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Jintiange combined with alfacalcidol improves muscle strength and balance in primary osteoporosis: A randomized, double-blind, double-dummy, positive-controlled, multicenter clinical trial

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ABSTRACT

Objective: To investigate the effectiveness of a Chinese patent medicine, Jintiange capsules with the main component of artificial tiger bone powder, combined with alfacalcidol on muscle strength and balance of the lower extremities in patients with primary osteoporosis.
Design: A randomized, double-blind, double-dummy, positive-controlled, multicenter clinical trial.
Subjects and methods: A total of 400 patients diagnosed with primary osteoporosis or osteopenia were recruited and randomized into the Jintiange or control groups. During the 52-week treatment, the participants in the Jintiange group were treated with Jintiange capsules (1.2 g each time, 3 times per day) and calcium carbonate simulant, while those in the control group were treated with calcium carbonate (element calcium 0.3 g, twice a day) and a Jintiange capsule simulant. Alfacalcidol (0.25 μg/d) was applied in both groups. The timed up and go test (TUG), chair rising test (CRT), and tandem gait test (TGT) were performed to evaluate balance, muscle strength and fall risk of the participants.
Results: There were 154 participants in the Jintiange group, and 157 participants in the control group were included in the per-protocol set. Comparing the data at week 52 from those at baseline, the TUG time decreased from 9.60 ± 2.25 s to 8.53 ± 2.06 s ($p < 0.001$) in the Jintiange group and decreased from 9.50 ± 1.91 s to 9.11 ± 1.95 s ($p < 0.001$) in the control group; the CRT time decreased from 11.49 ± 4.05 s to 8.57 ± 2.13 s ($p < 0.001$) and 11.17 ± 3.21 s to 9.74 ± 1.98 s ($p < 0.001$) in the Jintiange and control groups, respectively; the number of correct steps in the TGT increased significantly in both the control (7.40 ± 1.27 vs. 7.69 ± 0.87, $p < 0.01$) and Jintiange groups (7.21 ± 1.58 vs. 7.60 ± 1.12, $p < 0.001$). At the end of the study, the TUG and CRT

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results in the Jintiange group were superior to those in the control group (all p value < 0.05), while no obvious difference was found in the TGT between the two groups. At week 52, the high fall risk proportions in the Jintiange group were significantly lower than those in the control group according to TUG (3.25% vs. 9.55%, $p = 0.023$) and CRT (20.78% vs. 33.76%, $p = 0.01$).

Conclusion: Jintiange capsules combined with alfacalcidol can effectively improve muscle strength and the balance of the lower extremities and reduce fall risk in patients with primary osteoporosis/osteopenia.

The translational potential of this article: Artificial tiger bone powder, a traditional Chinese patent medicine, can improve muscle strength and balance and reduce fall risks effectively among patients with primary osteoporosis. It might be a therapeutic option for osteoporosis individuals combined with sarcopenia to improve their muscle function.

1. Introduction

Osteoporosis is a chronic bone disorder characterized by a loss of bone mass and destruction of bone microarchitecture, leading to an increase in bone fragility and fracture risk [1,2]. The latest epidemiological study showed that the prevalence of osteoporosis among the population aged over 40 years was 20.6% among women and 5.0% among men in mainland China [3]. In 2010, a report from the 27 countries of the European Union estimated that the prevalence of osteoporosis was 6.6% and 22.1% in men and women aged over 50 years, respectively, and the number of newly osteoporotic fractures reached 3.5 million. Among them, approximately half of fractures occur in the hip, spine or forearm [4]. With the increase in worldwide aging, osteoporosis and osteoporotic fractures will cause considerable economic burdens on individual families and society as a whole [5].

Poor balance and muscle strength are two of the main risk factors for fractures and falls in older adults, with an average percentage of 17% of falls occurring in individuals older than 65 years [6,7]. As the two most common risk factors amenable to interventions [8], there are some interventions for improving muscle strength and balance in patients with osteoporosis. Nevertheless, effective drugs to ameliorate these two deficits are still limited [9]. In patients with osteoporosis, physical exercise can significantly improve muscle strength and balance and reduce the risk of falls, but the efficacy depends on the type, duration and intensity of exercise [10–12]. However, inappropriate exercise approaches may lead to an increase in fracture risk, especially for elderly individuals who are not professionally and properly guided [13].

In addition to classic anti-resorption agents and anabolic agents used to treat osteoporosis, some Chinese patent medicines (CPMs) can play a positive role in preventing osteoporotic fractures [14]. Tiger bone powder is an effective traditional Chinese medicine for skeletal disorders such as osteoporosis, osteoarthritis, and rheumatoid arthritis that has anti-inflammatory, bone strengthening, accelerated fracture healing and pain relieving effects [15]. Because tigers are protected animals, using tiger bones for pharmacy and other products is forbidden. Therefore, scientists developed a Jintiange capsule composed of artificial tiger bone powder, whose components are almost the same as those of natural tiger bone powder [16]. Recently, a meta-analysis showed that Jintiange capsules effectively improve the bone mineral density (BMD) of the lumbar spine in patients with primary osteoporosis [17]. Another systematic review concluded that Jintiange capsules alone or combined with other anti-osteoporosis drugs ameliorate bone loss, easing pain and reducing adverse events [18].

Whether artificial tiger bone powder can help improve muscle strength and balance in primary osteoporosis patients remains unknown. The objective of this study was to investigate the effectiveness of Jintiange capsules combined with alfacalcidol on the muscle strength and balance of the lower extremities among patients with primary osteoporosis.

2. Subjects and methods

2.1. Patients

This is a post hoc analysis of a randomized clinical trial (ChiCTR-IPR-16008533). The subjects came from a randomized, double-blind, double-dummy clinical trial conducted in 16 centers in mainland China to evaluate the effectiveness and safety of Jintiange capsules in patients with primary osteoporosis, of which the primary and secondary outcomes, including BMD and bone turnover markers (BTMs), as well as safety data, have been published [19]. In brief, from November 2016 to May 2019, 400 patients diagnosed with primary osteoporosis or osteopenia with risk factors were enrolled. Inclusion criteria included (1) age $<$80 years and being male $>$50 years or female $>$45 years and not having a menstrual period for at least 1 year or $>$ 60 years for those whose menopausal age is unclear; (2) a T-score of BMD evaluated by dual-emission X-ray absorptiometry (DXA) $\leq$-2.5 standard deviation (SD) at lumbar spine 1–4 (L1-4) or FN or TH, a T-score between -2.5 SD and -1.0 SD, combined with one or more risk factors (evaluated by the International Osteoporosis Foundation questionnaire) or an Osteoporosis Self-assessment Tool for Asians (OSTA) score $\leq$ -1; and (3) a body mass index (BMI) between 18.5 and 28.0 kg/m^2. Exclusion criteria included (1) secondary osteoporosis, including primary hyperparathyroidism, rheumatoid arthritis, multiple myeloma, etc. or patients with hyperphosphatemia, bone tuberculosis and malignant bone tumor; (2) patients with severe concurrent diseases, including poorly controlled hypertension or diabetes, hepatic dysfunction (ALT or AST $>$1.5-fold of upper limit), or renal insufficiency (eGFR$<$60 ml/min); and (3) taking medicines that affect vitamin D metabolism in the past 3 months, drugs affecting bone metabolism in the past 6–12 months (estrogen, selective estrogen receptor modular, calcitonin, fluoride, synthetic steroids and parathyroid hormone in the past 6 months, or bisphosphonates in the past 12 months), and any other drug or treatment that researchers believe may interfere with this trial. The trial was performed with the approval of Peking Union Medical Hospital Ethics Committee (HS-1047) and in accordance with Declaration of Helsinki and good clinical practice (GCP) guidelines. Written informed consent was obtained from all the participants.

2.2. Study design and treatment

This is the post hoc analysis of the abovementioned clinical trial on Jintiange treatment in Chinese osteoporotic patients, where the sample size was calculated according to the primary outcomes of BMD changes as previously described [19]. A total of 400 participants were divided into Jintiange and control groups equally by the stratified block randomization method. The participants in the Jintiange group were treated with Jintiange capsules (0.4 g per capsule, containing 65 mg amino acids, 55 mg elemental calcium, and 35 mg phosphorus, 1.2 g, tid)

and calcium carbonate simulant (1 tablet, bid). The participants in the control group were treated with calcium carbonate tablets (elemental calcium 0.3 g, bid) and a Jintiange capsule simulant (3 capsules, tid). Alfacalcidol (0.25 μg, Qd) was applied in both groups. The course of treatment was 52 weeks for both groups. The participants were visited on day −14–0, day 0, week 4 ± 3 days, week 12 ± 5 days, week 24 ± 5 days, week 36 ± 5 days and week 52 ± 5 days. Serum levels of total 25-hydroxyl vitamin D (T25OHD) and other biochemical parameters were measured at each visit, while BMD of L1-L4, FN and TH were measured by DXA at baseline, week 24 and week 52, respectively, as previously reported [19].

2.3. Sample size calculation

The sample size was calculated according to BMD changes as the primary outcome for the superiority design. The calculation of the therapeutic efficacy in the aspect of BMD improvement is based on the standards from the "National Medical Products Administration" [20]. It was estimated that the improvements in BMD in the Jintiange group and the control group were 0.06 g/cm^2 and 0.03 g/cm^2, respectively, and the SD of BMD in the two groups was 0.1 g/cm^2. Based on 80% power and a one-sided 2.5% level of significance, the mean BMD in the Jintiange group was greater than that in the control group, the SDs of BMD in the two groups were equal, and R = 1. Considering a drop-out rate of 20%, the minimum sample size was 400 participants for the double-blind study, including 200 participants in the Jintiange group and 200 participants in the control group.

2.4. Evaluation of muscle strength and balance of the lower extremities

The functional ability and balance of patients were evaluated by three functional assessment tests. The timed up and go test (TUG) was used to evaluate the functional mobility, muscle function, gait speed and balance of the participants. The procedure of the TUG test involves the participant standing from a standard arm chair with an approximate seat height of 48 cm and an approximate armrest height of 68 cm, walking a distance of 3 m, turning, walking back and sitting down again [21,22]. In the TUG test, individuals who need more than 12 s to complete the test are assessed as having a high risk of falls; otherwise, they are assessed as having a low risk of falls.

The main purpose of the chair rising test (CRT) is to evaluate hip muscle strength [23]. The participant is asked to rise from a chair with an approximate seat height of 48 cm and then sit down, repeating the process five times. A CRT test time ≤10 s indicates a low risk of falls. If the participant cannot complete the process of standing up and sitting down for five times or takes more than 10 s to do so, then were assessed as having a high risk of falls.

The tandem gait test (TGT) is mainly used to evaluate the balance of the lower extremities [23]. The participant starts walking 8 steps in a straight line on a special ruler (approximately 10 cm wide and 3 m long), one foot is placed in front of the other, and the distance between the two feet should be less than 1 cm, which can be recorded as a correct or successful step. If the foot deviates from the straight line more than the width of the foot, then the step is recorded as incorrect. This test was repeated three times, and the best result was taken as the final result. The TGT result is expressed as the number of successful steps. A result of less than 8 successful steps shows poor balance ability and a high risk of falls, while taking 8 successful steps was assessed as indicating a low risk of falls.

2.5. Falls and fractures

During the follow-up, incidents of nonvertical fractures and falls were self-reported by the participants. Spine X-rays were conducted at baseline and the 52nd week to evaluate new vertebral fractures. The formulas for the fall incident rate and the fracture incident rate are as follows: the fall incident rate = (*the* number of falls /total number of participants) × 100%; the fracture incident rate = (*the* number of new fractures /total number of participants) × 100%. It should be noted that if a participant had experienced multiple falls or fractures, each was counted separately.

2.6. Dataset for analysis

According to the principle of intention-to-treat, the full analysis set (FAS) included all randomized participants taking our study drugs at least once. For those not completing the entire study process, the latest data were included in the analysis. General characteristics at baseline were analyzed in the FAS. The per-protocol population set (PPS) comprised participants who agreed with the study protocol, exhibited good compliance, did not take prohibited drugs during the study period, and completed a case report form. Efficacy data, including the TUG and CRT times and the number of correct steps in TGT, were analyzed in both the FAS and PPS.

2.7. Statistical analysis

All data were analyzed by SAS version 9.4. Normally distributed data are described as the mean ± SD, and abnormally distributed data are depicted as the median (Q1, Q3). Comparisons between groups were made with appropriate methods according to the type of data. Classified data at baseline and posttreatment were compared by the chi-square test or Fisher's exact test, including sex, diagnosis and new fractures. Data on baseline information were tested by a two-sided test. Repeated measures ANOVA was used to compare repeated measures at different visits, including BMD, the TUG and CRT times, the number of correct steps in TGT, and their changes at each visit were compared to baseline. Repeated measures are depicted as the estimated value ± standard error. Both in the Jintiange group and the control group, McNemar's test was used to analyze the change in the proportion of high fall risk at each visit compared with that at baseline. The incidences of new fracture and falls were tested by the chi-square test or Fisher's exact test. Bivariate analysis was performed in the PPS to evaluate the relationship between BMDs and the TUG/CRT/TGT results, as well as changes in BMDs and changes in the TUG/CRT/TGT results from baseline to week 52. Multiple regression analysis was performed, where the results of the TUG/CRT/TGT and their changes after treatment were the dependent variables, and the independent factors included age, sex, fracture history, new fracture, new fall, and serum T25OHD level at baseline. Statistically significant differences were considered when the p value ≤ 0.05.

3. Results

3.1. General characteristics of all subjects and BMD at baseline and week 52 in the PPS

A total of 199 patients in the Jintiange group and 200 patients in the control group received randomization and at least one dose of medicine and entered the FAS analysis. There were 166 participants in the Jintiange group and 168 participants in the control group at the 52-week follow-up, among which 154 participants in the Jintiange group and 157 participants in the control group were included in the PPS (Fig. 1). General characteristics are listed in Table 1. Except for height (median of 158.0 cm in the Jintiange group vs. 157.0 cm in the control group, p = 0.048), there were no statistically significant differences in the general characteristics between the two groups. Additionally, there were no significant differences in BMD at baseline or week 52 in L1-L4, the FN, or the TH between the control and Jintiange groups (Table 2), as previously reported [19].

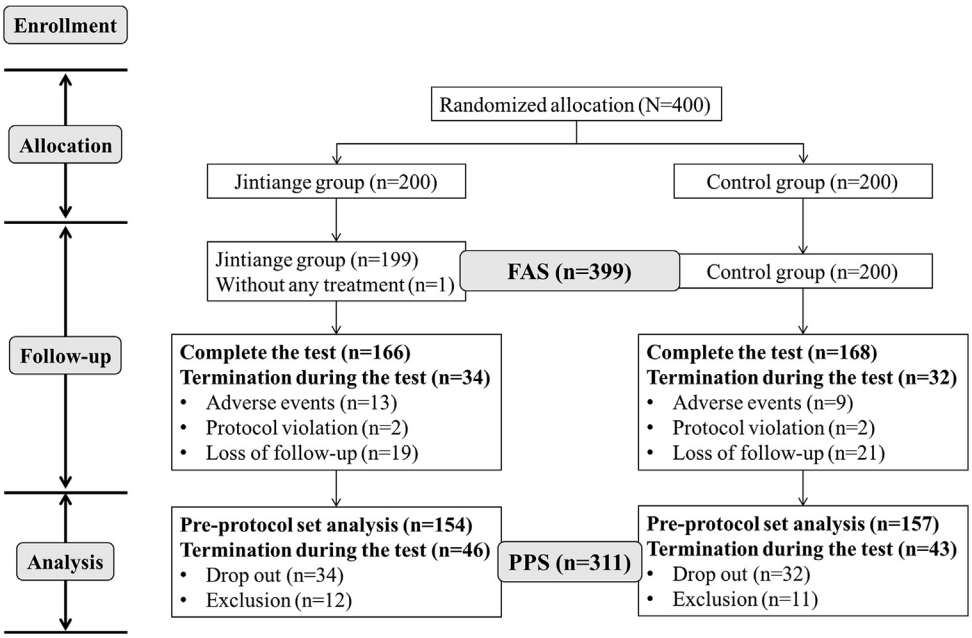

Fig. 1. Flow chart. Abbreviations: FAS, full analysis set; PPS, per-protocol set.

Table 1
Baseline characteristics of included subjects (FAS).

Characteristics	Control group (n = 200)	Jintiange group (n = 199)	p value
Age (years old)	62.88 ± 7.42	63.31 ± 7.02	0.555
Gender n (%)			0.473
Male	29 (14.50%)	24 (12.06%)	
Female	171 (85.50%)	175 (87.94%)	
Fracture history n (%)	60 (30.00%)	53 (26.63%)	0.455
Height (cm)	158.00 (155.00, 162.00)	157.00 (153.00, 161.00)	**0.048**
Weight (kg)	60.00 (54.00, 65.00)	58.00 (52.50, 64.00)	0.161
BMI (kg/m^2)	23.57 ± 2.50	23.42 ± 2.52	0.561
Systolic pressure (mmHg)	124.00 (117.00, 135.00)	122.00 (116.00, 132.00)	0.235
Diastolic pressure (mmHg)	75.00 (70.00, 80.00)	75.00 (70.00, 80.00)	0.637
Serum T25OHD (ng/ml)	17.69 (13.03, 24.23)	17.68 (12.56, 24.21)	0.953
BMD (g/cm^2)			
L1-L4	0.84 (0.75, 0.93)	0.84 (0.75, 0.92)	0.875
Femoral neck	0.70 (0.62, 0.77)	0.67 (0.62, 0.76)	0.344
Total hip	0.80 (0.71, 0.86)	0.78 (0.70, 0.84)	0.179
Diagnosis n (%)			0.573
Osteoporosis	111 (55.50%)	116 (58.29%)	
Osteopenia	89 (44.50%)	83 (41.71%)	

The normal distribution data is described as mean ± standard deviation, and the abnormal distribution data is depicted as median (interquartile: Q1, Q3). Abbreviations: FAS, full analysis set; BMI, body mass index; T25OHD, total 25-hydroxyl vitamin D; BMD, bone mineral density.

3.2. Comparison of muscle strength and balance before and after treatment

The muscle strength and balance evaluated by the TUG and CRT times and the number of correct steps in the TGT, before and after treatment, were included in the PPS analysis, and their percentage changes at each visit were compared with the baseline data within each group (as shown in Table 3). There were no significant differences in all of the indexes between the two groups at baseline.

The TUG time was 9.50 ± 0.17 s and 9.60 ± 0.17 s at baseline in the control and Jintiange groups, respectively (p = 0.654). At week 52, the TUG time was significantly shorter in the patients in the Jintiange group than in those in the control group (8.53 ± 0.16 s vs. 9.11 ± 0.16 s, p = 0.012), with the values decreasing by 1.07 ± 0.16 s (−8.77 ± 1.59%) and 0.39 ± 0.16 s (−2.91 ± 1.57%) in the Jintiange and control groups, respectively, compared with baseline (p < 0.001). The TUG time decreased significantly after week 4 in the Jintiange group, while it decreased significantly after week 24 in the control group (Table 3 and Fig. 2A).

Although compared with the data at baseline, the CRT times declined from week 4 in both groups (all p values < 0.05, Fig. 2B), the CRT time at week 52 was significantly shorter in the Jintiange group than that in the control group (8.57 ± 0.17 s vs. 9.74 ± 0.16 s, p < 0.001), and it decreased by −2.90 ± 0.23 s (−21.93 ± 1.51%) and −1.43 ± 0.22 s (−8.99 ± 1.48%) in the Jintiange and control groups, respectively. Since week 24, the decrease in CRT time was more obvious in the Jintiange group than in the control group (Table 3 and Fig. 2B).

The number of correct steps in the TGT and the change from baseline to each visit showed no significant differences between the Jintiange and control groups (Table 2), except for the number of correct steps at week 4 (7.58 ± 0.10 vs. 7.26 ± 0.10, p = 0.026). Compared to baseline, the

Table 2
BMD between two groups at baseline and week 52 (PPS).

BMD in different positions	Time point	Control group	Jintiange group	p value
L1-L4 (g/cm^2)	N	157	154	
	Baseline	0.851 ± 0.012	0.851 ± 0.012	0.961
	W52	0.866 ± 0.012***	0.859 ± 0.012**	0.667
Femoral neck (g/cm^2)	N	157	154	
	Baseline	0.695 ± 0.009	0.692 ± 0.009	0.820
	W52	0.702 ± 0.009	0.696 ± 0.009	0.605
Total hip (g/cm^2)	N	148	146	
	Baseline	0.791 ± 0.010	0.779 ± 0.010	0.355
	W52	0.792 ± 0.010	0.774 ± 0.010	0.209

The data of BMD is depicted as estimated value ± standard error (SE). "*", "**", and "***" stand for p < 0.05, p < 0.01, and p < 0.001 between data at baseline and at week 52 within each group, respectively. Abbreviations: PPS, per-protocol set; BMD, bone mineral density.

Table 3
Comparison of TUG, CRT and TGT between two groups and their changes at each visit compared to baseline (PPS).

		Baseline	W4	W12	W24	W36	W52
TUG	**Control (sec)**	9.50 ± 0.17	9.42 ± 0.18	9.32 ± 0.16	9.22 ± 0.14*	9.10 ± 0.14**	9.11 ± 0.16*
	Jintiange (sec)	9.60 ± 0.17	9.29 ± 0.18*	9.13 ± 0.16**	8.96 ± 0.14***	8.66 ± 0.14***	8.53 ± 0.16***
	p1	0.654	0.604	0.388	0.181	**0.024**	**0.012**
	Control (%)	-	+0.69 ± 1.69	−0.28 ± 1.56	−1.23 ± 1.31	−2.61 ± 1.41	−2.91 ± 1.57
	Jintiange (%)	-	−1.50 ± 1.71	−2.72 ± 1.58	−4.64 ± 1.32	−7.57 ± 1.42	−8.77 ± 1.59
	p2	-	0.362	0.272	0.068	**0.013**	**0.009**
CRT	**Control (sec)**	11.17 ± 0.29	10.68 ± 0.23*	10.57 ± 0.27*	10.26 ± 0.20***	10.01 ± 0.20***	9.74 ± 0.16***
	Jintiange (sec)	11.47 ± 0.29	10.73 ± 0.23***	10.34 ± 0.27***	9.63 ± 0.21***	9.19 ± 0.21***	8.57 ± 0.17***
	p3	0.466	0.873	0.549	**0.030**	**0.005**	**<0.001**
	Control (%)	-	−2.22 ± 1.48	−2.99 ± 2.08	−5.39 ± 1.55	−7.29 ± 1.84	−8.99 ± 1.48
	Jintiange (%)	-	−3.24 ± 1.52	−6.15 ± 2.14	−12.05 ± 1.58	−15.78 ± 1.89	−21.93 ± 1.51
	p4	-	0.632	0.290	**0.003**	**0.001**	**<0.001**
TGT	**Control (correct steps)**	7.40 ± 0.11	7.58 ± 0.10*	7.56 ± 0.09	7.75 ± 0.07***	7.79 ± 0.07***	7.69 ± 0.08**
	Jintiange (correct steps)	7.21 ± 0.12	7.26 ± 0.10	7.60 ± 0.09***	7.60 ± 0.07***	7.62 ± 0.07***	7.60 ± 0.08***
	p5	0.251	**0.026**	0.759	0.112	0.083	0.427
	Control (%)	-	+4.67 ± 1.87	+5.76 ± 4.07	+10.58 ± 4.40	+10.90 ± 4.60	+9.56 ± 4.35
	Jintiange (%)	-	+4.17 ± 1.90	+14.08 ± 4.12	+14.74 ± 4.45	+16.45 ± 4.66	+15.34 ± 4.41
	p6	-	0.850	0.152	0.506	0.397	0.351

Data was depicted as estimated value ± standard error (SE). Icons of "*", "**" and "***" stand for $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively, when data of post treatment compared with that at baseline within each group. P1~p6 are p values between the control and Jintiange groups at each visit. Abbreviations: PPS, per-protocol set; sec, seconds; W, week; TUG, timed up and go test; CRT, chair rising test; TGT, tandem gait test.

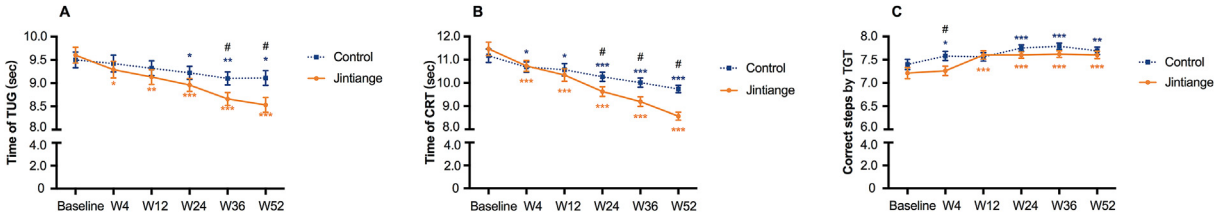

Fig. 2. Results of muscle strength and balance according to the TUG, CRT and TGT evaluations for the two groups (PPS). (A) TUG times of the control and Jintiange groups. (B) CRT times of the two groups. (C) The number of correct steps in the TGT for the two groups. Blue solid squares and orange solid circles represent the control and Jintiange groups, respectively. All data are depicted as the estimated value ± standard error. "*", "**" and "***" represent $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively, for posttreatment data compared with baseline data within each group. Blue and orange icons correspond to the control and Jintiange groups, respectively. #: significant difference between the control the test groups at each visit, $p < 0.05$. Abbreviations: PPS, per-protocol set; W, week; TUG, timed up and go test; CRT, chair rising test; TGT, tandem gait test.

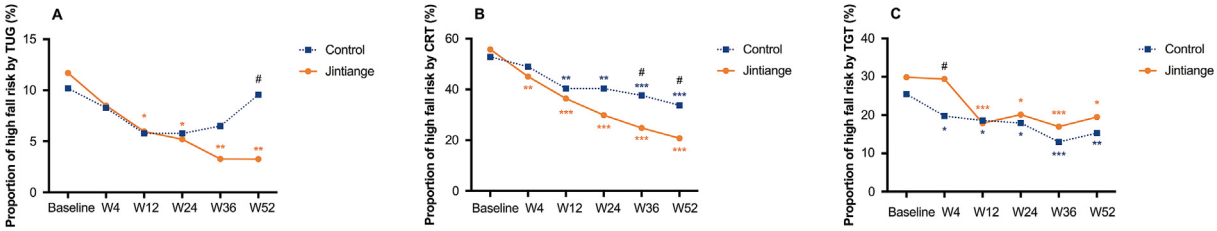

Fig. 3. Proportions of high fall risk according to the TUG, CRT and TGT evaluations for the two groups (PPS). (A) Proportion of high fall risk according to the TUG. (B) Proportion of high fall risk according to the CRT. (C) Proportion of high fall risk according to the TGT. Blue solid squares and orange solid circles represent the control and Jintiange groups, respectively. "*", "**" and "***" represent $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively, for posttreatment data compared with baseline data within each group. Blue and orange icons correspond to significant differences in the control and Jintiange groups, respectively. #: significant difference between the control and Jintiange groups at each visit, $p < 0.05$. Abbreviations: PPS, per-protocol set; W, week; TUG, timed up and go test; CRT, chair rising test; TGT, tandem gait test.

number of correct steps at week 52 increased significantly in both the control (7.40 ± 0.11 vs. 7.69 ± 0.08, $p < 0.01$) and Jintiange groups (7.21 ± 0.12 vs. 7.60 ± 0.08, $p < 0.001$), with increases of 9.56 ± 4.35% in the control group and 15.34 ± 4.41% in the Jintiange group (Table 3 and Fig. 2C).

3.3. Comparison of fall risk before and after treatment

As shown in Fig. 3 and Table 4, the proportions of high fall risk evaluated by the TUG, CRT, and TGT in the two groups decreased with a similar trend. At baseline, the proportions of high fall risk according to the TUG, CRT, and TGT were comparable between the two groups. At the last visit, the percentages of high fall risk were significantly lower in the Jintiange group than those in the control group according to the TUG (3.25% vs. 9.55%, $p = 0.023$) and CRT (20.78% vs. 33.76%, $p = 0.010$), but no significant difference between the two groups according to the TGT. In the Jintiange group, the high fall risk proportions declined obviously from week 4 according to the CRT and from week 12 according

Table 4
Proportions of high fall risk between two groups pre and post treatment evaluated by TUG, CRT and TGT (PPS).

		Baseline (%, n/N)	W4 (%, n/N)	W12 (%, n/N)	W24 (%, n/N)	W36 (%, n/N)	W52 (%, n/N)
TUG	**Control**	10.19% (16/157)	8.28% (13/157)	5.77% (9/156)	5.77% (9/156)	6.49% (10/154)	9.55% (15/157)
	Jintiange	11.69% (18/154)	8.50% (13/153)	5.96% (9/151)*	5.19% (8/154)*	3.27% (5/153)**	3.25% (5/154)**
	p1	0.672	0.945	0.943	0.824	0.190	**0.023**
CRT	**Control**	52.87% (83/157)	49.04% (69/153)	40.38% (63/156)**	40.38% (63/156)**	37.66% (58/154)***	33.76% (53/157)***
	Jintiange	55.84% (86/154)	45.10% (69/153)**	36.42% (53/151)***	29.87% (46/154)***	24.84% (38/153)***	20.78% (32/154)***
	p2	0.598	0.486	0.476	0.053	**0.015**	**0.010**
TGT	**Control**	25.48% (40/157)	19.75% (31/157)*	18.59% (29/156)*	17.95% (28/156)*	12.99% (20/154)***	15.29% (24/157)**
	Jintiange	29.87% (46/154)	29.41% (45/153)	17.88% (27/151)***	20.13% (31/154)*	16.99% (26/153)***	19.48% (30/154)*
	p3	0.387	**0.048**	0.872	0.625	0.325	0.329

Icons of "*", "**" and "***" stand for $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively, when data of post treatment compared with that at baseline within each group. P1, p2, and p3 are p values between the control and Jintiange groups by TUG, CRT and TGT, respectively. Abbreviations: PPS, per-protocol set; TUG, timed up and go test; CRT, chair rising test; TGT, tandem gait test.

to the TUG and TGT. From baseline to week 52, the high fall risk proportions in the Jintiange group decreased to the lowest according to the TUG (11.69% vs. 3.25%, $p < 0.01$) and CRT (55.84% vs. 20.78%, $p < 0.001$), and the proportions also decreased from 29.87% to 19.48% according to the TGT ($p < 0.05$). In the control group, the high fall risk proportions decreased significantly at week 52 according to the CRT (52.87% vs. 33.76%, $p < 0.001$) and TGT (25.48% vs. 15.29%, $p < 0.01$), while there was no significant change according to the TUG (10.19% vs. 9.55%, $p = 0.819$).

3.4. Falls and new fractures

The falls and new fractures during the entire study were analyzed in the FAS dataset. In the Jintiange group, 17 participants (8.81%) had 1.5 ± 0.9 falls, and 18 participants (9.47%) had 1.2 ± 0.4 falls in the control group. There were two cases of new fractures (1.04%) in the control group and two cases (1.05%) in the Jintiange group. No significant differences were found for the percentages of either falls or new fractures between the two groups.

3.5. The relationships between TUG/CRT/TGT and BMD

As the bivariate analysis showed (Supplementary Table 1), there were no significant correlations between BMDs at different sites or the results of the three tests for the evaluation of muscle strength at baseline, except for a weak but significant correlation between TH BMD and TUG time ($r = -0.174$, $p = 0.035$) and the number of correct steps in the TGT ($r = 0.168$, $p = 0.041$) in the control group and a positive correlation between BMD at L1-L4 and TUG time ($r = 0.168$, $p = 0.037$) in the Jintiange group. Similar results were found at week 52, where only BMD at L1-L4 weakly correlated with CRT time ($r = 0.219$, $p = 0.006$), and the correct steps positively correlated with BMD at the FN ($r = 0.160$, $p = 0.046$) and TH ($r = 0.222$, $p = 0.007$) in the control group. In addition, there were no relationships between the BMD changes and the changes in the TUG, CRT, or TGT from baseline to week 52 in the two groups.

3.6. Factors influencing muscle strength evaluated by the TUG, CRT, and TGT

As multiple regression analysis showed (supplementary Table 2), under most circumstances, age was associated with the TUG/CRT/TGT results (absolute values of $\beta = 0.037$–0.142, all p values < 0.01). Fracture history was associated with the TUG time in the Jintiange group at week 52 ($\beta = -1.019$, $p = 0.007$) and the CRT time in the control group at baseline ($\beta = -1.341$, $p = 0.014$). New falls had a significantly negative association with the number of correct steps in the TGT in the Jintiange group at baseline ($\beta = -7.799$, $p < 0.001$) and week 52 ($\beta = -8.188$, $p < 0.001$). The T25OHD level at baseline was positively associated with the number of correct steps in the TGT in the control group at baseline ($\beta = 0.014$, $p = 0.041$). Regarding the changes in the TUG, CRT, and TGT from baseline to week 52, the change in CRT time was positively associated with fracture history ($\beta = 1.106$, $p = 0.021$), and the change in the number of correct steps in TGT was negatively associated with the T25OHD level at baseline ($\beta = -0.013$, $p = 0.041$) in the control group, but there were no associations between these changes and the independent variables in the Jintiange group.

4. Discussion

Sarcopenia and falls are the main causes of osteoporotic fractures; thus, fall prevention helps reduce the risk of fractures [24–26]. Currently, the pharmacies that can effectively treat sarcopenia and improve balance and muscle strength are very limited. This clinical trial first demonstrates that artificial tiger bone powder, a CPM, combined with alfacalcidol can effectively improve muscle strength and balance as evaluated by the TUG, CRT and TGT in patients with primary osteoporosis/osteopenia and is superior to calcium combined with alfacalcidol. Artificial tiger bone powder may be a new adjuvant drug to treat sarcopenia and ameliorate losses of muscle strength and balance.

At present, vitamin D agents are one of the main drugs considered for preventing falls, improving muscle strength/balance and treating sarcopenia. The results of a meta-analysis suggest that vitamin D supplementation has a mild but significantly positive effect on global muscle strength [27]. However, the effect of vitamin D on muscle strength and balance in patients with osteoporosis remains controversial due to the high heterogeneity in terms of participants' characteristics and different assessments of muscle strength and balance across studies [28]. A meta-analysis indicates that vitamin D supplementation can decrease only 5% of falls in older women overall (risk ratio, $RR = 0.948$, $p = 0.004$); however, compared with vitamin D combined with calcium, vitamin D alone cannot reduce fall incidence ($RR = 0.994$, $p = 0.73$) or fracture rates ($RR = 0.949$, $p = 0.37$) [29]. Suzuki et al. reported that eldecalcitol alone can improve postural balance in older women with osteoporosis [30], while other studies indicated that eldecalcitol plus a bisphosphonate can improve the muscle strength of the back extensor and iliopsoas, dynamic sitting balance, and the TUG and CRT results of postmenopausal osteoporotic women compared with bisphosphonate only [31,32]. Alfacalcidol can increase muscle power, muscle function and balance in patients with osteoporosis or osteopenia [33]. For other anti-osteoporotic drugs, only denosumab has been recently reported to significantly improve appendicular lean mass and handgrip strength in postmenopausal women with osteoporosis after a mean treatment duration of 3 years [34].

In this study, muscle strength and balance of the lower extremities were significantly improved in both groups, which further confirms the positive effect of alfacalcidol on muscle strength and balance in osteoporosis patients. However, the improvement in the Jintiange group was more obvious than that of in the control group with calcium, suggesting

that Jintiange also has a certain effect on ameliorating muscle strength and balance in patients with osteoporosis/osteopenia. There are two potential mechanism by which Jintiange improves muscle strength and balance in osteoporosis patients. On the one hand, artificial tiger bone powder has been observed to significantly increase the wet weight of the gastrocnemius muscle of ovariectomized rats after 12 weeks of treatment and suppress osteoclasts by downregulating the osteoprotegerin (OPG)/receptor activator for nuclear factor κB and its ligand (RANKL/RANK) signaling pathway [16]. Recently, in mice overexpressing RANKL, Bonnet et al. found that a RANKL inhibitor restored muscle function by increasing muscle volume, muscle force and the temperature of the limb by reducing the expression of anti-myogenic and inflammatory genes (myostatin and protein tyrosine phosphatase receptor-γ) in the muscle [34]. Therefore, it is hypothesized that the inhibition of the OPG/RANKL/RANK signaling pathway may be the mechanism by which Jintiange improves muscle strength and function. On the other hand, artificial tiger bone powder has anti-inflammation and pain relief functions [15]. Previous studies have shown that Jintiange can significantly decrease pain scores (visual analog score) of those with primary osteoporosis with or without vertebral compressive fractures [35–37]. Similar to the results of these studies, our clinical trial also found that the pain score decreased after week 4 in the two groups, and the pain score in the Jintiange group was significantly lower than that in the control group after week 36 [19]. It is concluded that with pain relief, patients may be more willing to exercise, and proper physical exercise has been proven beneficial for muscle strength and balance in osteoporosis patients [11,38,39]. Further studies should be performed to confirm the mechanism by which Jintiange improves muscle strength and balance in osteoporosis patients.

Previous studies have shown that these three functional assessments for muscle strength and balance (the TUG, CRT and TGT) were useful evaluations of the risk of falls [22,23,33]. This study demonstrated that the percentage of high fall risk patients decreased in both groups after treatment, especially in the Jintiange group. However, there were no significant differences in the actual new falls or fractures between the two groups in our study, possibly due to the limited sample size and time of follow-up leading to the low number of events. Although only approximately 5% of all falls cause fractures, more than 90% of hip fractures result from falls [40,41]. Falls and fractures are inseparable. In osteoporosis patients aged 50 years or older, it has been reported that a history of falls predicts an increased risk of fracture within the next 12 months (odds ratio, OR = 6.67, $p < 0.0001$) and 24 months (OR = 4.43, $p < 0.0001$) [42]. A Canadian multicenter osteoporosis study showed that the number of falls in the past 12 months was an independent predictor of 2-year low-trauma nonvertebral fractures (≥2 falls: hazard ratio, HR = 1.9, $p = 0.001$; 1 falls: HR = 1.5, $p = 0.014$) among women with osteoporosis aged 65 years or older [43]. Therefore, a larger sample and longer follow-up time are needed for future studies to observe the potential efficacy of Jintiange on fall and fracture risks.

Several studies have shown that muscle strength, appendicular skeletal muscle mass, leg press strength, and short physical performance battery score are significantly positive correlated with BMD at the TH or the FN among those with sarcopenia and older adults [44–47]. However, the bivariate analysis of our study indicated only weak correlations between BMD and some of the TUG/CRT/TGT markers in the two groups. The disparities from previous studies may be due to the differences in the markers used to evaluate muscle strength (eg., the TUG/CRT/TGT used in the present study are alternative indicators), characteristics of subjects, interventions, duration, etc. Age and sex have been reported to be two vital determinants of muscle strength [48]. Similar to previous studies, we also found age to be significantly associated with most of the TUG/CRT/TGT results in both groups. As expected, fracture history was correlated with the TUG time at week 52 in the Jintiange group, which indicates that fracture history is still an influential factor in muscle strength and balance even after intervention. Similar results have been reported in women with osteoporosis and a history of vertebral fracture, among whom multicomponent resistance and balance exercise can improve muscle strength and balance to some extent, but not the TUG test [49]. Interestingly, the number of correct steps in the TGT were significantly related to new falls in the Jintiange group both at baseline and week 52, suggesting that Jintiange might decrease new falls at least partially by improving the balance of the lower extremities reflected by the TGT. Larger, longer prospective studies with more comprehensive markers to evaluate muscle strength and balance are needed to determine the factors influencing Jintiange efficacy.

There are limitations in this study. First, this study did not measure or analyze body composition, particularly muscle mass and the muscle-to-body weight ratio, which play an important role in muscle strength and balance. In addition, the muscle strength of the core body area was not evaluated. Second, a high fall risk may indicate a high fracture risk; however, fall risk is not equal to fracture risk, and because of the short follow-up time and the limited sample size of this study, cases of new fractures in the two groups are too few to calculate the hazard ratio. Thus, determining whether artificial tiger bone powder combined with alfacalcidol therapy reduces the incidence of new fractures and falls requires further study. Finally, both groups received alfacalcidol, so the effect of Jintiange could not be observed independently.

In conclusion, compared with the combined calcium carbonate and alfacalcidol treatment, the combined artificial tiger bone powder and alfacalcidol therapy effectively ameliorates the balance and muscle strength of the lower extremities and reduces the fall risk in patients with primary osteoporosis/osteopenia. Combined with previous clinical studies of BMD improvement by Jintiange alone or combined with other drugs, it is inferred that Jintiange may have broader benefits for patients with low bone mass. Prospective studies with longer follow-up and larger samples are needed in the future.

Author contributions

All authors made substantial contributions. Authorship was listed as follow: Conception and design of the study: WB Xia. Acquisition of data: O Wang, ZF Cheng, PJ Xia, L Wang, J Shen, XJ Kong, YH Zeng, AJ Chao, LM Yan, H Lin, HB Sun, Q Cheng, M Zhu, ZM Hu, ZL Zhang, H Tang, WB Xia. Analysis and/or interpretation of data: HT Liang, O Wang. Drafting the manuscript: HT Liang, O Wang. Revising the manuscript critically for important intellectual content: O Wang, WB Xia. Approval of the version of the manuscript to be published (the names of all authors listed as follow): HT Liang, O Wang, ZF Cheng, PJ Xia, L Wang, J Shen, XJ Kong, YH Zeng, AJ Chao, LM Yan, H Lin, HB Sun, Q Cheng, M Zhu, ZM Hu, ZL Zhang, H Tang, WB Xia.

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Data availability

The raw datasets generated and/or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Ethics approval

The trial was performed with the approval of Peking Union Medical Hospital Ethics Committee (HS-1047).

Consent to participate

All of the subjects agreed to participate in this study and signed informed consent forms.

Registration number

The registration number of this study is ChiCTR-IPR-16008533.

Declaration of competing interest

The authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2022.05.002.

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