CLINICAL ARTICLE

Fall Prevention and Anti-Osteoporosis in Osteopenia Patients of 80 Years of Age and Older: A Randomized Controlled Study

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Objective
To evaluate the effects of two fall-prevention and anti-osteoporotic protocols in elderly patients with osteopenia (OPA).

Methods: The present randomized controlled study included patients with OPA (n =123). The age of these patients was ≥80 years old, with the mean age of 83.54 ± 2.99 years, and the male-to-female ratio was 2.97:1.00. Fall-prevention guidance was given to all patients. Patients in the experiment group (n = 62) orally received 600 mg/d of calcium carbonate, 0.5 μg/d of alfacalcidol, and 70 mg/week of alendronate, while patients in the control group (n = 61) orally received 600 mg/d of calcium carbonate and 0.5 μg/d of alfacalcidol for 18 months. The grip strength, gait speed, bone turnover markers, serum calcium, serum phosphorus, parathyroid hormone (PTH), and bone mineral density were measured, and the Timed Up and Go (TUG) test and the chair rising test (CRT) were performed. Falls, fragility fractures, medication compliance, and side effects of the drugs were recorded.

Results: The serum levels of bone turnover markers (type I procollagen amino-terminal peptide [P1NP], type I collagen carboxyl terminal peptide [β-CTx], and osteocalcin [OC]) decreased, while the bone mineral density of the lumbar spine and bilateral femoral neck increased after treatment in the experiment group ($P < 0.05$, $P < 0.01$). The rate of change in bone mineral density of the bilateral femoral neck was higher in the experiment group than the control group (3.43% vs 0.03%, $P < 0.05$; 2.86% vs −0.02%, $P < 0.01$). After treatment, the proportion of patients with increased hip T scores in the experiment group (66.1%, 41/62) was significantly higher than the proportion (35.0%, 21/60) in the control group ($P = 0.001$). The incidence of fall decreased in both groups after treatment compared to that before treatment (54.8% vs 33.9% and 54.1% vs 36.7%, respectively; $P < 0.05$). The incidence of fragility fractures was lower in the experiment group than the control group (8.1% vs 20.0%, $P = 0.057$). During the intervention period, the incidence of fragility fractures in patients who did not fall (3.8%, 3/79) was significantly lower than that in patients who fell (32.6%, 14/43) ($P = 0.000$). The risk of fragility fractures was significantly lower in patients who did not fall compared to patients who fell (relative risk: 0.117, 95% confidence interval: 0.035–0.384).

Conclusion: The combination of alendronate sodium with alfacalcidol and calcium can significantly improve the bone mineral density of the lumbar spine and femoral neck. For older patients with OPA, subjectively paying attention to avoiding falls can significantly reduce the risk of fragility fractures.

Orthopaedic Surgery

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ELDERLY PATIENTS WITH OSTEOPENIA

Introduction

Osteoporosis (OP) is a skeletal disease characterized by decreased bone strength and increased risk of fracture. The term bone strength includes both bone mass and bone quality[1]. Fragility fractures refer to non-traumatic or minor traumatic fractures, which are not only clear manifestations of the decline in bone strength but also the final result of OP and its complications[2]. The spine, hip, and distal forearm are the most common sites of fragility fractures. Fragility fractures are an important cause of disability and shortened life span in the elderly, and bring a heavy economic burden to individuals and society.

China became an aging society in 2000 and by the end of 2015, the number of people over the age of 80 years old had reached 23.39 mn[3]. In 2006, there were nearly 70 mn patients with OP in China, and more than 200 mn patients suffered from osteopenia (OPA)[2]. It is estimated that by 2050, the number of patients with fragility fractures caused by OPA in China will reach 5.99 mn each year, and the corresponding medical expenditure will reach US$25.43bn[4]. OPA is a stage in the middle zone of fracture risk, according to the linear association between bone mineral density and high fracture risk. The absolute number of fractures in people with OPA is greater, However, it could easily be neglected in clinical prevention and treatment[5]. In a previous cross-sectional study of the investigators, it was found that 47.7% of fragility fractures in people over 80 years old occurred in the OP group, while 40.9% of fragility fractures occurred in the OPA group. The risk factors for fragility fractures include falls and reduced lumbar bone density, but the application of anti-OP drugs is limited to patients with fragility fractures or osteoporosis[6]. If treatment is only applied for patients with OP, many individuals who could benefit from measures to reduce the risk of fracture would be omitted.

The Guidelines for Diagnosis and Treatment of Primary OP (2017) issued by the Chinese Medical Association (CMA) recommend anti-osteoporotic drugs for patients with OPA who have met one of the following criteria: patients with previous fragility fractures in certain areas (upper humerus, distal forearm, or pelvis); and patients with probability of hip fracture in the next 10 years, as calculated by the Fracture Resistance Assessment Tool (FRAX), with a value of ≥3% or a probability of any of the major osteoporotic fractures of ≥20%[2].

Falls are an independent risk factor for fragility fractures in the elderly. Studies have demonstrated that 40%–50% of elderly people who are over 80 years old and live in the community fall at least once a year on average[7], and 87% of fractures in the elderly are correlated to falls[8]. However, falls are not included in the calculation of risk evaluation in the FRAX tool, which may underestimate the risk of fracture in the elderly population, thereby resulting in failure to obtain timely intervention. Meanwhile, the FRAX tool predicts the risk of fragility fractures in the next 10 years, which has relatively little practical significance for people over 80 years of age.

The focus of prevention of fragility fractures has shifted from anti-OP treatment alone to a combination treatment including fall prevention, with the importance of the latter receiving increasing attention[9]. Elderly people may have vitamin D-related risks, including nutritional deficiencies and reduced production of active vitamin D, as well as concurrent risks, including sarcopenia, weakness, and increased risk of falls. The China Association of Gerontology and Geriatrics (CAGG) recommends in the "2018 Chinese guideline for the diagnosis and treatment of senile osteoporosis" that administering active vitamin D or its analogues to elderly patients with OP can increase their muscle strength and balance, and reduce the risk of falls and osteoporotic fractures. Active vitamin D or its analogues can be combined with anti-OP drugs.

Bisphosphonates can effectively increase bone density and reduce the risk of fragility fractures, and are the drug of choice for elderly OP patients without contraindications[10]. At present, there are few interventions for the elderly and the OPA population in China and foreign countries, and the rates of timely diagnosis and effective treatment are low[11,12].

In this study, we concentrate on fall prevention interventions and anti-osteoporotic drugs for elderly OPA patients. In terms of new falls, fragility fractures and changes in bone mineral density, we compare the efficacy of the two combination therapies that include active vitamin D and calcium, with or without alendronate. At the same time, we observe patients' compliance and drug side effects, and explore coping methods. Then, we investigate patients with OPA who are living on their own and are ≥80 years old, and the application of interventions for fall prevention and anti-osteoporotic drugs. By observing the benefits and risks, the safe and effective ways to guarantee bone health, prolong independent living, maintain quality of life, and relieve the burden on society and family are explored.

Materials and Methods

Inclusion and Exclusion Criteria

From January 2017 to June 2017, 123 consecutive candidates were enrolled in the Outpatient Department of Geriatrics in our hospital. The mean age of these candidates was 83.54 ± 2.99 years (range, 80–93 years). Among these candidates, 92 candidates were male (74.8%) and 31 candidates were female (25.2%).

The inclusion criteria were: (i) patients who were ≥80 years old, patients with OPA who lived on their own, and patients who agreed to participate in the present study.

The exclusion criteria were as follows: patients with hyperthyroidism or hypothyroidism, patients with primary hyperparathyroidism or hypoparathyroidism, patients with Cushing's disease, patients with malignant tumors, patients with stage 4–5 chronic kidney disease (CKD), patients with cirrhosis, patients with grade 4 chronic obstructive pulmonary disease (COPD), patients who underwent subtotal gastrectomy, patients with chronic diarrhea, patients who received glucocorticoids or anti-osteoporotic drugs in the past 6 months, and patients with a history of fragility fracture.

Methods

A single-center, randomized, controlled, non-blind trial design was adopted. Based on previous sample size estimates, at least 114 candidates should be included, a total of 123 patients were included in this study. These patients were assigned into two groups, according to the randomized number table. One tablet per day of calcium D600 (Wyeth-Baigong Pharmaceutical, USA; containing 1.5 g of calcium carbonate, and providing 600 mg of elemental calcium and 125 IU of vitamin D3), 0.5 µg/d of alfacalcidol (TEVA Pharmaceutical Factory of Israel, separate loading by Kunming Becknorton), and 70 mg/week of alendronate (Merceton) were orally administered in patients in the experiment group, while one tablet per day of calcium D600 and 0.5 µg/d of alfacalcidol were orally administered in patients in the control group. Patients who had been previously taking calcium, vitamin D, active vitamin D, or its analogues stopped taking these drugs. Fall prevention education and guidance were given to all patients, and a follow-up was performed monthly for 18 months.

Ten mL of elbow venous blood was collected from the patients at 8.00–10.00 hours in fasting status, and the blood was immediately sent for analysis of hepatic and renal function (BUN, Cr, ALB, AST and ALT), serum electrolytes (K^+, Na^+, Cl_-, Ca^{2+}, Mg^{2+}, and inorganic phosphorus), and full-length parathyroid hormone (PTH) using a Beckman CX4CE automatic biochemical analyzer (USA). Type I procollagen amino-terminal peptide (PINP), type I collagen carboxy-terminal peptide (β-CTx), osteocalcin (OC), and 25-hydroxyvitamin D (25OHD) were detected using a Roche 601 immunoluminescence analyzer and the electrochemiluminescence method. The kit was produced by Roche Diagnostic (Germany). The plasma calcium level was the detected calcium value adjusted according to the albumin level, based on the following equation: plasma calcium (mmol/L) = the detected plasma calcium (mmol/L) + [0.8– 0.02 × albumin level (g/L)]. The eGFR was calculated using the MDRD formula.

A Lunar Prodigy dual energy X-ray bone mineral density (DXA) instrument (General Electric Medical Systems) was used by a specially trained technician to measure the bone mineral density and T-score of lumbar spine 1–4, the bilateral femoral neck, and the total hip. According to the World Health Organization (WHO) diagnostic criteria, the lowest T-value was used for diagnosis: normal bone mass was diagnosed when T ≥ −1, OPA was considered when −2.5 < T < −1, and OP was diagnosed when T ≤ −2.5[1]. The X-ray lateral plain film of the thoracolumbar spine was obtained in patients with obvious low back pain or a height decrease of >4 cm compared with their height at a younger age. X-ray lateral plain films of the thoracolumbar spine were obtained for 54.5% (67/123) of the patients recruited in this study.

Hepatic and renal function, serum calcium, serum phosphorus, and 24-h urine calcium quantification were assayed again at the 3rd, 9th, and 18th month during the therapy. Serum PTH, osteocalcin (OC), P1NP, β-CTx and 25OHD, muscle strength, gait speed, balancing function, and bone mineral density were re-evaluated after 18 months during the treatment period. The X-ray lateral plain film of the thoracolumbar spine was obtained from patients with obvious low back pain or shortened stature. During the observation period, 59.3% (73/123) of patients experienced new-onset falls, low back pain, or height loss, and all of them had the thoracolumbar spine X-rays in time.

The study protocol was approved by the Medicine Ethics Committee of Beijing Tongren Hospital, Capital Medical University, and was conducted in accordance with the Declaration of Helsinki.

Parameters

Body Mass Index
Body mass index (BMI) is a person's weight (kg) divided by the square of height (m). A BMI between 18.5 and 25 kg/m^2 indicates a normal weight. A person with a BMI of less than 18.5 kg/m^2 is considered underweight. A person with a BMI between 25 kg/m^2 and 29.9 kg/m^2 is considered overweight. A person with a BMI of 30 kg/m^2 or higher is considered obese.

PINP
PINP is an N-terminal product digested by type I procollagen during bone formation that eventually enters the blood. As a marker of bone transformation, PINP can be used to assess fracture risk and monitor OP efficacy. The reference range is 22–322 ng/mL.

β-CTx
β-CTx is the only collagen in bone tissue, accounting for more than 90% of the bone matrix. The level of β-CTx in serum is a specific index reflecting the activity and bone formation of osteoblasts and the rate of type I collagen synthesis. It can be absorbed by the liver and cleared by binding to mannose receptors on epithelial cells, so it is impacted by liver function. The reference range is <0.854 ng/mL.

Osteocalcin
Osteocalcin is a non-collagenic acid glycoprotein and is a vitamin K-dependent calcium-binding protein. OC levels are

used to monitor bone development and bone metabolism, and their levels are inversely related to age. OC detection can directly reflect osteoblast activity and bone formation. The reference range is 24–70 ng/mL.

25-Hydroxyvitamin D
25-hydroxyvitamin D (25OHD) is the main storage form of vitamin D in the human body. The overall vitamin D status can be determined by detecting 25OHD. The clinical application of 25OHD is mainly related to the diagnosis, treatment and monitoring of rickets (children), osteomalacia, postmenopausal OP, and renal osteopathy. The reference range is 20–100 ng/mL.

Serum Calcium
Serum calcium is related to many important functions of the human body and plays an important role in regulating calcium and phosphorus metabolism. Under the regulation and control of various factors in the body, the blood calcium concentration is relatively stable. The reference range is 2.25–2.75 mmol/L.

Basic Activities of Daily Living Assessment Scale (Barthel Index)
A specially trained nurse was assigned to assess the daily living ability of patients, in which >75 points was basically considered as self-care.

Muscle Strength
Muscle strength was assessed by grip strength measurement: the Jamar grip exerciser (Sammons Preston, USA) was used to measure the grip strength, and a grip strength of <30 kg in males and <20 kg in females was considered decreased muscle strength.

Usual Gait Speed
Muscle function was assessed by usual gait speed: The 6-m distance gait test with a gait speed of <0.8 m/s was considered decreased walking ability.

Timed Up and Go Test
The Timed Up and Go (TUG) test was used in the evaluation: Patients were instructed to stand up from a seating position with an armrest at normal height (the seat was approximately 48 cm in height and the armrest was approximately 68 cm in height), to walk at a normal walking speed for 3 m, return to their seat, and sit down again. Then, the time was recorded. A TUG score of >12 s reflected high risk of fall.

Chair Rising Test
The chair rising test (CRT) was also performed: Patients were instructed to stand and sit down five times from a chair of normal height (approximately 48 cm high), and the time was recorded. A CRT score of >10 s or <5 times was regarded as high risk of fall.

Bone Mineral Density
Bone density refers to the bone mass contained per unit volume (bulk density) or unit area (area density). The DXA method was used to measure the central axis bone (lumbar 1–4, femoral neck, and total hip). The decrease in bone mass was $-2.5 < T < -1$.

Statistical Analysis
The SPSS 19.0 software package was used for data analysis. The measurement data was first determined using the normality test. Normally distributed data was presented as mean ± standard deviation, and data after log transformation was presented as the mean with 95% confidence interval. The independent samples t-test was used to compare the means between these two groups, and a paired t-test was used to compare the self-comparison before and after treatment. Non-normally distributed data was presented as median (quartile), and the nonparametric test was used. Counting data was expressed in percentage, and the χ^2-test was used for comparisons between groups. $P < 0.05$ was considered statistically significant.

Results

General Data and Baseline Characteristics
There was no significant difference in mean age, gender ratio, BMI, ADL score, incidence of cerebrovascular disease, COPD 1–3, and CKD 3 between the two groups. The prevalence of coronary heart disease and type 2 diabetes mellitus was higher in the control group compared to the experiment group, and the difference was statistically significant ($P < 0.05$, Table 1).

Changes and Comparison of Laboratory Data before and after Treatment
There was no significant difference in serum calcium, eGFR, PTH, OC, and PINP between the two groups before treatment. The levels of inorganic phosphorus and 25OHD were higher in the experiment group compared to the control group, while the levels of β-CTx were lower compared to the control group. The difference was statistically significant ($P < 0.05$). There was no significant difference in serum calcium, inorganic phosphorus, PTH, and 25OHD levels between the two groups after treatment. The eGFR was higher in the experiment group compared to the control group, while OC, PINP, and β-CTx were lower in the experiment group compared to the control group. The difference was statistically significant ($P < 0.05$, $P < 0.01$).

In the experiment group, there was no significant difference in serum calcium, eGFR, PTH, and 25OHD levels before and after treatment, while the levels of serum inorganic phosphorus, OC, PINP, and β-CTx significantly decreased after treatment compared with those before treatment ($P < 0.01$). In the control group, there was no significant difference in serum inorganic phosphorus, eGFR, PINP, and β-CTx before and after treatment, while the levels of

TABLE 1 General data and baseline characteristics in the two groups

Item	Experiment group (n = 62)	Control group (n = 61)	P
Age (years)	83.16 ± 3.09	83.92 ± 2.85	0.161
Gender (M/F)	44/18	48/13	0.324
BMI (kg/m^2)	23.95 ± 2.93	24.20 ± 3.22	0.646
ADL (score)	100 (95,100)	100 (95,100)	0.385
Coronary heart disease (n [%])	22 (35.5)	34 (55.7)	0.024
Cerebral vascular disease (n [%])	19 (30.6)	21 (34.4)	0.654
Diabetes (n [%])	17 (27.4)	30 (49.2)	0.013
COPD (n [%])	7 (11.3)	5 (8.2)	0.563
CKD (n [%])	11 (17.7)	15 (24.6)	0.352

ADL, basic ADL assessment scale self-care ability score; BMI, body mass index; cerebrovascular disease, cerebral ischemia or old cerebral infarction history; CKD, grade 3 of chronic kidney disease; COPD, chronic obstructive pulmonary disease (grade 1–3).

serum calcium and 25OHD increased after treatment, and the levels of PTH and OC decreased compared to those before treatment. The difference was statistically significant ($P < 0.01$, $P < 0.05$; Table 2).

The PTH and β-CTx of the two groups of patients were in the normal range before and after the treatment. OC levels were generally lower than normal. The proportions of patients with OC < 24 ng/mL in the experiment group were 95.2% (59/62) and 100% (62/62) before and after treatment, respectively. For patients in the control group, the proportions were 91.8% (56/61) and 95% (57/60) before and after treatment, respectively, which is consistent with the characteristics of low bone turnover in elderly patients with reduced bone mass.

The proportions of patients with PINP <22 ng/mL in the experiment group were 17.7% (11/62) and 62.9% (39/62) before and after treatment, respectively; the difference was statistically significant ($P < 0.001$). For patients in the control group, the proportions were 9.8% (6/61) and 23.3% (14/60) before and after treatment; the difference was not statistically significant ($P = 0.074$). The difference in proportions between the two groups was not significant before treatment ($P = 0.204$), but the proportions of patients with PINP <22 ng/mL in the experiment group was significantly higher than in the control group after the treatment, suggesting that the alendronate in the experimental group inhibited osteoclast activity and further reduced bone turnover.

Before the treatment, the proportion of patients with vitamin D deficiency (25OHD <20 ng/mL) in the control group was significantly higher than that in the experimental group ($P = 0.048$); the difference was not significant after

TABLE 2 Comparison and changes in laboratory data between the two groups before and after treatment

Item	Treatment stage	Experiment group (mean ± SD, n = 62)	P[1]	Control group (mean ± SD, n = 61)	P[1]	Intergroup comparison P[2]
Blood calcium (mmol/L)	Before treatment	2.33 ± 0.10	0.896	2.31 ± 0.10	0.010	0.314
	After treatment	2.33 ± 0.10		2.35 ± 0.12		0.311
Inorganic phosphorus (mmol/L)	Before treatment	1.14 ± 0.17	0.003	1.08 ± 0.16	0.091	0.041
	After treatment	1.08 ± 0.14		1.04 ± 0.14		0.256
eGFR (mL/min)	Before treatment	77.78 ± 16.21	0.119	71.25 ± 21.86	0.519	0.064
	After treatment	81.46 ± 23.98		72.83 ± 19.44		0.034
PTH (pg/mL)	Before treatment	44.89 ± 23.68	0.072	45.48 ± 21.34	0.000	0.933
	After treatment	40.11 ± 19.81		35.36 ± 16.55		0.160
25OHD (ng/mL)	Before treatment	22.03 ± 10.04	0.354	17.95 ± 9.13	0.008	0.014
	After treatment	23.15 ± 9.23		20.79 ± 9.51		0.172
β-CTx (ng/mL)	Before treatment	0.23 ± 0.12	0.000	0.27 ± 0.13	0.612	0.039
	After treatment	0.12 ± 0.06		0.26 ± 0.16		0.000
OC (ng/mL)	Before treatment	13.38(9.91–15.40)	0.000	12.20(10.27–16.54)	0.015	0.625
	After treatment	8.96(7.19–10.03)		11.20(9.42–15.20)		0.000
P1NP (ng/mL)	Before treatment	33.12 ± 12.81	0.000	34.66 ± 11.69	0.695	0.668
	After treatment	21.31 ± 8.65		33.58 ± 24.18		0.000

β-CTx, type I collagen cross-linked C-terminal telopeptide; eGFR, estimated glomerular filtration rate; OC, osteocalcin; PTH, parathyroid hormone; P1NP, type I pre collagen amino terminal peptide; 25(OH)D, 25 hydroxy vitamin D.; P[1], t-test P-value of comparison on indexes between before and after treatment.; P[2], t-test P-value of comparison on indexes between experiment and control groups in the same treatment stage (before or after treatment).

treatment. The proportion of patients with different vitamin D levels before and after treatment in the two groups was not statistically different, and we did not provide vitamin D3 to patients in this study.

Changes and Comparison of Bone Mineral Density before and after the Treatment

The difference in L_{1-4}BMD was not statistically significant between the two groups before treatment. The bone mineral density value of the left femoral neck (LnBMD), the bone mineral density value of the right femoral neck (RnBMD), the bone mineral density value of the left total hip (LtBMD), and the bone mineral density value of the right total hip (RtBMD) were significantly lower in the experiment group compared to the control group, and the difference was statistically significant ($P < 0.01$). The difference in L_{1-4}BMD, LnBMD, LtBMD, and RtBMD was not statistically significant between the two groups after treatment, while RnBMD was lower in the experiment group compared to the control group ($P < 0.05$).

In the experiment group, L_{1-4}BMD, LnBMD and RnBMD were significantly higher after treatment compared to those before treatment, and the difference was statistically significant ($P < 0.01$). However, the difference in LtBMD and RtBMD was not statistically significant before and after treatment. Furthermore, there was no significant difference in bone mineral density at each site before and after treatment in the control group.

There was no significant difference in the rate of change in L_{1-4}BMD, LtBMD, and RtBMD between the two groups after treatment. The rate of change in LnBMD and RnBMD was higher in the experiment group compared to the control group ($P < 0.01$ and $P < 0.05$, respectively; Table 3).

In the experiment group, compared with before treatment, the patients with increased T score of lumbar spine 1–4 was 71.0% (44/62) after treatment, and the proportion of patients in the control group was 55% (33/60); the difference was of no significance ($P = 0.068$). In the experiment group, the percentage of patients with increased T score of the femoral neck was 58.1% (36/62) after treatment, and the proportion of patients in the control group was 35.0% (21/60); the difference was of significance ($P = 0.011$). The proportion of patients with increased hip T scores was 66.1% (41/62) after treatment in the experiment group, while the proportion was 35.0% (21/60) in the control group, the difference was significant ($P = 0.001$).

Comparison of Muscle Strength, Muscle Function, Balancing Function Fall, and Self-care Ability between the Two Groups

There was no significant difference in grip strength, gait speed, TUG, CRT, and the incidence of falls between the two groups before and after treatment.

After 18 months of intervention, there was no significant difference in grip strength and CRT between the experiment group and the control group. The gait speed was slower and the TUG was longer than that before treatment in both groups, and the difference was statistically significant ($P < 0.01$ and $P < 0.05$, respectively). The incidence of new onset falls in both groups was 35% (43/123), which was lower compared to that before treatment, and the difference was statistically significant ($P < 0.05$, Table 4).

There was no statistical difference in the ADL scores between the test group and the control group before treatment. After 18 months of intervention, the ADL scores of the two groups decreased, and the differences were statistically significant ($P < 0.01$, $P < 0.05$). The ADL score of the group after treatment was higher than that of the control group, and the difference was statistically significant ($P < 0.05$, Table 4).

There were no statistical differences in the ADL score, muscle strength, pace, TUG, and CRT distribution between the experimental group and the control group before and after the intervention (Table 5).

Comparison of the Incidence of Fragility Fractures between the Two Groups

During the 18-month treatment period, 21 fragility fractures occurred in 17 patients, in which 19.0% (4/21) were hip fractures, 47.6% (10/21) were vertebral fractures, 19.0% (4/21) were wrist fractures, and 14.3% (3/21) were fractures in other parts. One patient in the control group died of severe pneumonia at the 4th month after inclusion, and this patient was not included in the statistical analysis. The incidence of fragility fractures in the experiment group was 8.1% (5/62), which was lower than that in the control group (20.0% [12/60]) ($P = 0.057$), and the difference was close to statistical significance. Compared to the control group, the relative risk (RR) of fragility fractures in the experiment group was 0.403 (95% confidence interval [CI], 0.151–1.075), but there was no statistical significance.

Correlation between Fall and Fragility Fractures

The incidence of fragility fractures was 3.8% (3/79) in patients who did not fall during the intervention period, and this was significantly lower than that in patients who fell (32.6% [14/43]). The P-value was 0.000, and the difference was statistically significant. Furthermore, the risk of fragility fractures in patients who did not fall was significantly lower compared to that in patients who fell, and the RR was 0.117 (95% CI, 0.035–0.384).

Drug Compliance and Side Effects between the Two Groups

A total of 11 patients did not complete the drug therapy, among which 8 (12.9%) patients were from the control group. Among these patients, 5 patients stopped taking alendronate sodium for 5–9 months due to upper abdominal discomfort, 2 patients discontinued alendronate sodium for 3 months due to tooth extraction, and 1 patient suffered from poorly differentiated gastric cardia adenocarcinoma at the 18th month after inclusion. Furthermore, 3 (4.92%)

TABLE 3 Comparison and changes in bone mineral density between the two groups before and after treatment

Detection site	Treatment stage	Bone density (g/cm²)					Bone density change rate (%)		
		Experiment group (mean ± SD, n = 62)	$P^{[1]}$	Control group (mean ± SD, n = 61)	$P^{[1]}$	Intergroup $P^{[2]}$	Experiment group (n = 62)	Control group (n = 61)	$P^{[3]}$
L_{1-4}BMD (g/cm²)	Before treatment	1.129 ± 0.241	0.007	1.217 ± 0.237	0.060	0.054	—	—	—
	After treatment	1.178 ± 0.242		1.245 ± 0.268		0.154	5.07	2.30	0.174
LnBMD (g/cm²)	Before treatment	0.746 ± 0.054	0.000	0.793 ± 0.079	0.818	0.000	—	—	—
	After treatment	0.771 ± 0.063		0.791 ± 0.081		0.133	3.43	0.03	0.012
RnBMD (g/cm²)	Before treatment	0.746 ± 0.054	0.000	0.799 ± 0.085	0.540	0.000	—	—	—
	After treatment	0.767 ± 0.066		0.794 ± 0.072		0.031	2.86	−0.22	0.004
LtBMD (g/cm²)	Before treatment	0.822 ± 0.082	0.711	0.871 ± 0.104	0.857	0.004	—	—	—
	After treatment	0.810 ± 0.247		0.872 ± 0.104		0.082	−1.08	0.18	0.727
RtBMD (g/cm²)	Before treatment	0.823 ± 0.082	0.762	0.877 ± 0.098	0.853	0.002	—	—	—
	After treatment	0.815 ± 0.225		0.878 ± 0.094		0.050	−0.84	0.18	0.764

L_{1-4}BMD, Lumbar 1–4 bone mineral density; LnBMD, left femoral neck bone mineral density; LtBMD, left total hipbone density; RnBMD, right femoral neck bone mineral density; RtBMD, right total hipbone density.; $P^{[1]}$, t-test P-value of comparison on indexes between before and after treatment.; $P^{[2]}$, t-test P-value of comparison on indexes between experiment and control group in same treatment stage (before or after treatment).; $P^{[3]}$, t-test P-value of comparison on indexes between experiment and control after treatment.

TABLE 4 Comparison and changes in muscle strength, muscle function, balancing function fall, and self-care ability between the two groups before and after treatment

Item	Treatment stage	Experiment group (mean ± SD, n = 62)	$P^{[1]}$	Control group (mean ± SD, n = 61)	$P^{[1]}$	Intergroup comparison $P^{[2]}$
Grip strength (kg)	Before treatment	27.24 ± 8.61	0.494	28.89 ± 7.29	0.185	0.396
	After treatment	26.88 ± 8.33		27.85 ± 6.28		0.507
Gait speed (m/s)	Before treatment	0.97 ± 0.28	0.000	0.96 ± 0.24	0.001	0.584
	After treatment	0.85 ± 0.27		0.86 ± 0.27		0.879
TUG (s)	Before treatment	12.05 (9.57–15.15)	0.000	12.34 (9.73–15.99)	0.024	0.522
	After treatment	13.02 (11.15–17.52)		13.63 (10.51–16.32)		0.451
CRT (s)	Before treatment	14.11 (11.45–16.18)	0.322	14.88 (11.96–17.84)	0.469	0.393
	After treatment	13.56 (11.50–16.66)		14.74 (12.97–17.39)		0.551
Fall [n(%)]	Before treatment	34 (54.8)	0.026	33 (54.1)	0.035	0.934
	After treatment	21 (33.9)		22 (36.7)		0.747
ADL (score)	Before treatment	100 (95,100)	0.011	100 (95,100)	0.001	0.385
	After treatment	100 (90,100)		95 (90,100)		0.027

ADL, basic ADL assessment scale; self-care ability score; CRT, chair-rising test; Fall, falls have occurred in the past 18 months; TUG, Timed Up and Go test.; $P^{[1]}$, t-test P-value of comparison on indexes between before and after treatment.; $P^{[2]}$, t-test P-value of comparison on indexes between experiment and control groups in same treatment stage (before or after treatment).

subjects discontinued the administration of alfacalcidol and calcium carbonate due to severe constipation, death caused by severe pneumonia at the fourth month, and the manifestation of cardia adenocarcinoma at the 5th month after inclusion, respectively. In addition, hypercalcemia was detected in 4 patients (3.3%), among which 2 patients were from the experiment group and 2 patients were from the control group. A total of 10 patients had hypercalciuria (8.1%), among which 5 patients were from the experiment group and 5 patients were from the control group. After reducing the dosage of alfacalcidol to 0.25 μg/day, the calcium in the urine of these patients decreased to the normal range (Table 6).

Discussion

Pathogenesis and Treatment of Senile Osteoporosis
The etiology and pathogenesis of senile OP are multifaceted, including organ dysfunction caused by aging, reduction of bone turnover caused by endocrine factors, insufficient intake of vitamin D, insufficient skin synthesis and hydroxylation, oligomyosis, and the administration of multiple drugs

TABLE 5 Comparison and changes in self-care ability, muscle strength, muscle function, balancing function fall, and vitamin D levels between the two groups before and after treatment

Item	Experiment group (n = 62)		P-value (intra-group)	Control group (n = 61)		P-value (intra-group)	P-value (inter-group)	
	Before treatment	After treatment		Before treatment	After treatment		Before treatment	After treatment
ADL [n (%)]			0.316			0.063	0.242	0.085
Normal	37 (59.7)	33 (53.2)		30 (49.2)	20 (32.8)			
Mild	25 (40.3)	27 (43.6)		31 (50.8)	37 (60.7)			
Severe	0 (0.0)	2 (3.2)		0 (0.0)	3 (4.9)			
Died	0 (0.0)	0 (0.0)		0 (0.0)	1 (1.6)			
Muscle strength [n (%)]			0.857			0.399	0.649	0.263
Normal	31 (50.0)	30 (48.4)		28 (45.9)	23 (37.7)			
Decreased	31 (50.0)	32 (51.6)		33 (54.1)	37 (60.7)			
Uncompleted	0 (0.0)	0 (0.0)		0 (0.0)	1 (1.6)			
UGS [n (%)]			0.066			0.109	0.150	0.164
Normal	45 (72.6)	36 (58.1)		38 (62.3)	30 (49.2)			
Decreased	17 (27.4)	26 (41.9)		23 (37.7)	28 (45.9)			
Uncompleted	0 (0.0)	0 (0.0)		0 (0.0)	3 (4.9)			
TUG [n (%)]			0.363			0.090	0.782	0.367
Normal	30 (48.4)	24 (38.7)		28 (45.9)	21 (34.4)			
Decreased	32 (51.6)	37 (59.7)		33 (54.1)	36 (59.0)			
Uncompleted	0 (0.0)	1 (1.6)		0 (0.0)	4 (6.6)			
CRT [n (%)]			0.704			0.244	0.948	0.488
Normal	6 (9.7)	8 (12.9)		7 (11.5)	7 (11.5)			
Decreased	55 (88.7)	52 (83.9)		53 (86.9)	49 (80.3)			
Uncompleted	1 (1.6)	2 (3.2)		1 (1.6)	5 (8.2)			
25OHD [n (%)]			0.600			0.389	0.048	0.140
Sufficiency	13 (21.0)	13 (21.0)		7 (11.5)	9 (15.0)			
Insufficiency	22 (35.5)	27 (43.5)		14 (23.0)	19 (31.7)			
Deficiency	27 (43.5)	22 (35.5)		40 (65.6)	32 (53.3)			

Self-care ability: normal, ADL = 100; mild deficiency, ADL = 75–95, severe deficiency, ADL = 25–70; Muscle strength normal: grip strength test >30 kg for men, >20 kg for women; Muscle function normal: UGS > 0.8 m/s; TUG: normal: TUG < 12 s; CRT: normal < 10 s; Vitamin D levels: sufficiency, 25(OH)D > 30 ng/mL; insufficiency, 25(OH)D 20–30 ng/mL; deficiency, 25(OH)D < 20 ng/mL; P-value (intra-group), t-test P-value of comparison on indexes between before and after treatment; P-value (inter-group), t-test P-value of comparison on indexes between experiment and control group in same treatment stage (before or after treatment).
CRT, chair rising test; TUG, Timed Up and Go (TUG) test; UGS, usual gait speed.

in senile patients with concomitant diseases. In the present study, two anti-OP and fall prevention protocols were used to probe into the feasible of the treatment for elderly patients with OPA.

Multiple systematic reviews and meta-analyses have revealed that the combination of vitamin D with calcium could reduce the risk of hip, non-vertebral, and overall fractures, and the incidence of falls in the elderly population[8,11–14]. However, the systematic review and meta-analysis conducted by Bolland et al. suggested that vitamin D supplementation (excluding active vitamin D and its analogues) had no significant benefit in preventing fractures and falls, and increasing bone mineral density[15]. Active vitamin D and its analogues are active without the hydroxylation by renal 1α-hydroxylase. These are more suitable for the elderly and patients with impaired renal function, and are more advantageous than vitamin D in preventing bone loss, reducing falls, and reducing the incidence of fractures[16,17]. Alendronate can effectively improve lumbar vertebrae and femoral neck and total hip bone density, and reduce the risk

of fractures[18,19]. The National Osteoporosis Guideline Group (NOGG) indicated in the "Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men form the age of 50 years in the UK" that, considering the relatively low cost and broad antifracture spectrum, alendronate can be used as a first-line treatment for most patients[20].

Pharmacological Effects of Anti-osteoporotics

In the present study, calcium carbonate, alfacalcitol, and alendronate were used in the experiment group, and calcium carbonate and alfacalcitol were administered in patients in the control group. Active vitamin D and its analogues can increase intestinal calcium absorption, reduce secondary hyperparathyroidism, and inhibit bone resorption[21,22]. In the present study, blood calcium increased and PTH decreased in the control group after treatment, which was consistent with the above findings. However, among the bone turnover markers, only OC decreased ($P < 0.01$, $P < 0.05$). Furthermore, there was no significant difference in PINP and β-CTx

TABLE 6 Drug compliance and side effects between the two groups [n (%)]			
Reasons for discontinuation/reduction of drugs	Experiment group (n = 62)	Control group (n = 61)	Total (n = 123)
Upper abdominal discomfort	5 (8.06)	0 (0)	5 (4.01)
Tooth extraction	2 (3.22)	0 (0)	2 (1.63)
Severe pneumonia	0 (0)	1 (1.64)	1 (0.81)
Cardiac cancer	1 (1.61)	1 (1.64)	2 (1.63)
Severe constipation	0 (0)	1 (1.64)	1 (0.81)
Hypercalcemia	2 (3.22)	2 (3.28)	4 (3.25)
Hypercalciuria	5 (8.06)	5 (8.20)	10 (8.13)

before and after treatment. Bisphosphonates have high affinity with bone hydroxyapatite, which can specifically bind to the surface of bone with active bone remodeling, inhibit the function of osteoclast, and, thereby, inhibit bone resorption[23,24]. In elderly men and women, the activity of osteoblasts and osteoclasts decreases, and bone metabolism is in a low turnover state. The levels of OC, PINP, and β-CTx in the experiment group were significantly lower compared to those before treatment ($P < 0.01$), suggesting that as a bone resorption inhibitor, bisphosphonate can still effectively reduce bone turnover in the elderly. However, there was no significant difference in serum calcium and PTH before and after treatment, which was considered to be the combined effect of alendronate and alfacalcidol.

Some studies have revealed that alendronate can effectively improve the bone mineral density of the lumbar spine, femoral neck and total hip, and reduce the risk of vertebral, non-vertebral, and hip fractures[18,24,25]. Alfacalcidol may increase bone mineral density, improve muscle function and balancing ability, and reduce the risk of falls and the risk of vertebral and non-vertebral fractures in the elderly[10,17,21,22]. The bone mineral density of the lumbar spine and femoral neck in the experiment group was significantly higher compared to that before treatment ($P < 0.01$), and that in the control group was 2.3% higher than before treatment ($P = 0.06$). The bone mineral density of the bilateral femoral neck in the experiment group was higher compared to the control group ($P < 0.01$ and $P < 0.05$, respectively). This suggests that alfacalcidol and calcium might slightly increase the bone mineral density of the lumbar vertebral in elderly patients with OPA but have no effect on the bone mineral density of the hip. The combination of alendronate sodium with alfacalcidol and calcium can significantly improve the bone mineral density of the lumbar spine and femoral neck.

Fall Prevention in Fragility fractures

In a period of 18 months, the incidence of falls in both groups was significantly lower compared to that before treatment, but there was no significant difference between these two groups. Furthermore, 21 incidences of fragility fractures occurred in 17 patients. Based on the fact that there was no statistical difference in the incidence of falls, the incidence of fragility fractures in the experiment group was lower than that in the control group (8.1% *vs* 20.0%, $P = 0.057$),

suggesting that alendronate combined with alfacalcidol and calcium might further reduce the incidence of fragility fractures in elderly patients with OPA compared with the use of alfacalcidol and calcium.

Falling is an independent risk factor of fragility fractures in the elderly. In the present study, the risk of fragility fractures in patients who did not fall decreased 88.3% compared to that in patients who fell ($RR = 0.117$, 95% $CI = 0.035–0.384$). The risk factors for falls include environmental factors, physiological and pathological factors. In the present study, the muscle strength, muscle function, and balance function of the participants were assessed. The elderly were reminded of the risks and hazards of falls, suggestions were provided for the layout of the home environment and outdoor activities of the elderly, and the elderly were instructed to perform appropriate balance and resistance exercises, and to take alfacalcidol. After 18 months, the muscle strength of patients in these two groups did not increase, but gait speed and TUG decreased, suggesting that our treatment did not improve the patients' muscle function and balance. Meanwhile, during the treatment, we provided detailed guidance for fall prevention to patients and their families. The reason why the incidence of falls in both groups is significantly lower than before treatment may be related to the continuous reminder and guidance for patients to subjectively pay attention to safety in their daily activities and to improve the home environment. It also reminds us that medication alone cannot prevent the elderly from experiencing dysfunction, and functional training items should be added in the next study. Therefore, the fall intervention in this study is effective.

Limitations and Prospects

In the experiment group, during the whole course of treatment, 12.9% (8/62) of patients did not complete the use of alendronate due to upper abdominal discomfort, tooth extraction, and the discovery of gastric cardiac carcinoma. Furthermore, there was no occurrence of nephrotoxicity, mandibular necrosis, or atypical fracture. Upper gastrointestinal side effects are common causes of intolerance of oral bisphosphonates, including reflux, esophagitis, and esophageal ulcer[26], which are the local effects of oral bisphosphonates on esophageal and gastric mucosa. The incidence of these side effects is very low when the

instructions are followed and the drugs are taken correctly[27], suggesting that clinicians should carefully select patients and give detailed guidance on the correct medication methods. It remains controversial whether alendronate is associated with gastric cardiac carcinoma[28,29]. One patient suffered from gastric cardiac carcinoma in each group. Hypercalcemia and hyperuricemia are the common side effects of active vitamin D and its analogues. The overall incidence of the above side effects in the present study was 3.3% and 8.1%, respectively. Thus, regular monitoring of blood calcium and 24-hour urinary calcium is needed to adjust the dosage of drugs as necessary.

The present study suggests that the primary task to reduce the incidence of fragility fractures in the elderly population is to prevent falls. Hence, more intensive comprehensive intervention studies are urgently needed. Based on these findings, and as an anti-osteoporotic drug, alendronate sodium can increase bone mineral density in this population, and may further reduce the incidence of fragility fractures. However, it is necessary to carefully select suitable patients and to allocate a longer observation period to assess the benefits and risks.

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