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Efficacy and safety of alfacalcidol in Chinese postmenopausal women aged over 65 with osteoporosis or osteopenia

An open label, non-comparative, post marketing observational study

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Abstract

This study aimed to explore the therapeutic efficacy and safety of alfacalcidol among Chinese postmenopausal women (age >65 years) with osteoporosis or osteopenia.

A total of 62 postmenopausal women with osteoporosis or osteopenia (>65 years) were recruited from urban residential community of Beijing. The patients daily took oral calcium and alfacalcidol (Alpha D3, 1 μg) for 9 months. Safety and efficacy assessments were performed at baseline and regular intervals. Alfacalcidol was adjusted to a daily dose of 0.5 μg in case of hypercalcemia or hypercalciuria.

A significant improvement in "timed up and go test" and "chair rising test" was achieved 3 months after treatment. Significant decreases in bone turnover markers were observed 3 months after the treatment and lasted throughout the study. Nineteen patients discontinued due to adverse events (17 hypercalciuria, 1 hydronephrosis, and 1 stomach ache), while alfacalcidol was adjusted to a daily dose of 0.5 μg in 18 patients (29.0%). Increased serum creatinine was observed when compared to baseline ($P < .001$), but all the values were in normal range.

The treatment with 1 μg alfacalcidol can significantly improve muscle function and bone metabolism. Regular monitoring of urine calcium and timely dosage-adjustments are very important to guarantee the safety of alfacalcidol treatment in Chinese menopausal women.

Abbreviations: β-CTX = C-terminal telopeptide of type I collagen, 1, 25(OH)$_2$D = 1,25-dehydroxyvitamin D, 25(OH)D = 25-hydroxyvitamin D, BMD = bone mineral density, BMI = body mass index, CRT = chair rising test, FN = femur neck, iPTH = intact parathyroid hormone, P1NP = N-aminoterminal propeptide of type I collagen, TGT = tandem gait test, TH = total hip, TUG = timed up and go.

Keywords: alfacalcidol, efficacy, muscle function, osteoporosis, safety

1. Introduction

Osteoporosis is a skeletal disorder, which is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to high risk of bone fragility and osteoporotic fractures.[1] The deterioration of muscle power, function and balance also represent a dominating reason for falls, contributing to considerable morbidity, reduced functioning, and mortality in elderly.[2–5] Calcium and vitamin D supplements are essential steps in treating osteoporosis.[6] Calcitriol, an active form of

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vitamin D3, is well known for its effects on bone, calcium and phosphate homeostasis. Alfacalcidol, an analog of calcitriol, is widely used in osteoporosis prevention and treatment to enhance bone mass and muscle power. Although the efficacy and safety of alfacalcidol have been confirmed in some clinical researches, low incidence of adverse effects, such as hypercalcemia and hypercalciuria, were also reported.[7]

For alfacalcidol, a daily dosage of 0.5 μg to 1 μg is recommended for the management of osteoporosis.[8] If hypercalciuria or other side-effect is observed, alfacalcidol dosages could be adjusted to the range of 0.25 μg to 0.5 μg daily in clinical practice.[9–11] However, there were no enough evidences for the efficacy and safety of alfacalcidol in treating elderly patients with low bone mass in China. Our present clinical trial was designed to estimate the efficacy and safety of alfacalcidol at a daily dosage of 1 μg in postmenopausal Chinese women with osteoporosis or osteopenia.

2. Methods

2.1. Ethics statement

The study was approved by the Medical Ethics Committee of the Peking Union Medical College Hospital (PUMCH). All clinical investigations were conducted according to the principles in the Declaration of Helsinki. The participants in this study signed the written informed consent to empower the publication of their clinical details.

2.2. Participants

Eligible patients were postmenopausal women aged 65 years or more, with a history of osteopenia or osteoporosis confirmed according to the World Health Organization (WHO) criterion of osteoporosis issued in 1994). Sixty-two patients were randomly collected from outpatient clinic. General data, such as age fracture and medication history, were collected for each patient, and all of the patients filled a dietary calcium questionnaire recording diet for 3 days, based on which calcium content was calculated by a designated nutritionist.

Exclusion criteria:

1) allergic to vitamin D or any ingredients of the product;
2) within 3 months, receiving corticosteroid or other drugs which affect bone metabolism;
3) daily dietary calcium intake more than 800 mg;
4) undergoing anti-osteoporotic treatment with a daily dosage of calcium more than 300 mg or vitamin D more than 200 IU, or taking active vitamin D within 2 months;
5) receiving bisphosphonates therapy within 2 years;
6) with hypercalcemia (serum calcium no less than 2.7 mmol/L);
7) having hypercalciuria (urine calcium no less than 300 mg) or the history of kidney stones;
8) suffering metabolic or inherited bone diseases;
9) having serious chronic liver or renal diseases;
10) with severe degenerative joint diseases influencing lower limb activity;
11) having uncorrected severe visual impairment;
12) under physical therapy to improve muscle power and balance;
13) with severe gastrointestinal disease;
14) having body mass index (BMI) $\leq 18\,kg/m^2$ or $\geq 30\,kg/m^2$; and
15) with alcohol or drug addiction.

2.3. Study design (treatment and follow-up evaluation)

This open-label uncontrolled clinical trial lasted for 9 months. The subjects were daily given 1 μg oral alfacalcidol (Alpha D3, Specification: 1 μg/capsule) and 500 mg calcium (NaNuoKa, Specification: elemental calcium 500 mg/tablet).

Efficacy assessment: 1) Muscle function tests, including timed up and go (TUG) test, chair rising test (CRT) and tandem gait test (TGT), were carried out at the beginning and 3, 6, and 9 months after treatment, respectively; Risk evaluation: Patients completing TUG longer than 12 s were considered to be at high-risk; in CRT, an individual, who was unable to sit and rise 5 times and spent more than 10 seconds for the test, was specially considered to be at high risk of falling; In TGT, 1 patient could not perform 8 steps according to a specified standard (starting from a tandem position of both feet, and walking 8 steps with 1 foot in front of the other, with toe tips not touching the heel of the front foot and a maximal distance of 1 cm between the feet); 2) Bone mineral density (BMD) was assessed with dual-energy X-ray absorptiometry (DXA, GE LUNAR, Prodigy) at the beginning and 9 months later; 3) Serum intact parathyroid hormone (iPTH), C-terminal telopeptide of type I collagen (β-CTX), N-amino-terminal propeptide of type I collagen (P1NP) and 25-hydroxyvitamin D [25(OH)D] were measured with a fully automated electrochemiluminescence system (E170; Roche Diagnostics, Switzerland) at baseline, 3 months and 9 months after the treatment; 4) 1,25-dehydroxyvitamin D [1, $25(OH)_2D$] were tested through radioimmunoassay (DIAsource Immuno-Assays S.A., Belgium) at the beginning and 9 months later.

Safety assessment:

1) Biochemical indexes, including blood and urine routine, hepatic function and renal function, were tested at baseline, 3, 6 and 9 months after the treatment;
2) Serum calcium and 24-hour urine calcium were tested at baseline, 3, 6, and 9 months after the treatment; Hypercalcemia was determined when fasting serum calcium level was greater than 2.70 mmol/L (>10.8 mg/dL); Hypercalciuria was defined as a 24-hour urinary calcium level more than 300 mg/d (>7.5 mmol/d) at any time during the follow-up.
3) Renal ultrasound was carried out at baseline and at the end of the trial.

Treatment adjustment: In case of hypercalcemia or hypercalciuria, fasting plasma calcium or 24-hour urinary calcium was measured again within 1 week. If repeated value was not qualitatively reduced, the daily dosage of alfacalcidol was adjusted to 0.5 μg (Alpha D3, Specification: 0.25 μg/capsule).

Termination criteria: If elevated urine or serum calcium persisted after adjustment, patients should discontinue the treatment. Besides, patients would withdraw from the treatment if they presented any one of the following conditions: developing serious adverse events, the patients' own willingness to termination, or any circumstances requiring such termination according to investigators' judgments.

2.4. Statistical analysis

Continuous variables were described as mean, standard deviation and median. Categorical variables were displayed by absolute and relative frequencies (percentages). Percentages for categorical variables referred to the number of non-missing values. Student *t* test was applied to compare continuous data between 2 groups, and the analysis of categorical data was performed with chi-square

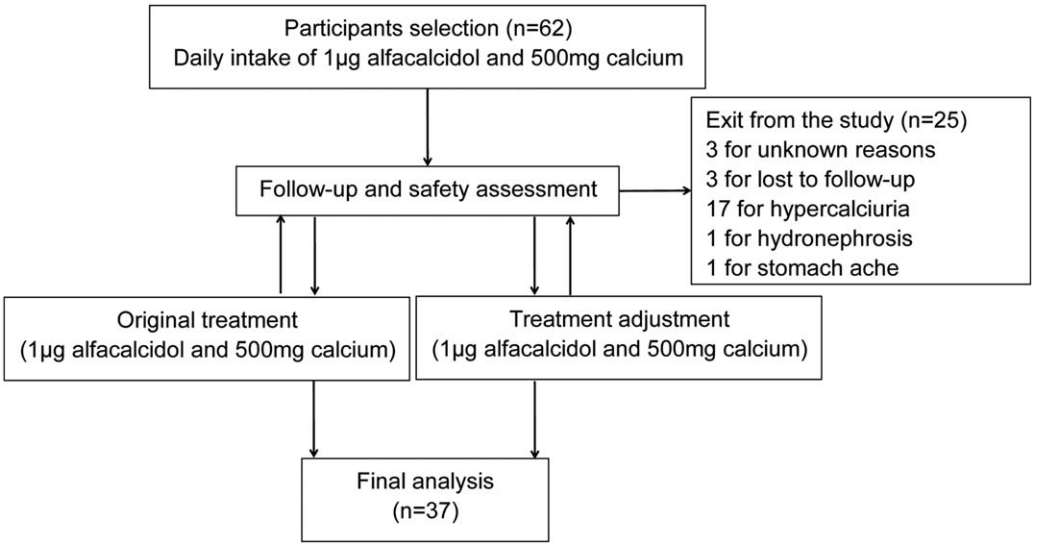

Figure 1. Flow chart for the procedure of the study. *Safety assessment: 1) Biochemical indexes, including blood and urine routine, hepatic function and renal function, were tested at baseline, 3, 6 and 9 months after the treatment; 2) Serum calcium and 24-hour urine calcium were tested at baseline, 3, 6, and 9 months after the treatment; 3) Renal ultrasound was carried out at baseline and at the end of the trial. **Treatment adjustment: In case of hypercalcemia or hypercalciuria, fasting plasma calcium or 24-hour urinary calcium was measured again within 1 week. If re-measured value was still high, the daily dosage of alfacalcidol was reduced to 0.5 μg. ***Termination criteria: If elevated urine or serum calcium persisted even after dosage adjustment, patients should discontinue the study. When any serious adverse events appeared, or patient wanted to quit or was judged by the investigator to discontinue, the patient dropped out of the study.

test. For the evaluation of alfacalcidol efficacy, paired *t* test was carried out. Only patients who completed the whole study were included in the efficacy analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. Study design

A total of 62 subjects were enrolled in the study. Alfacalcidol therapy was discontinued in 25 patients (40.32%). Three patients discontinued for unknown reasons, 3 were lost in follow-up, and 19 discontinued due to adverse events (17 hypercalciuria, 1 hydronephrosis, and 1 stomach ache). Of 37 patients who completed the investigation, 18 received dosage adjustments (lowering to 0.5 μg alfacalcidol). The study flow diagram is displayed in Figure 1.

3.2. Demographic data

The mean age of the 62 patients was 70.2 years. The average body height and weight were 154.6 cm and 60.8 kg, respectively. Mean BMI was 25.2 kg/m^2. Mean dietary calcium intake was 405.34 mg. (Table 1).

Table 1

Basic characters of the patients at baseline (n = 62).

Characteristic	Baseline
Age, years	70.23 ± 4.10
Weight, kg	60.78 ± 8.47
Height, cm	154.56 ± 5.10
BMI, kg/m^2	25.18 ± 3.07
Calcium intake, mg/d	405.34 ± 166.78
Serum calcium, mmol/L	2.35 ± 0.10
Urine calcium, mg/24h	168.95 ± 72.99
Serum creatinine, μmol/L	59.871 ± 9.359

BMI = body mass index.

3.3. Performance in muscle function tests

Alfacalcidol therapy was associated with a significant improvement in the outcomes of 2 muscle tests (TUG and CRT) ($P < .05$ in both tests) 3 months later, and the improvement lasted for the whole treatment (Table 2). The percentage of patients completing TUG was 91.9% at baseline and 100% at the end of trial ($P = .0073$), and for CRT, the figure rose from 62.2% (baseline) to 81.1% at the end of 9 months ($P = .0070$). Thereby, the mean time used for the TUG and CRT were decreased by 0.76 seconds (9.16 s at baseline) and 1.18 seconds (9.83 seconds at baseline), respectively (Fig. 2). The patients (n = 37) able to perform 8 steps in TGT accounted for 91.9% at baseline, which showed no significant improvement at the end of the study ($P = .2299$).

The results of different muscle function tests did not show significant changes after dosage adjustment.

3.4. BMD and bone metabolism

We calculated the changes in BMDs for the 37 patients who completed the study. At baseline, the BMD for total hip (TH) was

Table 2

Changes of the successful performance in percentages after alfacalcidol therapy.

	Successful performance in percentages of participants, %		
N = 37	TUG ≤12s	CRT ≤10s	TGT ≥8 steps
baseline	91.9	62.2	91.9
3 months	94.6*	78.4*	97.3
6 months	94.6*	80.6*	97.2
9 months	100.0*	81.1*	91.9

CRT = chair rising test, TGT = tandem gait test, TUG = timed up and go.
* $P < .05$ as compared to baseline.

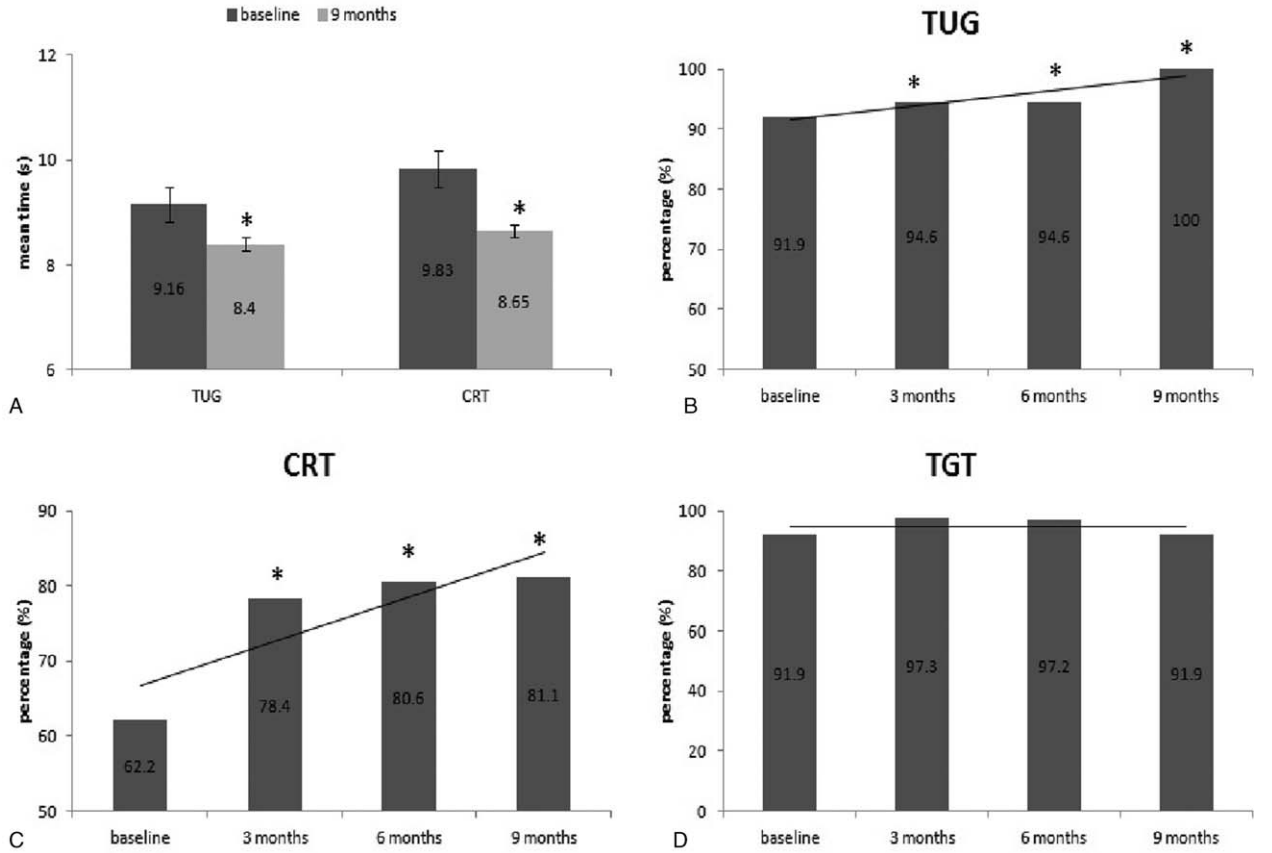

Figure 2. Changes in successful performances in different tests after alfacalcidol therapy. (n = 37). A. Mean time used for TUG and CRT at baseline and at the end of the study. B. Percentage of participants able to successfully accomplish TUG test at different time-points during follow-up. C. Percentage of participants able to successfully accomplish CRT test at different time-points during follow-up. D. Percentage of participants able to successfully accomplish TGT test at different time-points during follow-up. CRT = chair rising test, TUG = timed up and go.

$0.805 \pm 0.090\,g/cm^2$, for femur neck (FN) $0.735 \pm 0.088\,g/cm^2$, and for lumbar (L1–4) $0.951 \pm 0.132\,g/cm^2$. At the end of the study, BMD for TH was $0.799 \pm 0.087\,g/cm^2$, for FN $0.727 \pm 0.088\,g/cm^2$, and for L1–4 $0.957 \pm 0.143\,g/cm^2$. BMDs at these sites had no significant change, with *P* values of .7229, .7021, and .479, respectively (Table 3).

Significant decrease in β-CTX and P1NP were observed 3 months after the treatment ($P < .001$), which lasted through the study (Table 4). Serum iPTH had a similar change as that in β-CTX and P1NP (Table 4).

We also analyzed the difference in BMD between patients taking 1 μg and 0.5 μg, and found no statistical significance.

The patients had a low vitamin D status, with a mean figure for 25(OH)D at 12.98 ± 6.97 ng/mL (n = 62) and 1, $25(OH)_2D$ level at 32.50 ± 16.66 pg/mL. The mean value for 25(OH)D was 14.47 ± 7.68 ng/mL and for 1, $25(OH)_2D$ 34.67 ± 16.66 pg/mL. After alfacalcidol treatment, the value of 25(OH)D was significantly decreased, while 1, $25(OH)_2D$ showed no significant change (Table 4).

3.5. Safety assessment

At the points of 3, 6, and 9 months, there were 54, 41 and 37 patients, respectively. When daily alfacalcitrol dosage was adjusted to 0.5 μg, no patients had hypercalcemia while 17 (27.4%) dropped out because of repeated hypercalciuria. One patient was excluded because of transient ureteral calculus and

Table 3

Changes of BMDs in the 37 patients who completed the investigation.

BMDs, g/cm^2	Baseline	Deadline	*P* values
TH	0.805 ± 0.090	0.799 ± 0.087	.7229
FN	0.735 ± 0.088	0.727 ± 0.088	.7021
Lumbar (L1-4)	0.951 ± 0.132	0.957 ± 0.143	.479

BMD = bone mineral density, FN = femur neck, TH = total hip.

Table 4

Changes of bone metabolism markers (n = 37).

	Baseline	3 months	deadline	*P* value
β-CTX, ng/mL	0.35 ± 0.13	$0.27 \pm 0.11^*$	$0.30 \pm 0.13^*$	.0404
P1NP, ng/mL	43.23 ± 15.2	$35.79 \pm 14.10^*$	$33.36 \pm 14.50^*$	.0002
iPTH, pg/mL	40.69 ± 14.43	$29.39 \pm 10.94^*$	$31.36 \pm 11.20^*$	.0001
25 (OH)D, ng/mL	14.47 ± 7.68	$13.72 \pm 6.72^*$	$12.67 \pm 6.21^*$	<.0001
1,25 (OH)D, pg/mL	34.67 ± 16.66	34.72 ± 18.92	34.78 ± 26.19	.981

β-CTX = C-terminal telopeptide of type I collagen, 1, 25 (OH)2D = 1,25-dehydroxyvitamin D, 25 (OH)D = 25-hydroxyvitamin D, iPTH = intact parathyroid hormone, PINP = N-aminoterminal propeptide of type I collagen.

* $P < .05$ as compared to baseline.

hydronephrosis. Another 1 patient was excluded from this study due to stomach ache. Finally, 37 patients completed this 9-month study, and 18 of them received adjusted alfacalcidol dosage of 0.5 μg daily (29.0%). Serum creatinine raised from 59.871 ± 9.359 μmol/L (baseline) to 66.054 ± 8.714 μmol/L (9 months) ($P < 0.001$), but all the values were in normal range. However, no significant change was observed in the follow-up thereafter. At the end of the treatment, serum creatinine showed no significant difference between patients who had dosage adjustment to 0.5 μg and those without the adjustment (65.060 ± 7.004 μmol/L vs 66.900 ± 10.047 μmol/L, $P = .117$).

4. Discussion

Osteoporotic fracture is one of the most serious public health problems in elderly.[12] Osteoporosis and falls are the main risk factors for osteoporotic fracture. Calcitriol acts an important role in maintaining bone mass and muscle function, thus preventing falling and fractures. However, the elderly commonly have vitamin D deficiency and 1α- hydroxylation deficiency. Alfacalcidol is an analog of calcitriol and could be converted into an active form by liver 25-hydroxylase soon after it enters the body. Overseas, alfacalcitrol at a dosage of 1 μg is used to prevent fractures, but its efficacy and safety have not been fully certified in Chinese people. In the present study, we found that the daily treatment with l μg alfacalcidol in elderly patients significantly improved their muscle function and balance, and decreased their bone turnover rate. Although there was a higher risk of hypercalciuria, such dosage was relatively safe during the follow-up.

Muscle function tests, such as TUG, TGT, and CRT, are often used to evaluate the risk of falling. These tests are in line with the international guidelines for the assessment of patients' risk of falls.[2] In the present study, after 3 months of treatment with alfacalcidol, patients showed a significantly improved performance in TUG and CRT. This effect was further enhanced at the end of the therapeutic intervention. At the end of the trial, the mean time for completing TUG and CRT was decreased by 0.76 s and 1.18 s, respectively. Older patients, who need more than 12 s to complete the TUG, had higher risk of falls[13,14] and non-vertebral fractures.[15] A 10-year longitudinal study showed that the increase in TUG time-consuming was associated with elevated risk of non-vertebral fractures.[15] Therefore, patients can profit from the treatment of alfacalcidol, which is not only manifested in the improvement in the tests, but also in the reduction of fractures in the future.

Bone turnover markers (BTMs) are known to reflect the status of bone metabolism, and in several population-based epidemiological studies, were employed as predictors for bone loss and the incidence of osteoporotic fractures in women.[16–22] In this study, we showed that BMDs at all sites had no significant changes after alfacalcidol treatment, only the lumbar L1-4 BMD showing an increasing trend from 0.951 ± 0.132 g/cm^2 to 0.957 ± 0.143 g/cm^2. In fact, BTMs showed significantly decrease after 3 months of treatment that lasted through the study. As reported by N. Yoshimura et al[23] high P1NP and β-CTX levels in women might be regarded as predictors for future osteoporosis at lumbar spine. These BTMs, independent of baseline BMD status, could also predict future occurrence of spinal osteoporosis in women. Alfacalcidol therapy significantly reduced the frequency of falls,[24–26] maintained the levels of BMDs,[27–29] and thereby decreased the risk of fractures. Our study also certified the effect of alfacalcidol on reducing BTMs and maintaining BMDs. Changes in BMD may be more obvious in researches with longer duration or larger sample size. After treated with alfacalcidol, 25 (OH)D level showed a downward trend, while BTMs were evidently suppressed during study. These results suggested that alfacalcidol was negatively associated with BTM function.

Alfacalcidol, a vitamin D analog, is converted to the final active form of vitamin D, calcitriol, by 25-hydroxylation in the liver. It is independent of renal 1a-hydroxylase via bypassing the activation in the kidney and associated with a lower risk of hypercalcemia when compared to calcitriol.[30] Alfacalcidol was recommended for the treatment of osteoporosis.[31] Post marketing surveys on alfacalcidol in Japan with a daily dose ranging from 0.5 μg to 1 μg showed very low incidence of adverse effects, such as hypercalcemia and hypercalciuria.[7] In the present study, 62 elderly women with reduced bone mass were recruited. The mean 25(OH)D value of these patients was 14.47 ± 7.68 ng/mL, which indicated that the patients were in a vitamin D deficiency status. Their average urine calcium was 168.95 mg/d. After the treatment with a daily 1 μg alfacalcitriol, the 25(OH) D levels were significantly decreased. However, hypercalciuria was observed in 35 patients. When the daily dose of alfacalcitrol was adjusted to 0.5 μg, 17 of the 35 patients continued to show hypercalciuria. The ratio of hypercalciuria seemed to be higher than that in previous studies.[7] First of all, it may be attributed to different cutoff levels for defining hypercalciuria. It has been reported in previous studies that the risk of renal stones increased by almost 2.5 times when the 24-hour urinary calcium level was greater than 300 mg/d.[32] In the present study, we also detected a case of transient ureteral calculus and hydronephrosis. Thereby, doctors should pay more attentions on urine calcium levels when prescribing alfacalcidol. Second, urinary calcium excretion is dependent mainly on the amount of calcium in diet. It has been shown that about 6% to 7% of consumed dietary calcium is excreted through urine among normal individuals.[33] In the present study, we prescribed 500 mg additional calcium to each of the patients. Therefore, hypercalciuria may be also attributed to high calcium intake in some instances. High calcium intake directly suppresses PTH secretion, and reduces calcium re-absorption by renal tubule, leading to increased excretion of urine calcium. Third, some molecules may be involved in the development of hypercalciuria, like the over-expression of vitamin D receptor (VDR) in gut wall, which has been demonstrated in rats with genetically-determined hypercalciuria.[34] However, whether these events were caused by alfacalcidol alone, calcium supplements alone or both is unclear. In future study, we should explore the efficacy and safety of 1 μg alfacalcidol without supplementing extra calcium.

A significant increase in serum creatinine was also observed from 59.871 ± 9.359 μmol/L at baseline to 66.054 ± 8.714 μmol/L at the end of the study. However, serum creatinine levels of all the patients were in normal range during the follow-up examination, causing no renal function damage. The reason for the slight increase in creatinine may be explained by the muscle improvement after alfacalcidol treatment. Further studies are strongly recommended to verify our suspicions.

This primary study investigated the therapeutic efficacy and safety of alfacalcidol in Chinese postmenopausal women with osteoporosis or osteopenia, and some limitations in this study should be stated. First, there was no control group. We only performed comparisons before and after the treatment. Second, the case number was small and study period was short. Lastly, we did not compare the efficacy and safety of the drug between osteoporosis and osteopenia cases, which was partly because of the small sample size. As such, the results from the present study should be validated by larger cohort studies.

5. Conclusions

To sum up, daily treatment with 1 μg alfacalcidol can significantly improve muscle function and bone metabolism. During this period, regular and close monitoring on urine calcium are essential to avoid adverse effects through timely dosage adjustment. Further studies, especially case-control ones with larger sample size, are needed to verify our findings.

Author contributions

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Resources: Yan Jiang, Mei Li, Ou Wang.
Writing – original draft: Nan Li, Yan Jiang, Shuli He, Zhen Zhao, Jing Sun.
Writing – review & editing: Nan Li, Yan Jiang, Shuli He, Zhen Zhao, Jing Sun.

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