caused by other diseases such as chronic obstructive pulmonary disease)
2. Patients who had taken medications affecting bone metabolism within 6 months
3. Patients with other comorbidities

Data Collection

1.4.1 General Clinical Data We recorded patients' age, sex, BMI, long-term glucocorticoid use, history of diseases interfering with bone metabolism, and other risk factors for secondary OP.

1.4.2 TCM Syndrome Differentiation According to the "Guidelines for Clinical Diagnosis and Treatment of Primary Osteoporosis (Bone Atrophy) in TCM" and the "Diagnosis and Treatment Protocol for Osteoporosis by the Key Collaborative Group of the State Administration of Traditional Chinese Medicine," osteoporosis was differentiated into spleen-kidney yang deficiency, liver-kidney yin deficiency, and qi stagnation and blood stasis types. Two members of the osteoporosis expert outpatient clinic performed syndrome differentiation for enrolled patients.

1.4.3 Bone Mineral Density Measurement Dual-energy X-ray absorptiometry (DXA) was used to measure bone mineral density of the anteroposterior lumbar spine (L1-L4). Bone density is typically expressed as T-score. According to the Primary Osteoporosis Diagnosis and Treatment Guidelines (2022), a T-score ≤ -2.5 indicates osteoporosis, and a T-score ≤ -2.5 plus fragility fracture indicates severe OP. DXA was also used for body composition analysis to measure patients' muscle mass, fat mass, and bone mineral content. By comparing bone density and body composition among different syndrome types, we analyzed the impact of syndrome types on severe OP prevalence and bone-fat metabolism levels, as well as the correlation between different OP patient syndrome distributions and muscle, bone, and fat.

1.4.4 Serum Detection by Enzyme-Linked Immunosorbent Assay Between 8:00-9:30 AM, 4 mL of fasting elbow venous blood was collected from each patient. ELISA was used to detect 25(OH)D, 1,25-$(OH)_2$D, FGF-23, SEMA4D, and sRANKL levels.

Statistical Analysis

SPSS 25.0 software was used for statistical analysis. Normally distributed measurement data were expressed as ($\bar{x}\pm s$). Inter-group comparisons were performed using one-way ANOVA, with Bonferroni test for multiple comparisons. Count data were expressed as cases (%) and analyzed using ^{2} test. Pearson correlation analysis was used to examine correlations between bone mineral content, fat mass, muscle mass, and bone-fat metabolism indicators. $P<0.05$ was considered statistically significant.

Results

Comparison of General Conditions Among Different TCM Syndrome Types

A total of 108 patients meeting the criteria were included. According to different TCM syndrome types, patients were divided into 39 cases in the liver-kidney yin deficiency group, 53 cases in the spleen-kidney yang deficiency group, and 16 cases in the qi stagnation and blood stasis group. No statistically significant differences were found in age, BMI, or muscle mass among the three groups ($P>0.05$). However, significant differences were observed in bone mineral content and fat mass ($P<0.05$). The spleen-kidney yang deficiency group and qi stagnation and blood stasis group had higher bone mineral content than the liver-kidney yin deficiency group. The spleen-kidney yang deficiency group had lower fat mass than the liver-kidney yin deficiency group, while the qi stagnation and blood stasis group had higher fat mass than the spleen-kidney yang deficiency group (P<0.05) .

Comparison of Severe OP Rates Among Different TCM Syndrome Types

The severe OP incidence rate was 48.72% (19/39) in the liver-kidney yin deficiency group, 37.74% (20/53) in the spleen-kidney yang deficiency group, and 12.50% (2/16) in the qi stagnation and blood stasis group. The difference among the three groups was statistically significant (^{2}=6.32, P=0.04), with the liver-kidney yin deficiency group showing a higher severe OP rate than the qi stagnation and blood stasis group (^{2}=6.31, P=0.01).

Comparison of Bone-Fat Metabolism Levels Among Different TCM Syndrome Types

No statistically significant differences were found in 25(OH)D, 1,25-$(OH)_2$D, FGF-23, SEMA4D, or sRANKL levels among the three groups (P>0.05) .

Bone-Fat Metabolism Levels in Severe OP Patients with Different TCM Syndrome Types

No statistically significant differences were observed in 25(OH)D, 1,25-$(OH)_2$D, FGF-23, or SEMA4D levels among the three groups (P>0.05). However, significant differences were found in sRANKL levels (P<0.05), with the spleen-kidney yang deficiency group showing lower sRANKL than the liver-kidney yin deficiency group (P<0.05) .

Correlation Between Bone Mineral Content, Fat Mass, Muscle Mass, and Bone Metabolism Biochemical Indicators

Pearson correlation analysis showed that bone mineral content was positively correlated with fat mass and muscle mass. Fat mass was positively correlated with muscle mass, 1,25-$(OH)_2$D, FGF-23, SEMA4D, and sRANKL (P<0.05). 25(OH)D was positively correlated with 1,25-$(OH)_2$D, FGF-23, SEMA4D, and sRANKL (P<0.05). 1,25-$(OH)_2$D was positively correlated with FGF-23, SEMA4D, and sRANKL (P<0.05). FGF-23 was positively correlated with SEMA4D and sRANKL. SEMA4D was positively correlated with sRANKL (P<0.05) .

Discussion

OP is a systemic metabolic bone disease characterized by an imbalance between bone formation and resorption rates with increasing age. Current molecular-level research on OP pathogenesis primarily focuses on the differentiation, regulation, and balance of osteoblasts and osteoclasts. Primary aging is accompanied by many physiological changes, among which the physiological changes in muscle, bone, and fat are phenotypically obvious. Human muscle mass peaks at

30-40 years of age and gradually declines without resistance training, with an estimated 3-8% decrease per decade after age 30, and an even greater decline after age 60. Some individuals may lose 40% of muscle mass and strength by age 70-80. Declining muscle mass is usually accompanied by bone loss and increased fat mass, representing a systemic loss of bone minerals and deterioration of bone microstructure, as well as excessive body fat storage due to chronic energy imbalance, manifested as increased fat infiltration in skeletal muscle, which affects overall bone-fat metabolism levels.

In Traditional Chinese Medicine, osteoporosis is classified as "bone atrophy," a systemic chronic skeletal disease primarily caused by insufficient kidney essence, bone marrow depletion, and loss of bone nourishment. To further investigate the distribution pattern of TCM syndrome types and the muscle-bone-fat relationship in OP patients, we performed TCM syndrome differentiation, dividing patients into liver-kidney yin deficiency, spleen-kidney yang deficiency, and qi stagnation and blood stasis groups. Comparing general conditions among different syndrome types, we found no significant differences in age, BMI, or muscle mass, but significant differences in bone mineral content and fat mass. The spleen-kidney yang deficiency and qi stagnation and blood stasis groups had higher bone mineral content than the liver-kidney yin deficiency group. The spleen-kidney yang deficiency group had lower fat mass than the liver-kidney yin deficiency group, while the qi stagnation and blood stasis group had higher fat mass than the spleen-kidney yang deficiency group. We also found significant differences in severe OP rates among the three syndrome types, with the liver-kidney yin deficiency group showing a higher severe OP rate than the qi stagnation and blood stasis group, indicating that the liver-kidney yin deficiency type has a higher probability of developing severe OP.

As stated in *Suwen · Weilun*, "The kidney is the water organ; when water fails to overcome fire, the bones become withered and the marrow becomes empty, resulting in inability to support the body, leading to bone atrophy." Bone atrophy is a condition of deficiency in root and excess in branch, where kidney deficiency is the fundamental cause and spleen deficiency is the important pathomechanism. Disorders of spleen-kidney and other organ functions can lead to impaired water fluid metabolism, internal phlegm-dampness retention, and blood stasis in the uterine vessels, transforming into phlegm-fat that accumulates in the body, increasing body weight and fat mass. This study emphasizes the close relationship between muscle, bone, and fat from a holistic perspective. The spleen is the source of qi and blood production and the foundation of postnatal life. It transports the essence of food and water to the head, face, heart, and lungs. The essence reaching the head nourishes the muscles of the head and face, while that reaching the heart and lungs is distributed throughout the body's muscles under the action of heart and lungs, nourishing the muscles and making them strong. Robust muscles and strong bones are closely related to spleen-stomach transportation, ascending-descending functions, and distribution of water-grain essence. When spleen-stomach transportation function is obstructed, it leads to muscle wasting and weakness, as well as soft bones. The kidney stores essence, governs bones, and generates marrow, closely related to bone growth and development. The kidney is the congenital foundation and the root of yin-yang of the five viscera. As stated in *Suwen · Yinyang Yingxiang Dalun*: "The kidney generates bone marrow… the body corresponds to bone, and the organ corresponds to kidney." Kidney essence transforms into kidney qi, which divides into yin and yang. Kidney yin-yang coordinates the yin of all organs. *Suwen · Weilun* states: "The spleen governs the muscles of the body, and the kidney governs the bones and marrow of the body." Spleen deficiency leads to weakened limb muscles, while kidney deficiency leads to weak bones. Our growth and development are influenced by the abundance or decline of organ qi. When kidney qi is abundant, growth occurs; when deficient, weakness results, accompanied by organ decline, manifesting as systemic weakness externally. "When a person is born, essence is formed first." Essence is stored in the kidney. Congenital essence and postnatal essence transformed by spleen-stomach nourish each other, enabling the five viscera and six bowels to function without exhaustion, demonstrating the spleen-kidney relationship. In this study, this was manifested as lower bone mineral content and higher severe OP rate in the liver-kidney yin deficiency group compared to the other two groups.

On the other hand, lipid metabolism disorders are related to OP. Fat accumulation is mostly due to phlegm-fluid retention. Disorders of spleen-kidney and other organ functions can cause impaired water fluid metabolism, internal phlegm-dampness retention, and blood stasis in the uterine vessels, generating phlegm-fat that accumulates in the body, increasing body weight and fat mass. Furthermore, as recorded in *Lin Zheng Zhi Nan Yi An · Tanyin*: "In summary, the formation of phlegm-fluid must be triggered by deficiency of original qi and excess of yin over yang, leading to fluid congelation and impaired distribution… clear fluids become turbid, water accumulating in yin becomes fluid retention, and fluid congelation in yang becomes phlegm… when yang is excessive and yin is deficient, water qi congeals into phlegm; when yin is excessive and yang is deficient, water qi overflows as fluid retention." Kidney deficiency leads to original qi depletion, either yin or yang deficiency, causing impaired fluid distribution and internal water retention, generating phlegm-fat. In this study, the liver-kidney yin deficiency group also showed higher fat mass than the spleen-kidney yang deficiency group, validating the above theory.

Bone metabolism biochemical indicators include 25(OH)D, 1,25-$(OH)_2$D, FGF-23, SEMA4D, sRANKL, etc. Clinical bone metabolism indicators are commonly used for OP diagnosis, differential diagnosis, fracture risk prediction, and evaluation of treatment changes. 25(OH)D is derived from vitamin D and is the final metabolite of vitamin D, capable of converting to 1,25-$(OH)_2$D. Clinically, 25(OH)D is often used to evaluate vitamin D intake and utilization, maintaining normal blood calcium levels. Vitamin D is related to bone growth and calcium-phosphorus metabolism, promoting osteogenic differentiation of bone marrow mesenchymal stem cells to facilitate bone mineralization. When 25(OH)D is deficient, it indicates low vitamin D content in the body, affecting calcium absorption and further influencing bone strength. Studies have shown that supplementation of endogenous or exogenous 1,25-$(OH)_2$D can promote osteoblast bone formation.

FGF23 is a protein belonging to the fibroblast growth factor family, produced by osteocytes and primarily expressed in bone tissue, particularly in osteoblasts and osteocytes. Its function is to regulate phosphate homeostasis, 1,25-$(OH)_2$D, and parathyroid hormone levels. FGF23 can affect bone formation by regulating bone mineralization. In vitro studies have shown that upregulating FGF23 expression in mouse osteoblasts can increase bone mineralization, with dose-dependent increases in osteocalcin, osteopontin, and alkaline phosphatase. Other studies have shown that astragalus polysaccharides can prevent OP by enhancing osteoblast activity and regulating FGF23 protein expression in MC-3T3-E1 osteoblasts. Currently, most research suggests that FGF23 primarily regulates bone mineralization indirectly by inhibiting tissue-nonspecific alkaline phosphatase activity, thereby reducing hydrolysis of inorganic pyrophosphate.

Semaphorin 4D (Sema4D) is a glycoprotein transmembrane dimer and a signaling protein involved in axon guidance, with immunomodulatory activity, pro-angiogenic, and bone-forming effects. Sema4D is produced by osteoclasts and is currently considered a new target for OP treatment. It plays a key role in downregulating osteoblastogenesis, and its binding to osteoblast receptor PlexinB1 can inhibit osteoblast differentiation and function. Conversely, disruption of Sema4D/PlexinB1 signaling that activates osteoblast differentiation can lead to increased bone loss, and Sema4D overexpression may exacerbate OP. Further research on related factors influencing Sema4D expression is important for regulating bone metabolism.

sRANKL is the soluble form of RANKL and an important mediator of bone resorption. Serum osteoprotegerin (OPG) acts as a receptor for sRANKL, competitively blocking RANKL activation of its receptor RANK by binding RANKL, thereby inhibiting bone dissolution and protecting bones. This study examined correlations between bone mineral content, fat mass, muscle mass, and bone metabolism biochemical indicators, finding that fat mass was correlated with bone metabolism indicators, particularly 1,25-$(OH)_2$D, FGF-23, SEMA4D, and sRANKL. How fat mass specifically influences bone metabolism indicators requires further in-depth research.

In summary, with increasing age, spleen-kidney deficiency leads to muscle weakness and bone insufficiency, resulting in bone atrophy. Further internal water retention generates phlegm-fat, disrupting the dynamic balance between muscle-bone-fat in the body. In OP patients with different TCM syndrome types, there are certain differences in muscle, bone, and fat mass, and fat mass is correlated with bone metabolism biochemical indicators. Due to the relatively concentrated sample locality, this study could not deeply explore the correlation between TCM syndrome types and bone-fat metabolism indicators such as 25(OH)D, 1,25-$(OH)_2$D, FGF-23, SEMA4D, and sRANKL. Future research will expand the sample size and collection scope to provide better guidance for TCM prevention and treatment of OP.

Author Contributions

LIN Yanping: Conceptualization, methodology, writing-original draft; HUANG Jiachun: Investigation; GUO Haiwei, ZHAO Rui, YANG Haolin: Data collection and curation; WAN Lei, ZHU Genfu: Validation; HUANG Hongxing: Quality control, review & editing, supervision.

Conflict of Interest

The authors declare no conflict of interest.

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