

The Change of Bone Mineral Density by Bisphosphonates Therapy with Calcium-Antagonists in Osteoporosis

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Abstract – Imbalance in calcium and phosphorous metabolism due to aging or menopause leads to osteoporosis. In contrast to patients with normal blood pressure, hypertensive patients have a higher loss of calcium in the urine with its attendant risk of osteoporosis. The high blood pressure is associated with the risk of bone loss and abnormalities in calcium metabolism leading to calcium loss. So we retrospectively investigated the changes of bone mineral density (BMD) which drugs can have clinical influences over osteoporosis treatments of patients with calcium-antagonists as common antihypertensive drugs and with bisphosphonates which causes a most effective inhibition of osteoclasts resorption. As a result over 70 years of age group and within bisphosphonates group, alendronate 70 mg once-weekly group showed significant increase of BMD in lumbar area. Combination group of cilnidipine and maxmarvil[®] showed very significant decrease of BMD. In conclusion, it is desirable that combination therapy with calcium-antagonists is used carefully in the treatment of osteoporosis with high blood pressure.

Keywords: bone mineral density, bisphosphonates, alendronate, calcium-antagonists, cilnidipine

INTRODUCTION

The high blood pressure among elderly women is statistically associated with decreased bone mineral content at the femoral neck, which may increase the susceptibility to fractures (Cappuccio *et al.*, 1999). In contrast to patients with normal blood pressure, hypertensive patients have a higher loss of calcium in the urine with its attendant risk of osteoporosis. The high blood pressure is associated with the risk of bone loss and abnormalities in calcium metabolism leading to calcium loss (Cappuccio *et al.*, 1999).

The bone mineral density (BMD) is used for diagnosis of osteoporosis and provides an index of whole calcium balance. It implies that elevated blood pressure is inversely correlated with reduced BMD in with essential hypertension, indicating that high blood pressure is associated with abnormalities in calcium metabolism and insulin resistance (Gotoh *et al.*, 2005).

The aim of osteoporosis therapy is to increase bone mass and prevent fractures, leading to morbidity and mortality decrease. It includes 'treatment of pain, initia-

tion of physical activity and exercises, prevention of fractures, adaptation of life-style for skeletal health, bone-conscious nutrition, vitamin D and calcium supplements, hormone replacement therapy (HRT) for short periods only, antiresorptive therapy (bisphosphonates, raloxifene, calcitonin), osteoanabolic therapy (fluoride, strontium, anabolics, parathormone), and other medications (statins, growth factors, tetracyclins, leptin)' (Caren 2002, Reiner and Bertha 2003, Shun-ichi 2003).

Bisphosphonates, especially nitrogen-containing bisphosphonates, have a high affinity for certain structures on the surface of bone. Most of the bisphosphonates absorbed in the gastrointestinal tract is deposited on the bone within hours, especially in the acidic environment under the osteoclasts. This causes the most effective inhibition of osteoclasts resorption, as well as reactivation of the suppressed osteoblasts and thereby an overall positive bone-balance and increase in bone mass. In the long term, inhibition of resorption results in a positive calcium balance with a continuous increase in bone mass (Reiner and Bertha 2003). So we retrospectively investigated the changes of BMD which drugs can have clinical influences over osteoporosis treatments of patients with calcium-antagonists among antihypertensive drugs with bisphosphonates.

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METHODS

We did complete enumeration over total 868 outpatients to whom osteoporosis therapy were prescribed in a general hospital from Jan, 2004 to Dec, 2006.

Method was retrospective investigation of patient medical records. We investigated kinds of used drugs for total 868 outpatients, and the medical departments where patients were prescribed osteoporosis therapy and diagnosis. We focused on the kinds and frequencies of osteoporosis drugs and daily dose of calcium-antagonists among antihypertensive drugs, which were used for 90 patients taking calcium-antagonists among 120 patients taking antihypertensive drugs (Table I).

Also, we did investigational comparison for BMD to find out the influence of combination of osteoporosis therapy and calcium-antagonists to 49 patients taking calcium-antagonists among antihypertensive drugs at least for 6 months with confirmed change on more than two BMD tests.

BMD data obtained through quantitative BMD measurement of DXA (dual energy X-ray absorptiometry) was comparatively analyzed. LBMD (BMD of lumbar spine) and WBMD (BMD of Ward's) were used for data analysis. Initial observation value (the first observation value) and final value (the last observation value regardless of measurement frequencies) was used for measuring BMD. All data were represented by mean \pm SEM. Statisti-

cal comparison between groups and treatments was performed using student's *t*-test.

RESULTS

1. Analysis of patients taking osteoporosis drugs

(1) General characteristics of osteoporosis drugs medication group

Among 868 patients taking osteoporosis drugs, 78 patients (9.0%) were male and 790 patients (91%) were female. Mean age was 61.2 ± 14.7 years. Age grouped distribution was 170 patients under 49 years, 414 patients (48%) between 50 and 69 years of age and 284 patients over 70 years of age.

Analysis of medical department where osteoporosis drugs were prescribed showed even distribution including gynecology (GY) 220 cases (25%), orthopedic surgery (OS) 206 cases (24%), and medical endocrinology (ME) 111 cases (13%).

(2) Analysis of diagnosis (Repetition selection)

Diagnosis of 868 patients yielded 1,561 cases of osteoporosis to base our studies. Among them 392 cases (25%) state 'osteoporosis' followed by related skeletal and articular diseases in 148 cases (9.5%), back pain in 76 cases (4.9%) and fracture in 69 cases (4.4%). Apart from these, chronic diseases were such as diabetes, gastrointestinal and endocrinological diseases evenly distributed.

2. Analysis of combination therapy group of bisphosphonates and calcium-antagonists

Patients with calcium-antagonists therapy of total 120 patients with combination therapy were 90 persons, 12 male patients (13%) and 78 female patients (87%).

(1) Frequencies of the bisphosphonates

Analysis of prescribed the bisphosphonates in the combination therapy group with antihypertensive drugs ($n=90$) shows that bisphosphonate drugs (72 cases, 80%) was the most commonly prescribed drug and among them alendronate (ALD) was 33 cases (37%), risedronate (RSD) 27 cases (30%), maxmarvil[®] (MXM) of complex for ALD and calcitriol 16 cases (18%).

(2) Frequencies and dose analysis of calcium-antagonists medication ($n=90$)

Amlodipine (32 cases, 36%) was the most commonly used calcium-antagonists followed by nifedipine and cilnidipine (22 cases, 24%), lacidipine (8 cases, 8.9%). cal-

Table I. Drugs in combination therapy

Efficacy	General name
Osteoporosis drugs	Alendronate (ALD)
	Risedronate (RSD)
	Pamidronate (PAMD)
	Maxmarvil [®] (MXM)
	Raloxifene (RAXF)
	Menatetrenone (MENAT)
Calcium-antagonists	Salcatonine (R-SLT)
	Amlodipine (AMDP)
	Lacidipine (LADP)
	Lercanidipine (LCDP)
	Nifedipine (NFP)
	Cilnidipine (CNDP)
	Diltiazeme (DTZ)
Verapamil (VPM)	

We investigated kinds of used drugs in the combination drugs, osteoporosis drugs with antihypertensive drugs.

cium-antagonists dose of all the 90 cases was within reference range and it was medicated once or twice a day.

3. BMD analysis of calcium-antagonists medication group

Patients with change confirmation during more than two BMD tests were 49 persons (51%). Among them two persons (4.1%) were male and 47 persons were female (96%). Age grouped distribution were 14 persons under 49 years, 16 persons between 50 and 69 years and 19 persons over 70 years.

(2) Analysis grouped by the bisphosphonates (n=49)

Medication frequencies of bisphosphonates were ordered by 20 cases (41%) with ALD, 15 cases (31%) with risedronate (RSD) and 9 cases (18%) with maxmarvil® (MXM).

(3) Comparison analysis of BMD change within calcium-antagonists medication group

① Comparison of change between initial and final BMD (n=49)

Hypothesis testing about change between initial BMD and final BMD within calcium-antagonists medication group showed significant LBMD increase ($p=0.0017$) (Fig. 1).

② Comparison between initial and final BMD by age (n=49)

Age group of over 70 years showed significant increase in LBMD ($p=0.0036$) (Fig. 2).

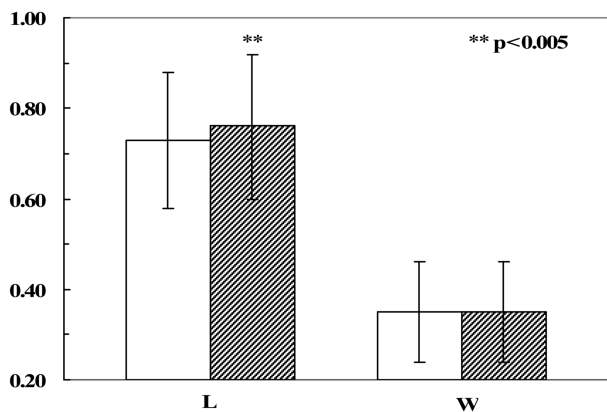


Fig. 1. Comparison of change between initial and final BMD within calcium-antagonists medication group showed significant LBMD increase (n=49). The area of lumbar and Ward's of femur is presented L and W, respectively. Initial BMD(□), final BMD(▨). ** $p<0.005$, significantly different from initial BMD.

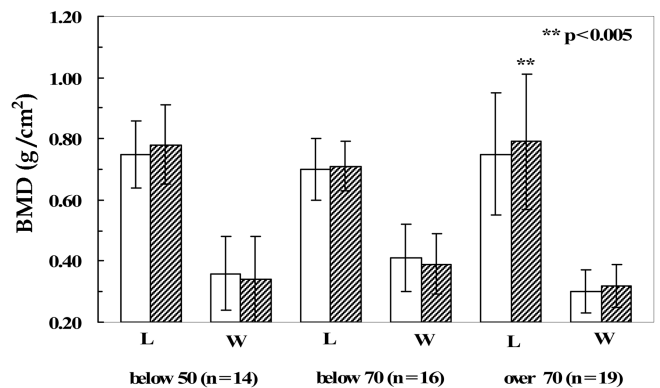


Fig. 2. Comparison between initial and final BMD by age within calcium-antagonists medication group (n=49); Over 70 years of age group showed significant increase in LBMD. ** $p<0.005$, significantly different from initial BMD.

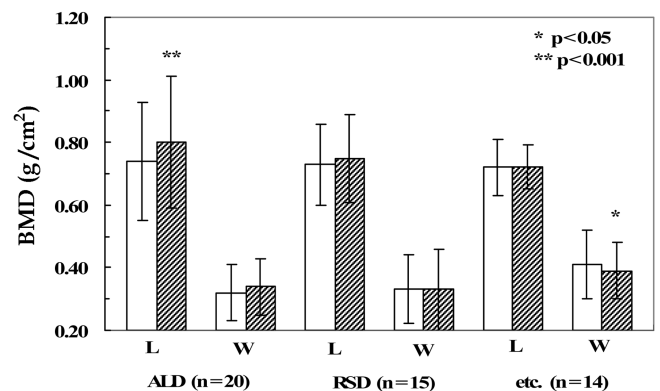


Fig. 3. Analysis grouped by osteoporosis drugs within calcium-antagonists medication group (n=49); ALD group showed significant increase in LBMD and other groups shows significant decrease in Ward's area of femur (WBMD) in the analysis grouped by osteoporosis drugs. * $p<0.05$, ** $p<0.001$, significantly different from initial BMD.

③ Analysis grouped by the bisphosphonates (n=49)

ALD group (n=20) showed significant increase in LBMD ($p=0.0004$) and other groups showed significant decrease in WBMD ($p=0.0393$) in the analysis grouped by bisphosphonates (Fig. 3).

④ Comparison of BMD change in the bisphosphonates and calcium-antagonists combination (n=41)

Analysis bisphosphonates dose shows that ALD 70mg once-weekly group is the most as 18 cases. Combination groups with more than two cases only were analyzed. BMD change is as follows. Combination of CNDP and MXM shows very significant decrease in WBMD ($p=0.0089$), and combination of AMDP, ALD in LBMD and combination of MXM in WBMD showed significant increase ($p=0.0385$, 0.0363) and also combination of

Table II. Comparison of BMD change in osteoporosis drugs and calcium-antagonists combination

Osteoporosis drugs	Calcium antagonist	Sites	BMD (g/cm ²)		
			Initial	Final	
ALD	AMDP	L	0.72 ± 0.12	0.77 ± 0.14*	(n=7)
		W	0.34 ± 0.06	0.35 ± 0.04	
	NFP	L	0.66 ± 0.08	0.71 ± 0.09	(n=8)
		W	0.30 ± 0.11	0.33 ± 0.14	
	LADP	L	0.94 ± 0.34	1.03 ± 0.37*	(n=4)
		W	0.30 ± 0.10	0.31 ± 0.07	
RSD	AMDP	L	0.78 ± 0.17	0.83 ± 0.21	(n=4)
		W	0.37 ± 0.21	0.36 ± 0.23	
	NFP	L	0.73 ± 0.08	0.76 ± 0.08	(n=5)
		W	0.33 ± 0.06	0.33 ± 0.10	
	CNDP	L	0.71 ± 0.18	0.69 ± 0.16	(n=5)
		W	0.29 ± 0.06	0.27 ± 0.07	
MXM	AMDP	L	0.71 ± 0.02	0.69 ± 0.01	(n=2)
		W	0.32 ± 0.07	0.36 ± 0.07*	
	LADP	L	0.70 ± 0.04	0.67 ± 0.06	(n=2)
		W	0.41 ± 0.07	0.39 ± 0.06	
	CNDP	L	0.83 ± 0.08	0.80 ± 0.05	(n=4)
		W	0.52 ± 0.09	0.45 ± 0.09**	

Combination groups with more than two cases only were analyzed. Bone mineral density (BMD) change is that combination of CNDP and MXM shows very significant decrease in WBMD. The BMD of lumbar and Ward's of femur is represented L and W, respectively.

* $p < 0.05$; ** $p < 0.01$, significantly different from initial BMD.

LADP and ALD showed significant increase in LBMD ($p = 0.0119$) (Table II).

DISCUSSION

During this study, patients with osteoporosis medication between 50 and 69 years of age were the most common age group. These are consistent with the increase of osteoporosis prevalence following hormone excretion decrease in the 50s, due to menopausal age (Kim *et al.*, 1988).

Distribution over medical department where osteoporosis drugs were prescribed shows high ratio for gynecology (GY) and orthopedic surgery (OS). Those are consistent with the facts that in case of GY, 91% of patients were female, mean age was 61 years, menopause made change of serum lipid metabolism and increased risk factor for osteoporosis, and in case of OS, aging causes degeneration of articulation. Diagnosis distribution showed that patients had not only skeletal disease and fracture but also more than two chronic diseases such as diabe-

tes mellitus or hypertension. Drugs for that also showed various pattern.

In comparing the initial and final bone mineral density (BMD) value in the osteoporosis drugs group only alendronate (ALD) medication group showed significant increase in LBMD (BMD of lumbar spine). ALD 70 mg once-weekly showed significantly greater increases in lumbar spine and hip BMD and greater reductions in markers of bone turnover than raloxifen 60 mg daily over 12 months in postmenopausal osteoporosis (Luckey *et al.*, 2004, Sambrook *et al.*, 2004). ALD 70 mg once-weekly yielded significantly greater BMD gains, in total hip BMD and lumbar spine BMD, and larger decreases in bone turnover marker levels than risedronate 35 mg once-weekly over 24 months, with no difference in upper gastrointestinal tolerability (Rosen *et al.*, 2005, Reid *et al.*, 2008). Comparative study of combination therapy group of osteoporosis drugs and calcium-antagonists was as follows. The amlodipine group and lacidipine group combined with ALD 70 mg once-weekly showed significant increase in LBMD. Amlodipine combined with maxmar-

vil® group showed significant increase in WBMD (BMD of Ward's), but cilnidipine group showed significant decrease in WBMD. These results are similar with those of ALD dose as following results.

The treatment with 1, 2.5, or 5 mg over 2 years, and 10 mg of ALD daily for 3 years increased significantly dose-related increases in the lumbar spine BMD (0.65%, 3.5%, 5.7%, and 8.8% respectively). Also, ALD produced dose-dependent decreases in bone turnover and increases in mineral density in the lumbar spine, and skeleton and reduces the incidence of fractures in postmenopausal women with osteoporosis (Bone *et al.*, 1997, Liberman *et al.*, 1995). Treatment with 5, 10 mg of ALD daily for 10 years, or the discontinuation of 20 mg of ALD daily for 2 years, the 10 mg group increased the BMD of 14% in lumbar spine. But smaller gains occurred in 5 mg group, and the discontinuation group resulted in the gradual loss of effect. This was associated with sustained therapeutic effects on bone density and remodeling (Bone *et al.*, 2004). Ten mg once-daily dosing is effective for increasing BMD and ALD 70 mg once-weekly dosing regimen provide patients with a more convenient, therapeutically equivalent alternative to 10 mg daily dosing (Schnitzer *et al.*, 2000). In the experiment of rat osteocyte, high dose (100 mg/kg) nifedipine or verapamil of calcium channel blockers (CCBs) inhibit load-induced bone formation by Ca⁺⁺ blocking effect on BMD (Jiliang *et al.*, 2002), but verapamil within clinical reference range (0.75 mg/kg) shows increase BMD and bone formation (Eva *et al.*, 2001). Nifedipine leads to a lower bone formation and epiphyseal growth plate activity, and also was affected bone physiology with consequences on bone growth and bone volume when compared with an untreated control group (Duriez *et al.*, 1993). Chronic nifedipine has not been shown to affect bone mineral content and BMD (Albers *et al.*, 1991).

CCBs are the most used drugs to treat mild-to-moderate hypertension and especially amlodipine of slow-onset, long-acting CCBs is commonly used for antihypertensive action and few adverse effects (Takao, 1998). Amlodipine is the most used drug in this study. Benidipine blocks calcium influx through L-type voltage dependent calcium channel greatly potentiate mineralization, calcium influx and alkaline phosphates (ALP) activity. Amlodipine partially elevate ALP activity and block the calcium influx at 10 µM in osteoblast-like cell (MC3T3-E1 cell) line (Nishiya and Sugimoto, 2001). Also benidipine blocks calcium influx more strongly than other CCBs by high affinity to calcium channel and has strong osteoblast differentiating ability. Other dihydropyridine derived CCBs also

stimulate osteoblast differentiation (Nishiya *et al.*, 2002).

CCBs receptors linked to voltage-regulate calcium channels have been reported in osteoblast-like osteosarcoma cell culture lines (Guggino *et al.*, 1988). The properties of calcium channels are largely conferred by their pore-forming α_1 subunit. And the dihydropyridine (DHP) is bound with high affinity the α_1 subunit of the DHP receptor protein (Mori *et al.*, 1996). Barry was reported that calcium channel α_1 subunits are expressed in human osteoblasts including both L-type and non L-type isoforms (Barry, 2000). Above facts suggest that L-type calcium channel plays an important role in ability for osteoblast and bone metabolism. So osteocyte reaction of CCBs related with L-type calcium channel is important.

It was reported, in an ovariectomy induced osteopenic rat model, that amlodipine was found to both promote femoral calcium deposition and inhibit its loss, but lacidipine was found only to inhibit calcium loss. The potent action of amlodipine and lacidipine compared to other drugs used to treat osteoporosis, and may lead to finding a novel therapeutic target for bone diseases such as osteoporosis, at least in hypertensive patients (Zekai *et al.*, 2008). But because there is no report about bone formation or bone metabolism of cilnidipine, in the case of combination therapy of cilnidipine and risedronate or maxmarvil®, BMD decrease in lumbar and femur area can not be compared. So we assume more in vitro experiment of osteocytes over all the dihydropyridine drugs including cilnidipine and more clinically prospective in vivo study should be done. Cilnidipine combination therapy group shows decreased trend of BMD but no statistical significance in nonparametric test (Wilcoxon signed rank test). So, more patients with calcium-antagonist combination therapy are needed in next study.

In conclusion, it is desirable that combination therapy with calcium-antagonists is used carefully in the treatment of osteoporosis with high blood pressure. In the case of combination therapy of osteoporosis drugs and above, BMD change between intervals need to be prospectively studied and when developing new calcium-antagonists clinical trial result related to various disease as well as in vitro result should be considered and applied to clinical conditions.

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