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Original Article

The effects of atorvastatin as an adjuvant for osteoporosis on bone metabolism and pain in elderly patients with osteoporosis

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Abstract: Objective: To study the effects of atorvastatin as an adjuvant in the treatment of elderly patients with osteoporosis, and its effect on bone metabolism, pain and other biochemical parameters. Methods: We recruited 108 elderly patients with osteoporosis for this study and recorded their baseline characteristics. All participants were randomized into the experiment group (n=54) or the control group (n=54). The control group received only alendronate sodium, while the experiment group received alendronate sodium and atorvastatin. The efficacies of the drugs in the two groups were measured using bone metabolic markers, recording bone mineral densities (BMDs) at different skeletal sites, and quantifying inflammatory cytokines and pain. The adverse effects on the two groups were also compared. All the parameters were recorded at baseline and at 6 months after treatment. Results: Compared with the control group, the experiment group had a significantly higher clinical effective rate (P<0.05). At month 6, the levels of osteoprotegerin, bone alkaline phosphatase, osteocalcin, N-MID osteocalcin, and 25-hydroxyvitamin D were significantly increased in both groups compared with the levels at baseline, and they were significantly higher in the experiment group compared with the levels in the control group (all P<0.05). At month 6, BMDs at the femoral neck, femur trochanter, lumber spine, and forearm were significantly increased in both groups compared with at the BMDs at baseline, and they were significantly higher in the experiment group compared with the levels in the control group (both P<0.01). The serum levels of IL-6 and the VAS (Visual analogue scale) and FPS-R (Faces pain scale revised) scores were significantly lower in both groups compared with the scores at baseline (P<0.01), and the scores were significantly lower in the experiment group compared with those in the control group (P<0.01). No statistical differences were observed between the groups in the occurrence of adverse effects (P>0.05). Conclusion: The combined use of alendronate sodium and atorvastatin in the treatment of elderly patients with osteoporosis can significantly improve the patients' conditions, alleviate inflammatory responses and pain, normalize bone metabolism, and increase BMDs at different skeletal sites compared with the use of alendronate sodium alone.

Keywords: Atorvastatin, osteoporosis, bone metabolism, pain, efficacy

Introduction

A common metabolic bone disorder, osteoporosis in the elderly is characterized by significant bone loss and by vulnerability to fragility fracture due to damage in the bone microarchitecture. Patients may complain of pain or tenderness at different skeletal sites, pain which may have serious impacts on their daily lives and health statuses, both physically and mentally [1, 2]. As the population ages, osteoporosis has been more commonly seen in the elderly in recent years. Therefore, it is essential to carry out research to seek a more scientific and effective treatment for the disease [3]. Bisphosphonates were often used for the treatment of osteoporosis. However, studies have shown that the long-term use of bisphosphonate results in discomfort in the gastrointestinal tract, and can even lead to esophageal cancer, side effects which have a great impact on treatment compliance [4]. Atorvastatin has proved to be an effective drug in preventing cardiovascular diseases and reducing cholesterol,

but its principal indications did not include osteoporosis. Previous studies have found that hyperlipidemia is linked to the occurrence and development of osteoporosis, which indicates that atorvastatin may promote osteoplastic proliferation by activating osteoblasts and increasing bone formation [5]. However, few studies have examined the use of atorvastatin in the treatment of bone metabolic disorders, especially its effects on indices related to bone metabolism. The purpose of this study was to investigate the effects of atorvastatin as an adjuvant in the treatment of elderly patients with osteoporosis, and its effect on bone metabolism, pain and other biochemical parameters.

Materials and methods

General information

We recruited 108 elderly patients with osteoporosis who received treatment at the departments of Geriatrics and Orthopedics in The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, from February 2017 to August 2018. All participants were diagnosed according to *Expert consensus on the diagnosis of osteoporosis in Chinese population* [6]. The study was approved by the Ethics Committee of The First Affiliated Hospital of USTC, and all participants and their relatives signed an informed consent before enrolling in the study. The participants were randomized into either the experiment group (n=54) or the control group (n=54).

Inclusion criteria: Patients who were diagnosed according to expert consensus on the diagnosis of osteoporosis in the Chinese population; patients who were sound in their gastrointestinal function and who didn't have any other metabolic disorders; patients who received no drugs for bone metabolism in the month before enrolling in the study; patients with no contraindications to the treatment or examination; patients with no malignant tumors; patients who were sound in their mental state, and patients with a complete medical history. Exclusion criteria: Patients who had severe heart, liver, or kidney disease; patients with a history of receiving atorvastatin and alendronate sodium; patients thought to have low treatment compliance; patients with a growth hormone deficiency, and patients with severe scoliosis.

Methods

The control group received alendronate sodium tablets (Beijing Winsunny Harmony Science & Technology Co., Ltd.) per os, 70 mg once per week; alfacalcidol capsules (Roche) per os, two capsules once per day; Caltrate with vitamin d 600 tablets (Wyeth Pharmaceutical Co., Ltd.) per os, two tablets once per day. On that basis, the experiment group also received atorvastatin calcium tablets (Pfizer Pharmaceutical Co., Ltd.) per os, one tablet per day. The two groups received treatment for 6 consecutive months.

Measurements

All patients had 3 mL of fasting blood drawn from the antecubital vein in the morning at baseline and at month 6 respectively. The blood sample was centrifuged at the speed of 3,500 r/min for 5 min to separate the blood serum, which was kept for laboratory tests. Bone metabolic markers including osteoprotegerin (OPG), bone alkaline phosphatase (BAP), osteocalcin (BGP), N-MID osteocalcin (N-MID) and 25-hydroxyvitamin D (25(OH)D) were measured. BMDs at the femoral neck, the femur trochanter, the lumbar spine, and the forearm were measured by dual-energy X-ray absorptiometry. Inflammatory cytokine IL-6 was also measured. VAS and FPS-R were adopted to assess the incidence of pain. The total score of VAS was 10, and the lower the score, the less the pain; FPS-R involves 6 facial expressions including smile and cry and is based on a scale of 0-10, the lower the score, the less the pain. The drugs' side effects in the two groups were recorded.

Assessment criteria

The definition of marked effect: the patient's condition significantly improved over the six months, and the BMDs at the various skeletal sites were back to their normal levels after treatment. The definition of effective: the patient's condition improved over the six months, and the BMDs at the various skeletal sites increased after the treatment. The definition of ineffective: The patient's condition and BMDs at the various skeletal sites showed no signs of

Table 1. Comparison of baseline characteristics between the two groups

	Gender (n)		Age (years)	Average course of disease (years)
	Male	Female		
The experiment group (n=54)	24	30	65.81±3.12	8.42±1.37
The control group (n=54)	25	29	65.74±3.10	8.38±1.36
t/χ^2	0.037		0.117	0.152
P	0.847		0.907	0.879

Table 2. Comparison of efficacy between the two groups

	Marked effect	Effective	Ineffective	Clinical effective rate
The experiment group (n=54)	30	21	3	51 (94.44%)
The control group (n=54)	21	23	10	44 (81.48%)
χ^2				4.285
P				0.038

improvement or even worsened after treatment. Total effective rate = (cases with a marked effect + cases of effective)/total cases * 100%.

All the data were statistically processed using the SPSS 20.0 software package. The measurement data were expressed as the mean ± standard deviation ($\bar{x}$ ± sd). The comparison of the treatment effects within a group was based on a paired *t*-test and between two groups on independent-sample *t*-tests. The enumeration data were expressed as a percentage (%) and were compared based on a chi-square test. A *P* value of <0.05 was considered significant.

Results

Baseline characteristics

The baseline characteristics including gender, age and the average course of disease were not significantly different between the groups (all P>0.05). See **Table 1**.

Comparison of efficacy between two groups

Compared with the control group, the experiment group had a significantly higher clinical effectiveness rate (P<0.05). See **Table 2**.

Comparison of bone metabolic parameters between the two groups

No statistical differences were observed between the two groups in bone metabolic markers at baseline (P>0.05). At month 6, OPG, BAP, BGP, N-MID and 25(OH)D were significantly increased in both groups compared with baseline (all P<0.01), and they were significantly higher in the experiment group compared with the control group (all P<0.01). See **Table 3**.

Comparison of BMDs at different skeletal sites in the two groups at baseline and month 6

No statistical differences were observed between the two groups in BMDs at different skeletal sites at baseline (P>0.05). At month 6, the BMDs at the femoral neck, the femur trochanter, the lumbar spine, and the femur had significantly increased in both groups compared with at the baseline levels (all P<0.01), and they were significantly higher in the experiment group than they were in the control group (all P<0.01). See **Table 4**.

Comparison of inflammatory cytokines in the two groups at baseline and month 6

No statistical differences were found between the two groups in inflammatory cytokines at baseline (P>0.05). At month 6, the serum IL-6 levels were significantly decreased in both groups compared with those at baseline (all P<0.01), and they were significantly lower in the experiment group compared with the control group (both P<0.01). See **Table 5**.

Comparison of pain in the two groups at baseline and month 6

No statistical differences were found between the two groups in the VAS and FPS-R scores at baseline (P>0.05). At month 6, the VAS and FPS-R scores had significantly declined in both groups compared with baseline (all P<0.01), and they were significantly lower in the experiment group compared to the control group (both P<0.01). See **Figure 1**.

Comparison of drug side effects between the two groups

The rate of side effects in the experiment group was 5.56%, and the rate in the control group

Table 3. Comparison of bone metabolic parameters between the two groups at baseline and at 6 months

Group	Time	OPG (pg/mL)	BAP (μg/L)	BGP (μg/L)	N-MID (ng/mL)	25OHD (nmol/L)
The control group (n=54)	Baseline	34.65±10.57###	10.05±5.71##	5.77±1.70###	10.58±5.67###	52.33±5.81###
	Month 6	45.36±16.02	13.25±6.49	8.02±2.96	14.85±10.96	66.47±6.22
The experiment group (n=54)	Baseline	34.68±11.49###	10.06±5.73###	5.82±1.71###	10.59±5.70###	52.29±5.90
	Month 6	53.22±15.96**	17.17±6.52**	9.68±3.13**	19.24±11.33*	74.07±8.96**

Note: Compared with the control group at 6 months, *P<0.01, **P<0.05. Compared within the group at 6 months, ##P<0.01, ###P<0.001. OPG: osteoprotegerin; BAP: bone alkaline phosphatase; BGP: osteocalcin; N-MID: N-MID osteocalcin; 25(OH)D: 25-hydroxyvitamin D.

Table 4. Comparison of BMDs at different skeletal sites between the two groups at baseline and at 6 months ($\overline{x}$ ± sd) g/cm^3

Group	Time	Femoral neck	Femur trochanter	Lumber spine	Femur
The experiment group (n=54)	Baseline	0.70±0.11###	0.67±0.03###	0.79±0.12###	0.71±0.06###
	Month 6	0.85±0.07	0.74±0.02	0.91±0.06	0.89±0.09
The control group (n=54)	Baseline	0.71±0.09###	0.68±0.04###	0.80±0.13###	0.73±0.08###
	Month 6	0.94±0.05**	0.89±0.06**	0.99±0.08**	0.98±0.05**

Note: Compared with the control group at 6 months, **P<0.01. Compared within the group at 6 months, ###P<0.001.

Table 5. Comparison of inflammatory cytokines between the two groups at baseline and at 6 months ($\overline{x}$ ± sd) μg/L

Group	Time	IL-6
The experiment group (n=54)	Baseline	164.48±43.01###
	Month 6	115.83±20.15
The control group (n=54)	Baseline	164.55±43.07###
	Month 6	70.26±19.44**

Note: Compared with the control group at 6 months, **P<0.01. Compared within the group at 6 months, ###P<0.001. IL-6: interleukin-6.

was 12.96%. No statistical differences were observed between the groups in the rate of adverse effects (P=0.184). See **Table 6**.

Discussion

According to published data [7, 8], there are over 200 million patients with osteoporosis worldwide, and over 90 million osteoporotic patients are in China, of which the elderly patients aged over 60 account for 56%, making China ranked first globally. Elderly patients with osteoporosis are increasing as the problem of population aging aggravates. Osteoporosis is a common bone metabolic disorder. As it develops, osteoporosis will cause severe damage to bone microarchitecture by gradually reducing the bone matrix and the levels of various minerals [9, 10]. With significantly declined levels of minerals, trabecular bone and cortical bone loss will occur, leading to increasing numbers of bone fracture cases. The current therapeutic principle for the elderly with osteoporosis is reducing bone loss while alleviating pain. Alendronate sodium is often used in the treatment.

Alendronate sodium is a bisphosphonate drug. It helps maintain bone mineral density by inhibiting osteoclast-mediated bone-resorption and improving bone formation. Previous studies have shown that atorvastatin plays a positive role in promoting the proliferation and differentiation of osteoblasts and restoring bone microarchitecture [11-13]. In this study, the experiment group had a significantly higher clinical effective rate than the control group. At month 6, the VAS and FPS-R scores in the two groups declined significantly, and the experiment group scored significantly lower than the control group. No statistical differences were observed between the groups in the occurrence of adverse effects. This study showed that patients with osteoporosis who received atorvastatin based on alendronate sodium had significantly better outcomes and suffered less pain than patients who received alendronate sodium alone.

Osteoporosis is a chronic degenerative disease. The mechanism by which osteoporosis develops is a decline of bone formation caused by an increase of osteoclast-mediated bone-resorption and the inhibited activity of osteo-

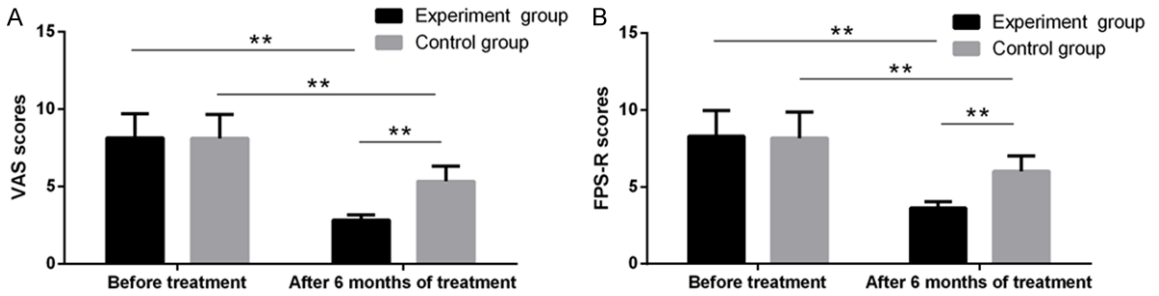

Figure 1. Comparison of incidence of pain in two groups at baseline and month 6. A. Comparison of VAS scorings between two groups, **P<0.01; B. Comparison of FPS-R scorings between two groups, **P<0.01. VAS, visual analogue scale; FPS-R, Faces pain scale revised.

Table 6. Comparison of side effects on drugs between two groups

	Nausea and vomiting	Dizziness and headache	Constipation	Myalgia	Rate of side effects
The experiment group (n=54)	2	1	0	0	3 (5.56%)
The control group (n=54)	1	3	1	2	7 (12.96%)
χ^2					1.763
P					0.184

blasts. Age, endocrine disorders, and other factors may also have an impact on the disease [14-16]. Studies have found a positive correlation between age and the severity of endocrine disorders [17]. Severe endocrine disorders damage the proliferation and differentiation of osteoblasts, resulting in an imbalance between bone resorption and bone formation. Bone loss is also more likely to occur due to bone metabolic disorders, aggravating osteoporosis. Bone metabolism can be indicated by biochemical markers, including OPG, BAP, BGP, N-MID, and 25(OH)D. This study showed that OPG, BAP, BGP, N-MID, and 25(OH)D were significantly increased at month 6 in both groups compared with baseline, and they were significantly higher in the experiment group compared with the control group. Moreover, BMDs at the femoral neck, the femur trochanter, the lumbar spine, and femur were significantly increased at month 6 in both groups compared with baseline, and the BMDs were higher in the experiment group compared with the control group. The results demonstrated that the use of atorvastatin as an adjuvant in treating the elderly patients with osteoporosis would effectively improve patients' bone metabolism and increase bone mineral density. This was probably because, on the one hand, the apoptosis of osteoclasts induced by alendronate sodium significantly increased bone mineral density by reducing bone loss and by prolonging the process of bone mineralization [18]; on the other hand, the transcription of the BMP-2 gene of the osteoblasts effectively enhanced by atorvastatin played an important role in restoring the microarchitecture of bone and increasing bone strength [19].

Our study demonstrated that osteoporosis is associated with varying degrees of inflammatory responses in its development, as evidenced by the abnormal rise of IL-6, which enhanced the activity of osteoclasts and therefore worsened the situation [20-22]. Our study showed that the level of IL-6 was significantly lower at month 6 compared with baseline, and the level was also significantly lower in the experiment group than it was in the control group. The results showed that the combined use of alendronate sodium and atorvastatin for treating elderly patients with osteoporosis could significantly reduce inflammatory responses. This is probably due to the inhibition of the ongoing inflammatory responses and the interrupting the proliferation and differentiation of osteoclasts, which stem the development of osteoporosis.

The study population was recruited from a single center and was therefore small. A multicenter analysis with a large population is need-

ed. Furthermore, an in-depth study with a larger study population and a longer time span is also needed to investigate in detail the mechanisms of atorvastatin on osteoporosis.

In conclusion, the combined use of alendronate sodium and atorvastatin in the treatment of elderly patients with osteoporosis can significantly improve patients' conditions, alleviate inflammatory responses and pain, normalize bone metabolism, and increase BMDs at different skeletal sites compared with the use of alendronate sodium alone. It is useful and is therefore worthy of clinical application.

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Disclosure of conflict of interest

None.

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