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Danqi Granules Combined with Alfacalcidol Tablets in the Treatment of Senile Osteoporosis and its Effect on Bone Metabolism and Cytokines

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Keywords

Danqi granules, Alfacalcidol tablets, Senile osteoporosis, Bone metabolism, Cytokines

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Abstract

Background This study investigated the effect of Danqi granules combined with alfacalcidol tablets in the treatment of senile osteoporosis and its influence on bone metabolism and cytokines, in order to provide reference for the clinical treatment of senile osteoporosis. **Methods:** A total of 130 patients with senile osteoporosis admitted to our hospital from January 2018 to January 2020 were selected and divided into control group and observation group according to a random number table method, with 65 cases in each group. Patients in Control group were treated with alfacalcidol tablets, and patients in observation group were treated with Danqi granules combined with alfacalcidol tablets. The clinical efficacy, bone metabolism, cytokines, joint dysfunction, pain, quality of life and occurrence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was obviously higher than that of control group (P<0.05); after treatment, the levels of alkaline phosphatase (ALP), anti-tartrate acid phosphatase (TRACP-5b), type I collagen C-terminal peptide (β-CTX) and tumor necrosis factor-α (TNF-α) levels in two groups were obviously lower than those before treatment (P<0.05), and those of observation group were obviously lower than those of control group (P<0.05). After treatment, the levels of insulin-like growth factor (IGF-I) and transforming growth factor-β (TGF-β1) in the two groups were obviously higher than those before treatment (P<0.05), and those of observation group were obviously higher than those of control group (P<0.05). After treatment, the scores of oswestry dysfunction index (ODI) and visual analog scale (VAS) in the two groups were obviously lower than those before treatment (P<0.05), and those in observation group were obviously lower than those in control

group (P<0.05). After treatment, the score of the MOS item short from health survey (SF-36) in the two groups was obviously higher than that before treatment (P<0.05), and that of observation group was obviously higher than that of control group (P<0.05). The adverse reaction rate in observation group was obviously lower than that in control group (P<0.05). **Conclusion:** Danqi granules combined with alfacalcidol tablets achieved a significant efficacy in treatment of senile osteoporosis, which could effectively relieve pain, regulate bone metabolism, ameliorate dysfunction and improve quality of life of patients with a safe and reliable effect.

1 Introduction

Senile osteoporosis is a metabolic bone disease associated with multiple factors, which is characterized by the decrease of bone mineral density and bone tissue. The clinical manifestations of patients include low back pain, rachiokyphosis, chest distress, shortness of breath, dyspnea and even spinal fracture, badly affecting the self-care ability and life quality of patients and bringing heavy economic burden to families and society [1-2]. Hence, how to prevent and treat senile osteoporosis is a clinical research focus currently. Alfacalcidol tablets are a drug capable of regulating calcium metabolism, which achieve excellent curative effect on diseases related to abnormality of bone metabolism such as vitaminD-resi-stantRickets and ricketsandosteomalacia [3]. Besides, bone metabolism belongs to the categories of “bone fistula” and “bone bi” in Traditional Chinese Medicine science, the dialectical therapy of which on “bone fistula” and “bone bi” has a long history [4]. The study of Chen et al. exhibited that Danqi granules composed of various traditional Chinese medicines like *Rhizoma Dioscoreae*, *Fructus Lycii* and *Herba Cistanches* had a good therapeutic effect on osteoarthritis [5]. At present, there is few research of Danqi granules combined with alfacalcidol tablets in treatment of senile osteoporosis. The present work aimed to investigate the curative effects of the two drugs above on senile osteoporosis and their impact upon bone metabolism and cytokines, trying to provide a reference for clinical treatment of senile osteoporosis.

2 Materials and methods

2.1 Clinical data

A total of 130 patients with senile osteoporosis admitted to our hospital from January 2018 to January 2020 were selected and divided into control group and observation group according to a random number table, with 65 cases in each group. The clinicopathological parameters of each case including sex, age, Body Mass Index (BMI) and course of disease were collected from each patient. There was no significant difference of general information (sex, age, BMI and course of disease) between two groups (Table 1, P>0.05). Inclusion criteria were: 1. meeting the diagnostic criteria of middle-aged and senile osteoporosis in *Chinese guideline for the diagnosis and treatment of senile osteoporosis*; 2. without other drug treatment received within 1 month [6]. Exclusion criteria were: 1. severe organ (heart, liver and kidney etc.) dysfunction combined; 2. allergic to the drug used in the study; 3. malignant tumor; 4. fracture; 5. mental disorder; 6. diseases of immune system or blood system.

Table 1 General information between two groups

Group	n	Sex（n）		Age（year）	BMI（kg/m^2）	Course of disease（year）
		Male	Female			
Observation	65	20	45	68.46±6.58	22.74±2.63	5.84±1.76
Control	65	22	43	69.20±6.84	22.60±2.74	5.61±1.57
χ^2/t		0.141		-0.629	0.297	0.786
P		0.708		0.531	0.767	0.433

2.2 Therapeutic method

Control group

Patients in Control group were treated with alfacalcidol tablets (0.25μg; Approval number for National Medical Products Administration (NMPA) approval No.: H20160263, TEIJIN PHARMA LIMITED, Tokyo, Japan, https://www.teijin-pharma.com/) for 6 months: oral administration, 0.5 μg/time and once a day.

Observation group

On a basis of the treatment in control group, observation group was additionally treated with Danqi granules (12g/bag; Z20050537, Handan Pharmaceutical Co., Ltd., Hebei, China, https://www.hanyao.com.cn/): oral administration, 1 bag/time and twice a day. The treatment lasted for 6 months.

Observational indicators

Clinical efficacy

The clinical efficacy was evaluated according to the following criteria [7]: markedly effective, increase of bone mineral density ≥ 50g/cm^3 and bone pain obviously disappeared; effective, increase of bone mineral density < 50g/cm^3 and bone pain mitigated; ineffective, bone mineral density and bone pain did not change or even deteriorated. Total effective rate = (the number of markedly effective and effective cases/the number of total cases) × 100%. Bone mineral density was determined through an EXA-PRESTO dual-energy X-ray absorptiometry (DXA; OsteoSys Co., Ltd., Shanghai, China, http://www.osteosyschina.cn/).

Bone metabolism

Venous blood (3 mL) of patients before and after treatment was harvested and centrifuged to detect the levels of alkaline phosphatase (ALP; JSAY105, Qingdao Jisskang Biotechnology Co., Ltd., Qingdao, China, http://www.jisskang.com/), anti-tartrate acid phosphatase (TRACP-5b; YS-E7055, Shanghai YSRIBIO industrial co., LTD., http://www.shyskits.com/) and type I collagen C-terminal peptide (β-CTX; CEA892Hu03, Nanjing SHRBIO Co., Ltd., Nanjing, China, http://www.njshrbio.com/) by enzyme linked immunosorbent assay (ELISA).

Cytokine

Venous blood (3 mL) of patients before and after treatment was collected and centrifuged, subsequent to which ELISA was adopted for the assessment on the levels of tumor necrosis factor-α (TNF-α; E-EL-M0049c, Elabscience Biotechnology Co.,Ltd., Hubei, China, https://www.elabscience.com/), insulin-like growth factor (IGF-I; DXT-105-01-100, ScienCell, San Diego, CA, USA, https://www.sciencellonline.com/) and transforming growth factor-β (TGF-β1; ARB13604, BALB, Beijing, China, http://www.bjbalb.com/).

Joint dysfunction, pain and quality of life

Before and after treatment, the joint dysfunction status of patients was evaluated through Oswestry disability index (ODI) [8] which primarily consisted of 6 items (standing, ability of life self-care etc.), as the higher score meant the more serious joint dysfunction; visual analogue scale (VAS) [9] was utilized to assess the pain of patients and the higher the score was, the more severe the pain was; the evaluation of life quality was made by the MOS item short from health survey (SF-36) [10] with the higher score indicating a better quality of life.

Adverse reaction

The adverse reactions like nausea and vomiting were viewed and recorded.

2.3 Statistical analysis

Statistical analysis was operated by SPSS 20.0 (IBM, Armonk, NY, USA). χ^2 test was employed to compare the enumeration data while the measurement data were performed as the means ± standard deviation and contrasted through Student's *t* test. A statistically significant difference was accepted when $P<0.05$.

3 Results

3.1 Clinical efficacy

After treatment, the total effective rate of observation group was 90.77% and that of control group was 75.38%, thus it could be seen that the total effective rate in observation group was notably higher than that in control group (Table 2, $P<0.05$).

Table 2 Clinical efficacy between two groups [n (%)]

Group	n	Markedly effective	Effective	Ineffective	Total effective rate
Observation	65	38 (58.46)	21 (32.31)	6 (9.23)	59 (90.77)
Control	65	24 (36.92)	25 (38.46)	16 (24.62)	49 (75.38)
χ^2					5.471
P					0.019

3.2 Bone metabolism index

The levels of ALP, TRACP-5b and β-CTX did not differ between two groups before treatment (Table 3, $P>0.05$), whereas those after treatment was prominently lower than before treatment (Table 3, $P<0.05$). In addition, the levels of ALP, TRACP-5b and β-CTX in observation group appreciably reduced in contrast with control group (Table 3, $P<0.05$).

3.3 Cytokine level

No marked difference of TNF-α, IGF-1 and TGF-β_1 levels between two groups before treatment was observed (Table 4, $P>0.05$). After treatment, TNF-α level was decreased while IGF-1 and TGF-β_1 levels were increased in both groups relative to before treatment (Table 4, $P<0.05$). In comparison with control group, TNF-α level declined and levels of IGF-1 and TGF-β_1 rose in observation group (Table 4, $P<0.05$).

3.4 ODI, VAS and SF-36 scores

There was no obvious difference of ODI, VAS and SF-36 scores between two groups before treatment (Table 5, $P>0.05$). ODI and VAS scores of two groups after treatment were dramatically lower than those before treatment (Table 5, $P<0.05$), whereas SF-36 score after treatment was higher than that before treatment (Table 5, $P<0.05$). Besides, a significant reduction of ODI and VAS scores as well as an elevation of SF-36 score was viewed in observation group when compared with control group (Table 5, $P<0.05$).

Table 3 Bone metabolism index between two groups

Group	n	ALP (U/L)		TRACP-5b (U/L)		β-CTX (ng/mL)	
		Before	After	Before	After	Before	After
Observation	65	84.62±8.72	60.55±8.24*	5.72±1.68	3.24±1.02*	0.58±0.20	0.30±0.10*
Control	65	85.77±9.30	68.32±7.73*	5.94±1.79	4.27±1.18*	0.54±0.18	0.38±0.11*
t		-0.727	-5.545	-0.723	-5.324	1.199	-4.339
P		0.468	0.000	0.471	0.000	0.233	0.000

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

Table 4 Cytokine level between two groups

Group	n	TNF-α (pg/mL)		IGF-1 (ng/mL)		TGF-β_1 (ng/mL)	
		Before	After	Before	After	Before	After
Observation	65	7.24±2.10	4.58±1.13*	158.62±20.34	218.42±15.76*	9.12±2.36	15.34±3.58*
Control	65	7.68±2.21	5.64±1.28*	162.52±18.58	192.35±16.33*	9.66±2.25	12.66±3.40*
t		-1.164	-5.005	-1.141	9.261	-1.335	4.376
P		0.247	0.000	0.256	0.000	0.0.184	0.000

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

Table 5 ODI, VAS and SF-36 scores between two groups（point）

Group	n	ODI		VAS		SF-36	
		Before	After	Before	After	Before	After
Observation	65	34.45±5.85	14.62±3.50*	5.22±1.16	2.14±0.68*	62.34±7.42	83.64±6.88*
Control	65	35.56±4.72	17.38±4.16*	5.43±1.24	3.04±0.75*	60.74±6.85	75.46±9.42*
t		-1.191	-4.093	-0.997	-7.167	1.277	5.654
P		0.236	0.000	0.321	0.000	0.204	0.000

Note: compared with before treatment, $^{a}P<0.05$.

Adverse reaction

The adverse reaction rate of observation group was 7.69% (5/65) with 2 cases of nausea and vomiting as well as 3 cases of dizziness and headache; the adverse reaction rate of control group was 21.54% (14/65) with 5 cases of nausea and vomiting, 7 cases of dizziness and headache as well as 2 cases of dysfunction of liver and kidney. The adverse reaction rate of observation group was notably lower than that of control group (χ^2=4.993，*P*=0.025).

Discussion

Osteoporosis is a common systemic metabolic bone disease prevalent among the elder, which is mainly characterized by damage of bone quality and bone structure, decline of bone density and elevation of bone fragility [11]. In recent years, with increasing aged population, the incidence of osteoporosis shows a rising tendency and the morbidity of fracture induced by osteoporosis increases as well, bringing great threat to physical health of people [12]. At present, alfacalcidol tablets are frequently applied to treat osteoporosis clinically and able to mitigate leg pain of patients. However, due to the limited body tolerance of the elder, the long-term treatment of alfacalcidol tablets may easily cause the abnormality of gastrointestinal tract and circulatory system, influencing the outcome of patients [13]. Therefore, how to alleviate pain, reduce adverse reactions as well as ameliorate dysfunction and prognosis in elderly patients is a hot topic of clinical research.

In Traditional Chinese Medicine, osteoporosis belongs to the categories of “bone fistula”, “bone bi” and “lumbago”, which is caused by deficiency of kidney essence, blood stasis blocking meridian, vital genesis insufficiency of bone marrow and malnutrition of tendon and bone, as promoting blood circulation for removing obstruction in collaterals, invigorate the liver and kidney and strengthening tendons and bones are major treatment strategies [14]. Danqi granules primarily comprises *Radix Rehmanniae Preparata*, *Herba Cistanches*, *Fructus Corni* (steamed), *Semen Cuscutae*, *Rhizoma Alismatis*, *Rhizoma Dioscoreae*, *Concha Ostreae*, *Herba Epimedii*, *Fructus Lycii*, *Cortex Moutan Radicis* and *Poria*, among which *Radix Rehmanniae Preparata*, with sweet flavor and slightly warm nature, acts on Jueyin Liver Meridian of Foot and Shaoyin Kidney Meridian of Foot to strengthen essence, replenish marrow, nourish yin and tonify blood; *Herba Cistanches*, with sweet flavor and warm nature, acts on Shaoyin Kidney Meridian of Foot and Yangming Large Intestine Meridian of Hand to tonify kidney yang and strengthen essence and blood; *Fructus Corni* with acid flavor and slightly warm nature acts on Jueyin Liver Meridian of Foot and Shaoyin Kidney Meridian of Foot to induce astringency and invigorate the liver and the kidney; *Semen Cuscutae* with acrid-sweet flavor realizes the effects on strengthening the kidney to stop nocturnal emission, reducing urination for preventing enuresis and tonify the liver and the kidney; *Rhizoma Dioscoreae* with sweet flavor and neutral nature acts on Taiyin Spleen Meridian of Foot and Shaoyin Kidney Meridian of Foot to tonify the spleen, lung and kidney, reinforce qi and nourish yin; *Herba Epimedii* with acrid-sweet flavor acts on Jueyin Liver Meridian of Foot and Shaoyin Kidney Meridian of Foot to strengthen tendons and bones, invigorate the kidney yang and dispel wind-damp; *Cortex Moutan Radicis* with acrid-bitter flavor and slightly cold

nature fulfills functions on clear heat, cool blood and promote blood circulation for removing blood stasis; *Concha Ostreae* acts on Jueyin Liver Meridian of Foot and Shaoyin Kidney Meridian of Foot to nourish yin for suppress hyperactive yang, resolve mass and relieve pain. All above drugs combined achieve effects on promoting blood circulation for removing obstruction in collaterals, invigorating the liver and kidney as well as strengthening tendons and bones. In our study, the total effective rate and SF-36 score appreciably increased while ODI and VAS scores dramatically decreased in observation group relative to control group. Those data implicated that Danqi granules combined with alfacalcidol tablets had a better curative effect in senile osteoporosis than the alone treatment of alfacalcidol tablets, which could effectively alleviate pain of patients, improve joint dysfunction and raise quality of life.

A previous research has demonstrated that the major pathological mechanism of osteoporosis is the abnormality of bone metabolism, severe bone loss and accelerated ratio of bone turnover [15]. ALP is an enzyme produced by osteoblasts. When the bone metabolism of the body is abnormal, calcium declines to induce activation of osteoblasts, leading to the upregulation of serum ALP level [16]. Both of TRACP-5b and β-CTX are biochemical markers reflecting bone resorption, the rise of which implied the increase of bone resorption and serious bone loss [17]. TNF-α is a regulatory factor of osteoclasts, which is involved in bone resorption and the process of inflammatory response [18]; IGF-I and TGF-β1 can both participate in the procedure of bone formation, and the down-regulation of their levels suggests that bone density of patients reduces [19]. The consequences of the present work showed marked upregulation of ALP, TRACP-5b, β-CTX and TNF-α levels and notable down-regulation of IGF-I and TGF-β1 in both groups after treatment in contrast with before treatment, as the amelioration of those factors above in observation group was better than that in control group, indicating the Danqi granules combined with alfacalcidol tablets was able to mediate bone metabolism of patients with senile osteoporosis, effectively advance bone formation and inhibit bone resorption. Alfacalcidol tablets are a derivative of vitamin D, which can modulate blood calcium level by promoting intestinal absorption of calcium and phosphate so as to repress bone resorption, elevate bone density and improve sclerotin. Moreover, modern pharmacology presents that Danqi granules facilitate the absorption of calcium ion, promote its transfer to the bone and accelerate the generation of bone matrix collagen, thereby effectively advancing bone formation and raising bone density. In the meanwhile, Danqi granules induce osteoblast proliferation and ameliorate osteoblast function to suppress bone resorption process and enhance sclerotin. Liu et al. revealed that Danqi granules combined with zoledronic acid was able to balance bone resorption and formation, providing a good foundation for cure of osteoporosis [20]. Furthermore, our study showed that the adverse reaction rate in observation group was lower than that in control group, which implicated that Danqi granules combined with alfacalcidol tablets mitigated the toxic side effect of drugs, possessing a safer and more reliable therapeutic effect.

In conclusion, Danqi granules combined with alfacalcidol tablets achieved a significant efficacy in treatment of senile osteoporosis, which could effectively relieve pain, regulate bone metabolism, ameliorate dysfunction and improve quality of life of patients with a safe and reliable effect.

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Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

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

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

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

Supplementary Material

Not applicable

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