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Original Article

Regulating spleen and stomach can improve bone and joint function of knee osteoarthritis patients complicated with osteoporosis

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Abstract: Objective: This study was designed to determine the influences of spleen and stomach conditioning treatment in Traditional Chinese Medicine (TCM) on patients with both knee osteoarthritis (KOA) and osteoporosis (OP). Methods: The medical records of 108 patients with both KOA and OP treated in Wuhan No. 1 Hospital between February 2020 and December 2021 were retrospectively studied. Among them, 58 patients treated with western medicine alone were assigned to a control group, and 50 patients who received spleen and stomach conditioning treatment in TCM based on western medicine treatment were assigned to an observation group. The efficacy on the two groups was compared. The joint function, pain, inflammatory factors and bone turnover markers in the two groups before and after treatment were analyzed, as well as the incidence of adverse reactions after treatment. The prognosis of the patients at 12 months after treatment was counted, and the influencing factors of poor prognosis were analyzed by multivariate analysis. Results: The observation group showed a notably higher total effective rate than the control group (P<0.05). After treatment, the observation group had notably higher Lysholm score, but notably lower Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and visual analogue scale (VAS) scores than the control group (all P<0.05). After treatment, the bone turnover markers (beta collagen degradation products (β-CTx) and procollagen type I amino-terminal propeptide (P1NP)) in both groups decreased notably (P<0.05), with notably lower levels of them in the observation group than those in the control group (both P<0.05). Additionally, after the treatment, the inflammatory indexes (interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)) in both groups decreased notably (all P<0.05), with notably lower levels of them in the observation group than those in the control group (all P<0.05). Moreover, the observation group presented a notably lower incidence of adverse reactions than the control group (P<0.05). The rate of poor prognosis in the observation group was notably lower than that in the control group. According to multiple logistic regression analysis, older age, higher BMI, higher Kellgren-Lawrence grading based on X-ray and history of bone fracture were independent risk factors for poor prognosis, and spleen and stomach conditioning treatment was an independent protective factor. Conclusion: Additional TCM spleen and stomach conditioning treatment can substantially improve the efficacy in patients with both KOA and OP by adjusting the inflammatory factors and bone turnover markers of patients, improving their joint function, alleviating their pain, and strongly preventing adverse reactions, so it is of great clinical application value.

Keywords: Spleen and stomach conditioning treatment, bone and joint function, osteoarthritis, osteoporosis

Introduction

Knee osteoarthritis (KOA), the most common form of arthritis in the elderly, is related with severe functional limitations of the lower extremities and is one primary cause of disability worldwide [1]. Reportedly, KOA can give rise to functional limitations and disability, affecting about 4% of the elderly in the community [2]. With the aging of society and the rising prevalence of obesity, the incidence of osteoarthritis (OA) is also growing [3]. Approximately 27% of adults aged 26 or above suffer from OA according to imaging results, while among adults aged 45 or above, 19-28% suffer from KOA and 27% suffer from hip OA [4]. With the main pathological and physiological features of degenerative destruction of cartilage, KOA is accompanied by contracture or relaxation of articular ligament, sclerosis or degeneration of subchondral bone

capsule, contracture of articular capsule, synovial hyperplasia of joint and periarticular hyperosteogeny [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are currently the first-line drugs for the treatment of OA. Small doses of topical/oral administration of NSAIDs can exert a good effect on relieving pain in patients with KOA [6]. Celecoxib, as a common Nonsteroidal anti-inflammatory drug, is clinically used to treat OA, which can effectively alleviate inflammation and pain in patients [7]. However, long-term oral medication of NSAIDs has obvious side effects, such as liver and kidney injury and cardiovascular disease [8]. Surgical treatment is suitable for patients with advanced KOA, because it can significantly improve the quality of life of patients, but it is traumatic and requires postoperative rehabilitation treatment and high cost [9]. Osteoporosis (OP) is a systemic bone disease characterized by increased bone fragility, destruction of bone microstructure and decrease of bone mass. Both of them are frequently seen in the elderly and prone to bone and joint diseases [10, 11]. However, the correlation of the two diseases is still controversial.

KOA patients comorbid with OP are mainly characterized with lower limb movement dysfunction, local swelling, deformity and chronic joint pain, thus posing great impacts on patients' health and quality of life [12]. Currently, most of the western medicines are used to relieve clinical symptoms and improve knee joint function, lacking specific therapeutic regimen. Among them, calcitonin is extensively adopted in the clinical treatment of KOA comorbid with OP, which can effectively treat OP and relieve pain, but its long-term effect is not satisfactory if it is adopted alone [13].

KOA can be classified as "arthromyodynia" and "bone rheumatism" in traditional Chinese medicine (TCM), which is considered to be triggered by the deficiency of vital Qi, the invasion of exogenous evils such as wind, cold and dampness, the obstruction of phlegm and blood stasis and the obstruction of meridians [14]. TCM believes that the spleen and stomach provide the material basis of the acquired constitution, and healthy spleen and stomach function means abundant Qi and blood, and can thus resist the evil of wind, cold and dampness, protecting the human body from diseases [15]. Therefore, TCM theory holds that the spleen and stomach are strongly bound up with the development and progression of KOA, and the principle of regulating spleen and stomach should be used throughout the whole treatment of KOA [16]. The regulation of spleen and stomach in TCM also takes a therapeutic part in diseases including kidney diseases and gastrointestinal diseases [17, 18]. However, the application of regulating spleen and stomach in the treatment of KOA patients with OP is rarely studied.

Accordingly, this study was conducted to observe the effects of regulating and tonifying spleen and stomach with TCM principal on the joint function of patients with both OA and OP.

Materials and methods

Patient data

The medical records of 118 patients with both KOA and OP treated in Wuhan No. 1 Hospital between February 2020 and December 2021 were retrospectively studied. Among them, 58 patients treated with western medicine alone were assigned to the control group, and 50 patients who received spleen and stomach regulating treatment in TCM based on the western medicine treatment were assigned to an observation group. This study was performed with approval from the Medical Ethics Committee of Wuhan No. 1 Hospital (ethnical approval number: 20190233).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients confirmed with OA comorbid with OP. The diagnosis of OA was based on the diagnostic guidelines of Orthopaedic Branch of China Medical Association [19], and that of OP was based on the diagnostic guidelines of China Medical Association [20]; (2) Patients with initial diagnosis; (3) Patents who had not received any KOA-related treatment; (4) Patients with good treatment compliance; and (5) patients with complete clinical data.

Exclusion criteria: (1) Patients comorbid with serious basic diseases such as disease of the heart, brain, liver or kidney or tumor. (2) Patients comorbid with other diseases affecting bone metabolism, such as thyroid diseases, gonadal

diseases, diabetes mellitus, rheumatoid arthritis. (3) Patients who were allergic to the drugs in this study. (4) Patients whose Kellgren-Lawrence grade was above III according to X-ray.

Therapeutic regimen

The control group: The patient was orally given celecoxib capsules (Suzhou Puqiang Pharmaceutical Co., Ltd., China, lot number: 0408064), at 0.2 g each time, once a day, for two weeks; glucosamine hydrochloride tablets (Jiangsu Zhengda Qingjiang Pharmaceutical Co., Ltd., China, lot number: 20151103), at 0.75 g each time, twice a day, for 12 weeks; and alendronate sodium vitamin D3 tablets (Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd., China, lot number: CN9089), at 70 mg each time, once a week, for 12 weeks.

The observation group: On the basis of control group, the patients in observation group were given spleen and stomach conditioning treatment additionally. Specifically, the acupoints of Qihai, Guanyuan, Zusanli, Liangqiu, Sanyinjiao, etc. were stimulated after sterilization. Each point was given acupuncture for 30 minutes each time, once every two days, for 10 times in total.

Evaluation criteria of efficacy

Markedly effective: After treatment, the swelling, pain and tenderness of the affected limb joint disappeared and the joint activity returned to normal; Effective: After treatment, the swelling, pain and tenderness of the affected limb joints were alleviated, and the joint activity was not restricted; Ineffective: After treatment, the swelling, pain, tenderness of the affected limb joint and joint activity were not greatly alleviated.

Evaluation criteria of scales

The joint function was evaluated by the Lysholm knee function score and Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The Lysholm knee function score evaluates the patient's knee joint function, which consists of eight questions, such as pain, uneasiness and squatting posture. It has a total score of 100 points, with a score <70 representing poor knee joint function [21]. WOMAC consists of three dimensions: joint function, pain and stiffness, with a score of 0-100. A higher score suggests more serious joint dysfunction [22]. The joint pain was evaluated through the visual analogue scale (VAS). It has a total score of 100, with a lower score indicating lighter pain [23].

Outcome measures

Primary outcome measures: The efficacy on the two groups was compared after 12 weeks' treatment. The joint function of the two groups was compared before and after treatment for 12 weeks.

Secondary outcome measures: Venous blood (5 mL) was acquired from each patient before treatment and after 12 weeks of treatment, followed by 10-min centrifugation (3000×g, 4°C) to acquire serum. Then the enzyme-linked immuno-sorbent assay (ELISA) was adopted for quantification of beta collagen degradation products (β-CTx), type I procollagen N-terminal propeptide (P1NP), and inflammatory indexes (interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)). The kits were purchased from the MyBioSource Company (MBS2531055, MBS2021241, MBS335481, MBS2019894, MBS824943). The patients were followed up for 12 months after treatment and the knee joint function at the last follow-up was recorded. The improvement of joint pain after 12 weeks of treatment was compared between the two groups, and the adverse reactions were counted. According to the Lysholm knee function score, the patients were divided into two groups: Good-prognosis group (70-100 points) and poor-prognosis group (<70 points). Multiple logistic regression was used to analyze the risk factors of poor prognosis.

Statistical analyses

This study adopted SPSS26.0 software for statistical processing of data. Inter-group comparison was conducted using the independent samples t-test, and intra-group comparison was conducted using the paired t test before and after treatment. Counting data was expressed in percentage, and their inter-group comparison was performed using the X^2 test. Multiple logistic regression was used to analyze

Table 1. Comparison of baseline data between the two groups (n, %)

	Control group (n=58)	Observation group (n=50)	t/X^2	*P* value
Age (years)	64.5±6.9	65.2±6.4	0.544	0.588
Gender			0.125	0.723
Male	19 (32.76)	18 (36.00)		
Female	39 (67.24)	32 (64.00)		
BMI (kg/m^2)	24.15±3.21	23.68±3.18	0.762	0.448
Kellgren-Lawrence grading based on X-ray			0.785	0.675
I	19 (32.76)	13 (26.00)		
II	22 (37.93)	19 (38.00)		
III	17 (29.31)	18 (36.00)		
Heavy manual labor occupation			0.251	0.616
Yes	16 (27.59)	16 (32.00)		
No	42 (72.41)	34 (68.00)		
Disease site			0.552	0.458
Unilateral	35 (72.92)	33 (66.00)		
Bilateral	13 (27.08)	17 (34.00)		
Fracture history	8 (13.79)	5 (10.00)	0.365	0.546
Alcoholism history	12 (20.69)	14 (28.00)	0.785	0.376
Smoking history	15 (25.86)	16 (32.00)	0.494	0.482

BMI, body mass index.

Table 2. Comparison of treatment efficacy between the two groups (n, %)

	Control group (n=58)	Observation group (n=50)	X^2	P
Markedly effective	23 (39.66)	32 (64.00)		
Effective	21 (36.21)	14 (28.00)		
Ineffective	14 (24.14)	4 (8.00)		
Total effective (%)	44 (75.86)	46 (92.00)	0.025	5.035

the risk factors of poor prognosis. P<0.05 suggested a notable difference.

Results

Baseline data of patients

According to comparison of baseline data between the two groups, there were no significant differences in age, gender, body mass index (BMI), X-ray-based Kellgren-Lawrence grading, heavy manual labor occupation, disease site, fracture history, alcoholism history and smoking history before the treatment (all P>0.05, **Table 1**).

Comparison of efficacy between the two groups

According to comparison of efficacy between the two groups, the observation group showed a significantly higher total effective rate than the control group (92.00% vs. 75.86%, P<0.05, **Table 2**).

Improvement of joint function and pain in the two groups before and after treatment

Before therapy, the two groups were not greatly different in Lysholm score, WOMAC and VAS score (all P>0.05), while after therapy, the observation group had notably higher Lysholm scores than the control group and notably lower WOMAC and VAS scores than the control group (all P<0.05, **Figure 1**).

Changes of bone turnover markers before and after treatment

The bone turnover markers (β-CTX and P1NP) in the two groups were evaluated before and after the treatment. According to the comparison, after the treatment, the β-CTX and P1NP levels in both groups decreased notably (both

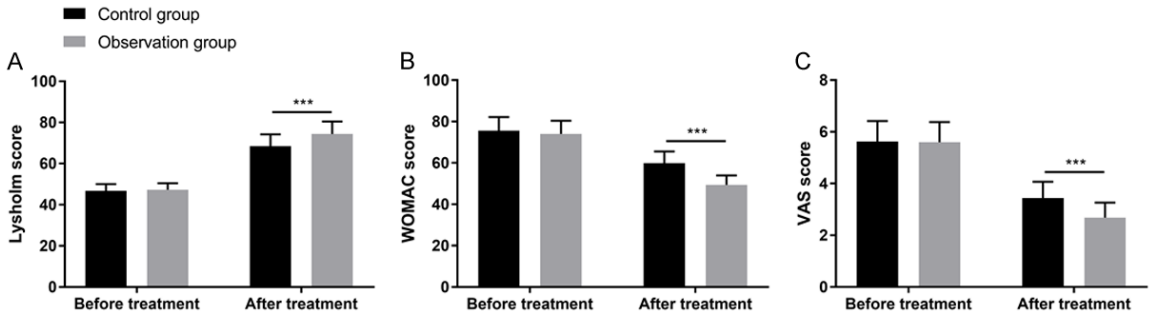

Figure 1. Effects of therapeutic regimen on joint function and pain of patients. A. After treatment, the observation group got a notably higher Lysholm score than the control group (***P<0.001). B. After treatment, the observation group got a notably lower WOMAC than the control group (***P<0.001). C. After treatment, the observation group showed a notably lower VAS score than the control group (***P<0.001). WOMAC: Western Ontario and McMaster University Osteoarthritis Index; VAS: Visual analogue scale.

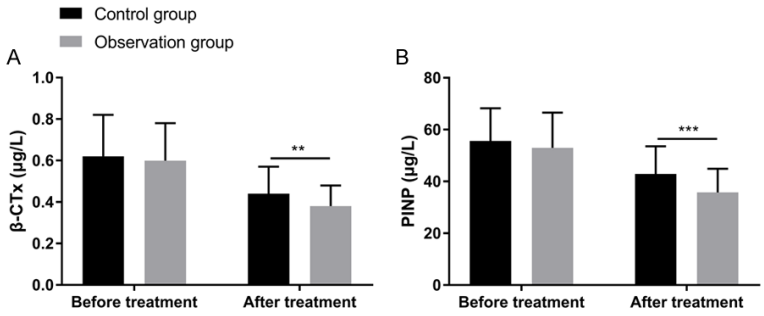

Figure 2. Changes of bone turnover markers before and after treatment. A. After treatment, the observation group showed a notably lower β-CTX level than the control group (***P<0.001). B. After treatment, the observation group showed a notably lower P1NP level than the control group (***P<0.001). β-CTX: beta collagen degradation products (β-CTx); P1NP: Procollagen type 1 N-terminal propeptide.

P<0.05), with lower levels of them in the observation group than those in the control group (all P<0.05, **Figure 2**).

Changes of inflammatory factors before and after treatment

Before the treatment, the two groups were not greatly different in IL-1β, IL-6 and TNF-α levels (all P>0.05), while after the treatment, the L-1β, IL-6 and TNF-α levels in both groups decreased notably (all P<0.05), with significantly lower levels of them in the observation group than those in the control group (all P<0.05, **Figure 3**).

Comparison of adverse reactions between the two groups

According to the statistics of adverse reactions in the two groups, the observation group showed a significantly lower total incidence of adverse reactions than the control group (6.00% vs. 18.97%, P<0.05, **Table 3**).

Prognosis and univariate analysis

According to the prognosis of patients 12 months after treatment, there were 17 cases with poor prognosis in the control group and 6 cases with poor prognosis in the observation group, so the poor prognosis rate in the observation group was lower than that in the control group. According to the prognosis of all patients, the patients were re-divided into good-prognosis group (n=85) and poor-prognosis group (n=23). According to comparison, there were significant differences in age, BMI, Kellgren-Lawrence grading based on X-ray, bone fracture history and therapeutic regimen between the two groups (all P<0.05, **Table 4**).

Multivariate analysis

According to multiple logistic regression analysis of the factors with differences in univariate analysis, older age, higher BMI, higher Kellgren-Lawrence grading based on X-ray and history of bone fracture were independent risk factors for poor prognosis, and spleen and stomach regulating treatment was an independent protective factor (**Table 5**).

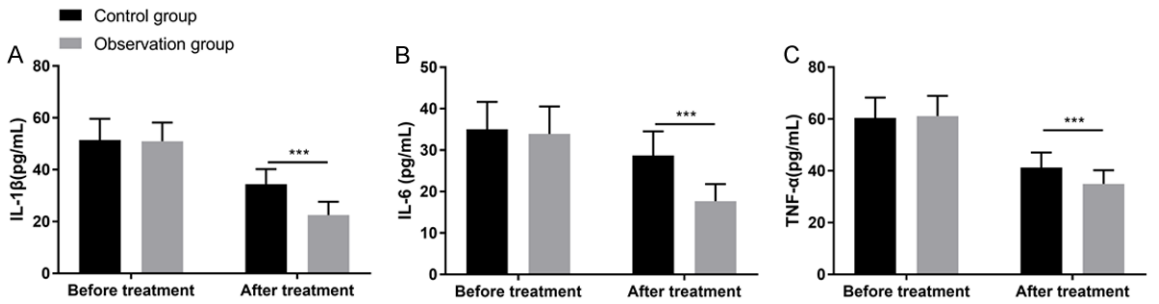

Figure 3. Changes of inflammatory factors before and after treatment. A. After treatment, the observation group showed A notably lower IL-1β level than the control group (***P<0.001). B. After treatment, the observation group showed a notably lower IL-6 level than the control group (***P<0.001). C. After treatment, the observation group showed a notably lower TNF-α level than the control group (***P<0.001). IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

Table 3. Comparison of adverse reactions between the two groups (n, %)

	Control group (n=58)	Observation group (n=50)	X^2	P
Gastrointestinal discomfort	4 (6.90)	0 (0.00)		
Joint swelling	4 (6.90)	2 (4.00)		
Rash	3 (5.17)	1 (2.00)		
Total adverse reactions	11 (18.97)	3 (6.00)	4.001	0.045

Table 4. Univariate analysis of the factors affecting the prognosis

	Good prognosis group (n=85)	Poor-prognosis group (n=23)	t/X^2	*P* value
Age (years)	64.5±6.9	65.2±6.4		
Gender			2.034	0.154
Male	32 (37.65)	5 (21.74)		
Female	53 (62.35)	18 (78.26)		
BMI (kg/m^2)	24.15±3.21	23.68±3.18		
Kellgren-Lawrence grading based on X-ray			7.856	0.020
I	30 (35.29)	2 (8.70)		
II	32 (37.65)	9 (39.13)		
III	23 (27.06)	12 (52.17)		
Heavy manual labor occupation			1.265	0.261
Yes	23 (27.06)	9 (39.13)		
No	62 (72.94)	14 (60.87)		
Disease site			2.473	0.116
Unilateral	49 (65.33)	19 (82.61)		
Bilateral	26 (34.67)	4 (17.39)		
Fracture history	7 (8.24)	6 (26.09)	5.448	0.020
Alcoholism history	19 (22.35)	7 (30.43)	0.647	0.421
Smoking history	23 (27.06)	8 (34.78)	0.528	0.468
Therapeutic regimen			4.801	0.029
Treatment with western medicine alone	41 (48.24)	17 (73.91)		
Combined spleen and stomach conditioning therapy	44 (51.76)	6 (26.09)		

BMI, body mass index.

Table 5. Multivariate analysis of the factors affecting the prognosis

Factors	B	S.E.	Wals	Sig.	Exp (B)	95% C.I. of EXP (B)	
						Lower limit	Upper limit
Age	0.131	0.050	6.989	0.008	1.140	1.034	1.256
BMI	0.242	0.094	6.592	0.010	1.274	1.059	1.533
Kellgren-Lawrence grading based on X-ray	1.098	0.432	6.455	0.011	2.998	1.285	6.993
Fracture history	2.420	0.822	8.668	0.003	11.243	2.246	56.296
Therapeutic regimen	-1.666	0.662	6.337	0.012	0.189	0.052	0.691

Discussion

Modern medical research has revealed that the increase in the components of cartilage matrix fibers in patients with both KOA and OP and the decrease in the components of mucopolysaccharide make the function of the cartilage matrix have more decomposition and unbalanced anabolism [24]. The decrease in the synovial fluid level in the articular cavity, the increase in the subchondral bone tissue density, and osteophytes at the edge of the cartilage all result in long-time protective spasm around the diseased joint muscles, finally limiting the joint activity of patients and reducing their quality of life [25].

In TCM, KOA is considered to be triggered by invasion of pathogenic wind, cold and dampness, which blocks Qi and blood. Strengthening spleen and stomach can nourish limbs [26]. In this study, the observation group showed a notably higher total effective rate than the control group, suggesting a great improvement in efficacy under combination treatment with spleen and stomach conditioning. Non-steroidal anti-inflammatory drugs are recommended for KOA patients with severe pain symptoms. Celecoxib has been confirmed to be effective in relieving pain in KOA patients. Glucosamine hydrochloride tablets are slow-acting drugs to relieve the symptoms of osteoarthritis, and they are also crucial drugs for the pain management of osteoarthritis. Alendronate sodium vitamin D3 is a single compound preparation of bisphosphonates combined with vitamin D, which is the basic anti-OP drug [27]. This study has revealed that after combination treatment with spleen and stomach conditioning in TCM, the knee joint function of patients was better improved and the pain was alleviated. Liu et al. [28] have mentioned that acupuncture at foot acupoints such as Sanyinjiao and Zusanli can strongly relieve pain in patients' feet. These acupoints belong to the spleen meridian and stomach meridian, which can effectively regulate the spleen and stomach and relieve pain. Tillu et al. [29] have revealed that acupuncture at the acupoints of spleen meridian and stomach meridian of KOA patients can strongly alleviate patients' pain and improve their knee function. The meta-analysis of Sun et al. [30] compared the therapeutic effects among acupuncture, sodium hyaluronate, radiofrequency electrotherapy and non-steroidal anti-inflammatory drugs, among which acupuncture on acupoints has a greater beneficial effect on KOA patients, because it can better relieve pain, improve knee joint function and inflammation.

Inflammation is the common pathogenesis of KOA and OP, and NF-κB signaling pathway is a crucial inflammatory signaling pathway, which has been verified to regulate cell differentiation, proliferation, as well as inflammation, and participate in the onset and progression of KOA and OP [31, 32]. The activation of the NF-κB signaling pathway can upregulate inflammatory factors such as IL-1 β, IL-6 and TNF-α, promote cartilage destruction and synovitis, triggering KOA, and it can also stimulate osteoclast formation while inhibiting osteoblasts, inducing OP [33]. According to quantification of inflammatory indexes including IL-1β, IL-6 as well as TNF-α in the two groups before and after treatment in this study, the levels of these decreased greatly after treatment in both groups, and the observation group showed notably lower levels than the control group. The results imply that inflammation of the two groups was alleviated after treatment, and the combination treatment can better lower the inflammation levels of patients and achieve anti-inflammatory effect. Serum P1NP and β-CTX are common markers of bone turnover, which can sensitively

reflect the situation of bone formation and bone resorption, so they are the preferred biochemical indexes of bone metabolism for OP diagnosis and treatment [34]. In this study, the observation group showed notably lower β-CTX and P1NP levels than the control group, implying the therapeutic regimen with spleen and stomach regulating treatment could help alleviate bone metabolism disorder, thus promoting the recovery of bone and joint function. According to results in this study, the control group and observation group had an incidence of adverse reactions of 18.97% and 6.00%, respectively, indicating that the combination treatment can greatly reduce the adverse reaction rate of patients.

However, this study still has some limitations. Firstly, the specific mechanism of the influence of regulating spleen and stomach has not been fully revealed and further animal experiments are needed for exploration. Secondly, the long-term prognosis is still unclear, and research is required to explore the influence of regulating spleen and stomach on long-term prognosis.

To sum up, combination treatment with regulating spleen and stomach with TCM principal can substantially improve the treatment efficacy in patients with both KOA and OP by adjusting the inflammatory factors and bone turnover markers of patients, improving their joint function, alleviating their pain, and strongly preventing adverse reactions, so it is of great clinical application value.

Disclosure of conflict of interest

None.

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