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Effects of Bushen Tongluo prescription on inflammatory, immune function and bone metabolism indicators in RA patients with osteoporosis

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Keywords

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Abstract

Background We aim to explore the effect of adjunctive therapy with Bushen Tongluo (BSTL) prescription on rheumatoid arthritis (RA) patients with osteoporosis, thus providing theoretical basis for clinical treatment. **Methods** 96 RA patients with osteoporosis were selected as study subjects and divided into the control group (n=48) and observation group (n=48). Patients of the control group were treated with methotrexate and vitamin D calcium chewable tablets, while those of observation group were treated with BSTL prescription based on the control group. The clinical efficacy, improvement of joint clinical symptoms, the levels of inflammatory factors, immune function indicators and bone metabolism indicators were compared. **Results** The total effective rate in the observation group was significantly higher than that in the control group. After treatment, the joint function index, joint tenderness index and joint swelling index were lower, and the indexes in the observation group were decreased. The levels of interleukin-6, c-reactive protein, erythrocyte sedimentation rate were lower following the treatment, and the levels in the observation group were lower. The immunoglobulin A (IgG) and IgM levels in the observation group were lower than that in the control group. Blood calium, blood phosphorus and bone mineral density levels were higher in two group after treatment, and those in the observation group were obviously increased compared to the control group. **Conclusion** BSTL prescription adjunctive therapy for RA patients with osteoporosis has a good clinical efficacy, which can effectively improve the patients' clinical symptoms and related indicators, worthy of clinical promotion.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease mainly characterized by joint synovitis and symmetrical and destructive pathological changes within the joint. Patients diagnosed with RA tend to have a long disease course, easy recurrence, and high disability rate [1, 2]. The main clinical manifestations of RA are joint swelling and pain, morning stiffness, cartilage destruction and joint space narrowing, which, without prompt and effective treatment, lead to joint stiffness, deformity and dysfunction, severely affecting the life quality of patients [3]. In addition, RA can involve other tissues of the body in addition to the joints, which is often accompanied by complications such as vasculitis and osteoporosis. Osteoporosis is a systemic skeletal system disease characterized by reduced bone mass, microarchitectural deterioration of bone tissue, and enhanced bone fragility, which increases the risk of fracture and affects the treatment and prognosis of RA patients [4, 5]. At present, the treatment of RA patients with osteoporosis in Western medicine is mainly based on calcium supplements, non-steroidal anti-inflammatory drugs, anti-rheumatic drugs and immunosuppressive agents. Although these agents have been proposed to be effective, there are many side effects and poor compliance in patients.

With the wide application of traditional Chinese medicine (TCM) in clinical practice, many scholars have adopted TCM to treat RA patients with osteoporosis [6], which has achieved a significant curative effect. Bushen Tongluo (tonifying kidney and dredging collaterals) prescription has the effects of activating blood circulation and dredging collaterals, tonifying kidney and liver, and strengthening the tendons and bones. Yinyanghuo, Buguzhi, and Gusuibu in the Bushen Tongluo prescription used in this study can tonify the kidney to eliminate dampness and strengthen the tendons and bones. Shudihuang can enrich the blood and nourish Yin, benefit the liver and the kidney. Shanzhuyu can tonify the liver and kidney, and invigorate Qi and blood. Danshen and Danggui are able to nourish the blood and promote blood circulation, remove blood stasis and relieve pain. Jixueteng is able to invigorate blood and promote blood circulation, and dredge the collaterals to stop pain. Xuduan has the ability to tonify the liver and kidney, and strengthen the tendons and bones. Duzhong has kidney-tonic and anti-inflammatory effects. The whole prescription has the efficacy of invigorating the kidney and liver, activating blood circulation and eliminating stasis, strengthening the tendons and bones, and dredging the collaterals to stop pain.

In this study, we investigated the clinical efficacy of Bushen Tongluo prescription combined with Western medicine for the treatment of RA patients with osteoporosis, and analyzed its effects on inflammatory factors, immune function and bone metabolism in RA patients with osteoporosis. The reports were reported below.

2. Materials and methods

2.1 Clinical data

2.1.1 Study subjects

A total of 96 RA patients with osteoporosis who treated in our hospital from August 2017 to August 2018 were selected as the study subjects, which were divided into the control and the observation groups according to the random number table method, with 48 cases in each group. Observation group was made up of 11 males and 37 females, with age of 55-76 years (a mean age of 65.78±8.24 years) and a disease duration of 3-22 years (mean disease duration of 10.34 ± 2.47 years). Control group included 9 males and 39 females, with age of 53-74 years (a mean age of 63.69 ± 7.25 years) and a disease duration of 4-25 years (mean duration of 9.63±2.38 years). There were no significant differences in gender, age and disease duration between the two groups (P>0.05), but the data were comparable. This study was approved by the ethics committee of our hospital, and all patients have signed written informed consent. The sample size was estimated using the formula: $n = Z^2P(1-P)/E^2$.

2.1.2 Inclusion and exclusion criteria

Inclusion criteria: all patients met both the RA classification criteria established by the American

College of Rheumatology/European League Against Rheumatism in 2010 and the osteoporosis diagnostic criteria established by the World Health Organization in 1994 [7]. Exclusion criteria: patients combined with major diseases of heart, liver, kidney and other important organs. Those had used estrogen, fluoride, and other drugs affecting bone metabolism for approximately 1 month, those combined with secondary osteoporosis due to other diseases, those diagnosed with bone tuberculosis, bone tumor and other diseases, and those who were allergic to drugs used in this study.

2.2 Treatment

2.2.1 Control group

The control group was given methotrexate and vitamin D calcium chewable tablets. Patients were orally administrated methotrexate tablets (Shanghai Xinyi Pharmaceutical Co., Ltd., H31020644), once a week, 10 mg each time, and D calcium chewable tablets (American A&Z Pharmaceutical Inc.) via oral administration at 2 capsules once a day for 2 months.

2.2.2 Observation group

The observation group was treated with Bushen Tongluo prescription on the basis of the control group. The components of the prescription were: Yinyanghuo (*Epimedium brevicornum*) 20 g, Shudihuang (*Rehmannia glutinosa*) and Shanzhuyu (*Cornus officinalis*) 12 g, Danshen (*Salvia miltiorrhiza*), Danggui (*Angelica sinensis*), Jixueteng (*Spatholobus suberectus*), Xuduan (*Dipsacus asper*) and Duzhong (*Eucommia ulmoides*) 10 g, Buguzhi (*Psoralea corylifolia*) and Gusuibu (*Davallia mariesii*) 15 g, Gancao (*Glycyrrhiza uralensis*) 5g. After the addition of 500 ml of water, the combination of herbs was decocted to 250 ml with one dose per day, and the decoction was taken half an hour after breakfast and evening, respectively, and was taken for 2 months.

2.3 Clinical efficacy evaluation

The evaluation of efficacy referred to the *Criteria of diagnosis and therapeutic effect of diseases and syndromes in traditional Chinese medicine* [8]: markedly effective: the disappearance of joint pain, the absence of joint swelling, and the normal joint motion function and the main indicators of laboratory examination; effective: significant reduction in joint pain, swelling and morning stiffness, and evident improvement in joint motion function and main indicators of laboratory examination; ineffective: no improvement in the joint pain, swelling, morning stiffness, motion function and main indicators of laboratory examination. Total effective rate = (markedly effective + effective) cases/total cases×100%.

2.4 Observational indexes

2.4.1 Improvement of joint clinical symptoms

Joint tenderness index [9]: according to the degree of tenderness and limitation of passive activity, joint tenderness can be divided into 4 grades: 0 for no tenderness, 1 for mild tenderness, 2 for moderate tenderness, 3 for severe tenderness. Joint tenderness index = 1 × joint number of grade 1 of tenderness + 2 × joint number of grade 2 + 3 × joint number of grade 3.

Joint swelling index: based on the presence or absence of swelling of soft tissue and joint with effusion, the joint swelling was divided into 3 grades, with 0 for no swelling, 1 for soft tissue swelling, 2 for soft tissue swelling and joint with effusion. Joint swelling index = 1 × joint number of grade 1 of swelling + 2 × joint number of grade 2.

Joint function index [10]: in accordance with the limitation of joint mobility and impact on daily life, the joint function was classified into four grades. Grade I: the joint function was intact, and patients' daily life and work were not restricted, grade II: patients were able to engage in daily life, but had one or more joints of limited mobility, grade III: patients had obvious mobility limitation on the joint, and could only perform general tasks or take care of themselves partially, and grade IV: patients lost mobility and could not take care of themselves. Joint function index = 1 × joint number of grade II of joint function + 2 × joint number of grade III + 3 × joint number of grade IV.

2.4.2 Inflammatory factors

Before and after treatment, 3 ml of fasting elbow venous blood was collected from all patients and centrifuged at 3000 r/min for 15 min to separate plasma. The levels of interleukin-6 (IL-6, SEKH-0013, Solarbio, Beijing, China), C-reactive protein (CRP, SEKH-0138, Solarbio, Beijing, China) were detected by enzyme-linked immunosorbent assay in a microplate reader (Model 680 Microplate Reader, BIO-RAD, CA, USA), and erythrocyte sedimentation rate (ESR) were measured in Westergren method.

2.4.3 Immune function

Before and after treatment, 3 ml of fasting venous blood was drawn from the patients, and the upper layer containing the serum was centrifuged for testing. The levels of serum immunoglobulin A (IGA, SEKH-0207, Solarbio, Beijing, China), immunoglobulin G (IgG, H569, Nanjing JanchengBoenginering Institute, Nanjing, China) and immunoglobulin M (IgM, SEKH-0218, Solarbio, Beijing, China) were detected by enzyme-linked immunosorbent assay in a microplate reader.

2.4.4 Bone metabolism

The concentrations of blood calcium (Ca) and phosphorus (P) were measured by automatic biochemical analyzer (DXC800, Beckman Coulter, Fullerton, CA, USA). The bone mineral density (BMD) of lumber L1-L4 in all patients was measured by a dual energy X-ray analyzer (DEXA; DPX-IQ, Lunar Corp, Madison, WI, USA).

2.5 Statistical analysis

Statistical analysis was performed using SPSS 20.0, and count data were compared by χ^2 test, and measurement data were presented as mean ± standard deviation ($\bar{x}\pm s$), and were compared by *t* test, and $P<0.05$ was taken as statistically significant.

3. Results

3.1 Bushen Tongluo prescription improved the clinical efficacy in RA patients with osteoporosis

The total effective rates in the observation group and the control group were 95.83% and 81.25%, respectively. The total effective rate in the observation group was significantly higher than that in the control group ($P<0.05$). The data were shown in Table 1

.

Table 1 Bushen Tongluo prescription improved the clinical efficacy in RA patients with osteoporosis

Group	Cases	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	48	21 (43.75)	25 (52.08)	2 (4.17)	46 (95.83)
Control group	48	15 (31.25)	24 (50.00)	9 (18.75)	39 (81.25)
χ^2					5.031
P					0.025

3.2 Bushen Tongluo prescription improved the joint clinical symptoms in RA patients with osteoporosis

Before treatment, there was no significant difference in joint function index, joint tenderness index and joint swelling index between the two groups ($P>0.05$); however, after treatment, the joint function index, joint tenderness index and joint swelling index in the two groups were significantly lower than those before treatment ($P<0.05$), and the indexes in the observation group were significantly lower than those in the control group ($P<0.05$), based on the description in Table 2.

3.3 Bushen Tongluo prescription decreased the inflammatory factors in RA patients with osteoporosis

Before treatment, there was no significant difference

in IL-6, CRP and ESR levels between the two groups (P>0.05), whereas after treatment, the levels of IL-6, CRP and ESR in the two groups were significantly lower than those before treatment (P<0.05), and the levels in the observation group were significantly lower than those in the control group (P<0.05), as referred in Table 3.

Table 2 Bushen Tongluo prescription improved the joint clinical symptoms in RA patients with osteoporosis

Group	Cases	Joint function index		Joint tenderness index		Joint swelling index	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	2.85±0.62	1.15±0.43[a]	11.89±2.35	4.76±1.59[a]	10.78±2.08	5.15±1.46[a]
Control group	48	2.77±0.59	1.67±0.37[a]	12.15±2.24	6.23±1.71[a]	11.36±2.24	6.47±1.63[a]
t		0.648	-6.351	-0.555	-4.362	-1.315	-4.179
P		0.519	0.000	0.580	0.000	0.192	0.000

Note: compared with before treatment, [a]P<0.05.

Table 3 Bushen Tongluo prescription decreased the inflammatory factors in RA patients with osteoporosis

Group	Cases	IL-6 (pg/mL)		CRP (mg/L)		ESR (mm/h)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	41.24±9.35	13.42±3.29[a]	31.24±6.91	10.24±2.35[a]	30.29±5.95	8.24±2.15[a]
Control group	48	43.25±8.73	21.56±5.78[a]	29.85±7.14	17.42±3.48[a]	31.34±6.07	15.77±3.36[a]
t		-1.089	-8.480	0.969	-11.846	-0.856	-13.078
P		0.279	0.000	0.335	0.000	0.394	0.000

Note: compared with before treatment, [a]P<0.05.

3.4 Bushen Tongluo prescription decreased the immune function indicators in RA patients with osteoporosis

Before treatment, there was no significant difference in the levels of IgA, IgG and IgM between the two groups (P>0.05). After treatment, the levels of IgG and IgM in the observation group were significantly lower than those before treatment (P<0.05), while the IgA level had no significant difference (P>0.05). The level of IgG in the control group was significantly lower than that before treatment (P<0.05), and there was no significant difference in the levels of IgA and IgM between before and after treatment (P>0.05). Meanwhile, there was no significant difference in the levels of IgA, IgG and IgM between the two groups (P>0.05), according to Table 4.

3.5 Bushen Tongluo prescription increased the bone metabolism indicators in RA patients with osteoporosis

Before treatment, there was no significant difference in the levels of Ca, P and BMD between the two groups (P>0.05); however, after treatment, the levels of Ca, P and BMD in the two groups were

significantly higher than those before treatment (P<0.05), and the levels in the observation group were significantly higher than those in the control group (P<0.05), as illustrated in Table 5.

Table 4 Bushen Tongluo prescription decreased the immune function indicators in RA patients with osteoporosis

Group	Cases	IgA (g/L)		IgG (g/L)		IgM (g/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	3.05±1.02	2.75±0.67	20.24±3.65	14.26±3.15[a]	2.15±0.62	1.79±0.75[a]
Control group	48	3.11±1.13	2.96±0.85	19.57±3.88	15.24±2.78[a]	2.23±0.68	1.92±0.86
t		-0.410	-1.344	0.871	-1.616	-0.602	-0.789
P		0.683	0.182	0.386	0.109	0.548	0.432

Note: compared with before treatment, [a]P<0.05.

Table 5 Bushen Tongluo prescription increased the bone metabolism indicators in RA patients with osteoporosis

Group	Cases	Ca (mmol/L)		P (mmol/L)		BMD (g/cm^2)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	2.13±0.12	2.88±0.34[a]	1.11±0.08	1.42±0.15[a]	0.70±0.07	0.84±0.06[a]
Control group	48	2.08±0.15	2.31±0.29[a]	1.13±0.06	1.24±0.12[a]	0.71±0.05	0.77±0.07[a]
t		1.803	8.837	-1.386	6.492	-0.805	5.260
P		0.075	0.000	0.169	0.000	0.423	0.000

Note: compared with before treatment, [a]P<0.05.

4. Discussion

RA belongs to the category of "Wangbi" according to the beliefs of TCM, with a complex pathogenesis. It has been proposed in the theory of TCM that the main causes of RA are deficiency of genuine Qi, invasion of pathogenic factors, coagulation of phlegm and stasis of blood, and it is based on kidney deficiency, and blood stasis is the incidental of the disease. Osteoporosis has been attributed to the categories of "Gubi" and "Gulou", according to the theories of TCM, which is believed to be caused by deficiency of liver, spleen and kidney, deficiency of Yin and Yang within the Qi and blood, and stasis of meridian blood. As such, the treatment of RA with osteoporosis should be based on the principles of invigorating the kidney and liver, clearing and activating the collaterals, activating blood circulation and removing stasis, and strengthening the tendons and bones. The results of this study showed that the total effective rate in the observation group was significantly better than that in the control group, which indicated that Bushen Tongluo prescription combined with Western medicine for the treatment of RA with osteoporosis had the significant effect and can significantly improve its clinical efficacy.

Joint pain, swelling, and joint dysfunction are

common clinical symptoms in RA patients with osteoporosis, and improvement of these clinical symptoms is significant in the treatment of this disease. This study demonstrated that the joint function index, joint tenderness index, and joint swelling index in both groups after treatment were significantly lowered compared with those before treatment, and the reduction was more significant in the observation group, which indicated that the combination of western medicine and Bushen Tongluo prescription could effectively improve the clinical symptoms of joints in RA patients with osteoporosis. This is related to the pharmacological effects of TCMs in Bushen Tongluo prescription [11-13], icariin in Yinyanghuo can promote the proliferation and inhibit the apoptosis of chondrocytes in human osteoarthritis, and then improve joint function. Danshen has the effects of easing joint movement and relieving pain. The water decoction of Jixueteng has an analgesic efficacy, and total flavonoids within Jixueteng have anti-rheumatic arthritis effects. Duzhong has analgesic pharmacological effects.

Previous studies have confirmed that the occurrence and development of RA are closely related to the levels of inflammatory factors [14], and the levels of IL-6, CRP, ESR in the peripheral blood and synovial fluid of RA patients were significantly increased. In this study, we found that the levels of IL-6, CRP, and ESR in both groups were significantly decreased after treatment, and the levels in the observation group were significantly lower than those in the control group, which indicated that the Bushen Tongluo prescription can effectively reduce the levels of inflammatory factors and ameliorate the inflammatory response of the body in RA patients with osteoporosis. Yuehui Liu and other scholars found that the extract of Duzhong could reduce the contents of IL-6 and TNF-α in the serum of patients with ovariectomized osteoporosis, inhibit the expression of IL-6, and then ameliorate the inflammatory response [15]. Icariin, a potent component in Yinyanghuo, inhibited the synthesis and secretion of IL-6 by intervening in the expression of pro-inflammatory factor TNF-α, and also inhibited the expressions of other inflammatory mediators, thus achieving the effect of ameliorating the body inflammatory response. Yong Xiao et al. discovered [16] that Bushen Jiangu capsules reduced hs-CRP and ESR levels in RA patients. Besides, a study by Aihua Li and others [17] showed that Bushen Huoxue Tongluo formula can effectively reduce the levels of IL-6 and CRP in elderly RA patients. The results of this study are consistent with their findings, which suggested that Bushen herbs can effectively inhibit the secretion of inflammatory factors and attenuate inflammatory responses in the joints.

IgA, IgG, and IgM are all important immunoglobulins in the body, and increased levels of all three can suggest a disorder of the body's immune function. The pathogenesis of RA is closely associated with immune dysfunction, and elevated levels of body immunoglobulins induce the body to produce a large number of autoantibodies. Meanwhile, the immune complexes can deposit in large numbers in the joints, causing joint diseases. In this study, we found that after the adjuvant treatment with Bushen Tongluo prescription, the levels of IgG and IgM in RA patients with osteoporosis were all significantly decreased, and the level of IgA was not significantly different from that before treatment, which indicated that Bushen Tongluo prescription could inhibit the body's excessive immune response and alleviate immune damage. Modern pharmacological studies [18] have confirmed that Yinyanghuo has an important regulatory effect on the main immune organs and immune cells in the body, and can regulate the secretion and expression of related immune cells, and then improve the immune function. In addition, Shudihuang, Danshen, and Jixueteng all have the effect to modulate immune function.

Ca, P, and BMD can reflect the degree of osteoporosis, in which BMD is also the important basis for predicting the risk of fracture. RA patients with osteoporosis have imbalance of bone metabolism, that is, the increased level of bone absorption is higher than that of bone formation, resulting in the decline of BMD, bone pain, and the risk of fracture and even disability [19]. In this study, we found that after treatment, the levels of Ca, P, and BMD in both

groups were significantly higher than those before treatment, and the levels in the observation group were significantly higher than those in the control group, which suggested that the Bushen Tongluo prescription can effectively regulate bone metabolism and contribute to the recovery of osteoporosis. Based on the administration of calcium supplementation therapy, this prescription can promote the body's regulation of minerals and prevent the loss of minerals, which in turn accelerates bone formation, inhibits bone resorption and reduces bone loss, thus promoting the recovery of osteoporosis. Previous studies [20] have shown that Yinyanghuo, Gusuibu, and Buguzhi can inhibit osteoclastic bone resorption by up-regulating the expressions of OPG and OPG/RANKL. Also, they can up-regulate the expressions of BMP-Smads and Wnt/β-catenin signaling pathway related proteins, promote osteoblast bone formation, and then exert an effect in regulating the balance of bone metabolism. Danshen can promote the proliferation of osteoblast like cells, increase the secretion of bone matrix, accelerate bone tissue formation and improve BMD. Meanwhile, it can also promote the proliferation of osteoblast and inhibit the activity of osteoclasts by regulating the expression of transforming growth factor, which in turn effectively regulates and improves bone metabolism [21]. Duzhong can increase estrogen levels and reduce the loss of calcium and phosphorus by suppressing the expressions of IL-6 and TNF-α, thereby suppressing bone resorption and promoting bone formation.

5. Conclusion

The adjuvant therapy of Bushen Tongluo prescription for RA patients with osteoporosis has a good clinical efficacy, which can effectively improve the patients' clinical symptoms, reduce the inflammatory response, enhance immune function, and significantly improve the patients' bone metabolism.

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Not applicable.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization, W. J. Z. and W. J. Z.; Data curation, Y. H. Z.; Formal analysis, W. J. Z. and W. J. Z.; Methodology, Y. H. Z.; Writing-original draft, W. J. Z. and W. J. Z.; Writing-review and editing, W. J. Z., W. J. Z. and Y. H. Z.; All authors have read and agreed to the published version of the manuscript.

Ethical Approval and Consent to Participate

The experiments were conducted in accordance with the principles approved by the Animal Care and Use Committee of our hospital. All patients have signed written informed consent.

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Availability of Data and Materials

The data presented in this study are availability on request from the corresponding author.

Supplementary material

Not applicable.

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