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Prevention of osteoporotic fractures among high-risk groups of post-menopausal women

Key Messages

1. When bone mineral density and its changes are used as an endpoint measure, anti-resorptive drugs—alendronate and calcitonin—demonstrate better treatment effects compared with exercise or calcium supplements alone in high-risk patients.
2. Tai Chi exercise was beneficial for both the retardation of bone loss and enhancement of body function, including muscle strength and body balance factors, which may be associated with a better chance of fall prevention for high-risk subjects.

Introduction

Menopausal and age-related loss of bone mass and its associated fractures is a universal health problem among post-menopausal women, especially high-risk patients with established osteoporosis (PEO) (low bone mineral density [BMD] and one or more fragility fractures) and fast bone loss.[1] The prevalence of osteoporosis among the Chinese elderly in Hong Kong, as evidenced by osteoporotic fractures, is high. Osteoporotic fractures are the fifth most commonly occurring condition in a subject's medical history.[2]

Anti-bone resorptive drugs are effective in the treatment of high-risk Caucasian patients.[1,3] Non-pharmacological approaches such as physical exercise are beneficial for prevention of bone loss and falls among the elderly.[4]

Aims and objectives

The aim of this study was to investigate the effects of two popular anti-resorptive drugs (alendronate and calcitonin) and Tai Chi exercise on prevention of bone loss and reduction of fall-related intrinsic risk factors in Hong Kong Chinese post-menopausal women identified with established osteoporosis or as fast bone losers.

Materials and methods

Setting and subjects

This study was conducted from July 1999 to December 2002. Post-menopausal Chinese women, identified as having established osteoporosis (with a Colles' fracture) and as fast bone losers (with annual trabecular bone loss at the non-dominant distal radius over 3%) were recruited. Women on drug treatment or diagnosed with diseases known to affect spontaneous bone loss and women who had more than 2 hours of regular exercise per week were excluded. The subjects were randomised into four groups for both fast bone losers (n=86) and women with established osteoporosis (n=85).

Grouping and interventions

1. Alendronate group: 10 mg alendronate plus 1200 mg of calcium supplement per day. Subjects maintained their original lifestyle.
2. Calcitonin (nasal spray) group: 200 IU/day of salmon nasal spray plus 1200 mg of calcium supplement per day. Subjects maintained their original lifestyle.
3. Standard exercise group: subjects participated in regular Tai Chi exercise, 45 min/day, 3 days/week, which was modified to enable all subjects to practise (http://www.no-fall.org). Calcium was also supplemented (1200 mg/day).
4. Placebo-control group: subjects maintained their original lifestyle. Calcium was also supplemented (1200 mg/day).

Main outcome measures

BMD measurements

1. Dual-energy X-ray absorptiometry (DXA)—the BMD in g/cm^2 was measured at the spine and the non-dominant hip.

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Table 1. Anthropometrical data and bone mineral density at baseline and percentage changes at follow-up in fast bone losers

Parameters*		Controls		Tai Chi		Alendronate		Calcitonin	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
No. of subjects		19	-10.5%	20	-20%	24	-22.5%	23	-17.4%
		Mean±SD		Mean±SD		Mean±SD		Mean±SD	
Age (yrs)		55.6±3.4		53.9±3.7		54.3±3.4		54.5±3.0	
YSM (yrs)		5.0±3.0		4.5±3.2		4.5±2.6		4.3±2.7	
BMI (kg/m^2)		22.4±3.8		24.4±2.5		22.3±2.2		22.6±2.4	
DXA	Spine	0.80±0.12	-1.5%†	0.92±0.10†‡	-0.3%	0.83±0.09	4.1%†§	0.82±0.13‡	0.4%
	F-Neck	0.68±0.09	-0.2%	0.75±0.08	0.6%	0.72±0.09	3.5%§	0.69±0.10	-2.4%
	F-GT	0.53±0.08‡	2.2%‡	0.61±0.07‡	-1.9%	0.57±0.08	5.0%§	0.56±0.08	-1.6%
pQCT	tBMD	163±64	0.0%	178±54	-0.8%	179±50	1.4%	176±59	-2.0%
	iBMD	483±124	-0.8%‡	495±71	-0.9%	499±90	1.0%	492±110	-1.9%
	cBMD	1248±256	1.0%‡	1275±163	-1.9%§	1251±174	0.4%	1276±127	-0.7%

* YSM denotes years since menopause, BMI body mass index, DXA dual-energy X-ray absorptiometry, pQCT peripheral quantitative computed tomography, tBMD trabecular bone mineral density, iBMD integral bone mineral density, and cBMD cortical bone mineral density
† Significant difference compared with placebo control between the 2 corresponding groups
‡ P<0.05 (comparing baseline and follow-up)
§ P<0.01 (comparing baseline and follow-up)

Table 2. Anthropometrical data and bone mineral density at baseline and percentage changes at follow-up in patients with established osteoporosis

Parameters*		Controls		Tai Chi		Alendronate		Calcitonin	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
No. of subjects		24	-4.2%	19	-26.3%	22	-13.6%	20	-15.0%
		Mean±SD		Mean±SD		Mean±SD		Mean±SD	
Age (yrs)		55.6±3.4		53.9±3.7		54.3±3.4		54.5±3.0	
YSM (yrs)		5.0±3.0		4.5±3.2		4.5±2.6		4.3±2.7	
BMI (kg/m^2)		22.4±3.8		24.4±2.5		22.3±2.2		22.6±2.4	
DXA	Spine	0.70±0.09	-0.7%†	0.73±0.11†‡	-2.3%	0.72±0.10	5.1%†§	0.69±0.10	2.9%†‡
	F-Neck	0.63±0.06	-0.1%	0.63±0.09	-2.4%‡	0.64±0.12	2.5%§	0.63±0.07	0.2%
	F-GT	0.52±0.05‡	1.0%‡	0.49±0.08‡	2.4%	0.50±0.08	5.2%§	0.49±0.06	1.4%
pQCT	tBMD	148±52	-2.1%	143±66	-0.1%	127±44	3.2%‡	138±56	1.9%
	iBMD	434±78	-0.4%§	393±92	-1.4%	376±77	0.7%	403±84	0.6%
	cBMD	1147±180	-1.5%†‡	1059±177	-0.8%§	1053±212	0.0%	1084±129	0.7%†

* YSM denotes years since menopause, BMI body mass index, DXA dual-energy X-ray absorptiometry, pQCT peripheral quantitative computed tomography, tBMD trabecular bone mineral density, iBMD integral bone mineral density, and cBMD cortical bone mineral density
† Significant difference compared with placebo control between the 2 corresponding groups
‡ P<0.05 (comparing baseline and follow-up)
§ P<0.01 (comparing baseline and follow-up)

2. Peripheral quantitative computed tomography (pQCT)—the non-dominant distal radius was measured using multi-slice pQCT. The distal 10 tomograms were used to calculate average trabecular BMD (tBMD) in a core volume (central 50% of the total bone area) and integral BMD (iBMD) within the total measured volume. The six proximal tomograms obtained from distal diaphysis were used to determine the pure cortical compartment as cortical BMD (cBMD). Measurements of BMD with DXA and pQCT were carried out at baseline, and 6 and 12 months follow-up.

Bone metabolic markers

1. Bone formation marker: serum bone-specific alkaline phosphatase (BALP) was measured with a specific lectin precipitation method.
2. Bone resorption marker: urinary deoxypyridinoline (Dpd) was measured by a commercially available ELISA kit, Pyrilinks-D.

Functional tests

1. Muscle strength: both handgrip and quadriceps muscle isometric strength were measured. The subjects were instructed to perform three consecutive measurements and the maximum value was used for comparison.
2. Body balance: measured using the Smart Balance Master system.

Fragility fractures

Cases of fracture occurring during the follow-up period and the fracture mechanism were documented.

Statistics

Multiple ANOVA was used for data comparison between treatment and placebo control groups. Changes in both BMD and functional parameters were calculated after excluding dropouts.

Results

Subject dropout

The overall dropout rate at the 12-month follow-up ranged from 4.2% to 26.3% (mean, 14.9%). The highest dropout rate was in the Tai Chi group for those with established osteoporosis (26%) [Tables 1 and 2].

Table 3. Handgrip strength (kgf^{-1}) of non-dominant hand in fast bone losers (FBL) and non-fractured hand in patients with established osteoporosis (PEO)

	Groups	Baseline	Follow-up	Changes	P value
FBL	Control	20.9±4.0	20.8±4.6	-0.2%	0.875
	Tai Chi	20.6±4.0	21.3±4.3	5.8%	0.504
	Alendronate	21.2±4.7	21.2±4.1	2.4%	0.990
	Calcitonin	21.6±3.3	21.4±2.7	0.5%	0.825
PEO	Control	21.8±4.2	21.8±3.3	2.4%	0.962
	Tai Chi	17.8±5.0	19.6±4.2	14.5%	0.085
	Alendronate	21.2±3.9	22.1±4.1	5.8%	0.259
	Calcitonin	20.2±3.3	20.7±3.0	3.5%	0.252

Table 4. Quadriceps muscles strength (kgf^{-1}) of non-dominant leg in fast bone losers (FBL) and patients with established osteoporosis (PEO)

	Groups	Baseline	Follow-up	Changes	P value
FBL	Control	15.8±5.1	16.3±4.4	7.5%	0.615
	Tai Chi	15.2±5.6	17.3±2.2	14.2%	0.124
	Alendronate	17.8±5.0	17.3±3.0	1.1%	0.525
	Calcitonin	16.6±3.2	17.7±3.6	7.0%	0.430
PEO	Control	17.5±4.7	19.4±2.7	16.9%	0.015*
	Tai Chi	14.4±4.1	16.3±4.4	16.4%	0.035*
	Alendronate	18.2±5.1	19.2±5.0	8.9%	0.285
	Calcitonin	17.6±4.7	18.3±3.7	8.4%	0.484

* P<0.05 (comparing baseline and follow-up)

BMD measurement

Tables 1 and 2 summarise the baseline anthropometric and BMD measurements at baseline and at follow-up (12-month data). Alendronate was associated with a significant increase in BMD at all skeletal sites compared with the placebo control and other intervention groups.

Body functional tests

Tables 3 and 4 summarise the results of functional tests at baseline and follow-up for fast bone losers and women with established osteoporosis, respectively.

1. Muscle strength—although not a significant increase, an average 5.8% increase in handgrip strength for fast bone losers and 14.5% for PEO doing Tai Chi was found (Table 3). Quadriceps strength generally improved in both fast bone losers and PEO among the Tai Chi group (Table 4), but only control and Tai Chi subjects in the PEO group showed a significant increase.
2. Body balance—a 7-8% significant improvement was found in overall balance in both Tai Chi and control groups in fast bone losers and 5% improvement in the calcitonin group with established osteoporosis (Table 5) was demonstrated.

Table 5. Body balance and its changes in fast bone losers (FBL) and patients with established osteoporosis (PEO)

	Groups	Baseline	Follow-up	Changes	P value
FBL	Control	68±7	73±6	8%	0.006*
	Tai Chi	68±7	73±7	7%	0.008*
	Alendronate	71±9	74±9	3%	0.055
	Calcitonin	69±7	70±7	2%	0.423
PEO	Control	70±7	72±8	3%	0.217
	Tai Chi	70±7	71±8	1%	0.509
	Alendronate	74±6	75±5	2%	0.445
	Calcitonin	68±8	71±6	5%	0.029†

* P<0.01 (comparing baseline and follow-up)
† P<0.05 (comparing baseline and follow-up)

Fractures recorded

A total of four fracture cases were recorded in the control, alendronate, and calcitonin groups.

Discussion

The most serious clinical consequence of osteoporosis is fragility fractures, more frequently seen in elderly PEO.[1-3] It is known that rate of bone loss is at its peak within 10 years after the onset of menopause. We found an age difference of 7 years between fast bone losers with a mean age of 54 years and PEO with a mean age of 61 years. Strategies aimed at preventing or reducing osteoporosis should be implemented well before substantial bone loss occurs, especially in women identified as fast bone losers.[5]

Evaluation of BMD of these subjects demonstrated that anti-resorptive alendronate was on average better than calcitonin for increasing or maintaining BMD within the treatment period. The use of calcitonin showed on average better effects on BMD and body balance in PEO than fast bone losers, consistent with many randomised, double-blind, placebo-controlled studies conducted in Caucasian women.[6] The placebo effects of calcium supplementation also implied retardation of menopausal and/or age-related bone loss in fast bone losers (average annual rate of bone loss <3%).[7] Similar to the finding of our recent Tai Chi intervention study,[8] low weight-bearing Tai Chi exercise was able to retard rate of bone loss at the weight-bearing spine and hip compared with placebo control.

Post-menopausal bone loss was reported to be associated with high bone turnover, which can be monitored using both bone-forming (eg serum bone alkaline phosphatase) and resorption (eg urinary hydroxyproline) biochemical markers. Exercise showed osteogenic effects while the two agents used for this project, ie alendronate (a bisphosphonate-synthetic stable analogue of natural pyrophosphate) and calcitonin (a naturally occurring hormone involved in calcium homeostasis) were strong inhibitors of bone resorption by inducing osteoclast apoptosis thereby suppressing menopausal or age-related high bone turnover.

Our current study did not set prevention of osteoporotic fractures as the endpoint or outcome measure because of the short study duration. Although it is known that high BMD or slow rate of bone loss is associated with a lower fracture risk, the use of surrogate endpoints such as BMD to predict fracture risk should be approached with caution. The relationship between BMD changes and fracture risk reduction when using anti-resorptive therapies is in some cases uncertain, and may be confounded by many other

factors, such as intrinsic functional criteria, including muscle strength, body balance, and coordination.

We documented four fractures related to falls or low energy impact injury—two in fast bone losers and two in PEO. No fall-related injuries were reported in the Tai Chi group. Long-term and large-scale prospective studies are needed to test the apparently beneficial effects of Tai Chi exercise.

Long-term follow-up is also needed to further assess the benefits and cost-effectiveness of exercise in neuromuscular coordination and the interaction between exercise and drug treatment for the prevention of osteoporotic fractures.

Conclusion

This randomised trial demonstrated that alendronate and calcitonin have a more beneficial effect on BMD at multiple skeletal sites compared with exercise alone in postmenopausal women with either fast bone loss or established osteoporosis. When compared with non-exercising placebo controls and the drug treatment groups, Tai Chi exercise was beneficial for both retarding bone loss and enhancing body functions, including muscle strength and body balance, which could be associated with a reduction in the number of falls.

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