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Author's Contribution
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Krzysztof Napierała[1(B,D,E)], Tomasz Miazgowski[2)C,D,E,F)], Krzysztof Hoszowski[3(B)], Róża Bieńkowska[3(B)], Roman Lorenc[4(B)], Stanisław Czekalski[5(G)]

[1] *Oddział Nefrologii, Wojewódzki Szpital Zespolony, Szczecin*
[2] *Klinika Endokrynologii, Nadciśnienia Tętniczego i Chorób Przemiany Materii, Pomorska Akademia Medyczna, Szczecin*
[3] *Niepubliczny Zakład Opieki Zdrowotnej Centrum, Warszawa*
[4] *Zakład Biochemii Klinicznej, Centrum Zdrowia Dziecka, Warszawa*
[5] *Klinika Nefrologii, Transplantologii i Chorób Wewnętrznych, Akademia Medyczna, Poznaniu*

The effect of clodronate on bone mineral density and serum osteocalcin in postmenopausal women with osteopenia – a prospective, randomized, placebo-controlled study

Key words: *clodronate, osteocalcin, bone mineral density*

SUMMARY

Background. *The efficacy of bisphosphonates in treatment of established osteoporosis has been well-documented; less data have been published on their efficacy in the prophylaxis of postmenopausal bone loss in women with osteopenia. The aim of study was to evaluate the effect of clodronate on bone loss in early postmenopausal women with vertebral osteopenia.*

Materials and methods. *Forty five women aged 52.3±3.8 yr with a lumbar spine (Spine) t-score between -1 and -2.5 SD received clodronate 400 mg/day or placebo for 12 months. Bone mineral density (BMD) was measured by DXA in Spine and femoral neck (Femur). Serum osteocalcin (OC) was assessed by RIA. BMD and OC were measured at the baseline, after 1 year of treatment and after further 1 and 2 years of follow-up.*

Results. *BMD slightly decreased in clodronate group: Spine by 0.2% after 1 year (N.S.), 0.5% after 2 years (N.S.) and 0.9% after 3 years ($P<0.05$ vs. placebo group); Femur by 0.2%, 0.9% and 1.3% (N.S.). OC did not change in placebo group but significantly decreased in clodronate group (15.2%; $P<0.05$).*

Conclusions. *Clodronate 400 mg daily given postmenopausal women with osteopenia is effective in decreasing OC but an effect on BMD is just detectable and its clinical significance is unclear.*

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Adres do korespondencji / Address for correspondence
dr hab. med.Tomasz Miazgowski, Klinika Endokrynologii, Nadciśnienia Tętniczego i Chorób Przemiany Materii, Pomorska Akademia Medyczna, ul. Arkońska 4, 71-455 Szczecin
tel. +48 91 4316241, fax +48 91 4542042, e-mail: miazgowski@interia.pl

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BACKGROUND

Within the past decade, osteoporosis has been receiving increased attention as a disease entity of growing proportion. Since the introduction of alendronate in the mid 1990s, bisphosphonates (BPs) revolutionized the treatment of osteoporosis. BPs are potent antiresorptive compounds, which bind to bone and decrease osteoclast-induced bone resorption, and are currently widely used for treatment of established osteoporosis. However, data from the NORA Study, a longitudinal, observational study of more than 200,000 postmenopausal women not previously diagnosed with osteoporosis, showed that almost three quarters of the new fractures occurred in those women who were not osteoporotic by current guidelines and most of fractures affect individuals with osteopenia [1]. Some of the earlier studies suggest that the effects of BPs on bone mass gain and reduction of fracture rate inversely correlate with a baseline bone mineral density (BMD) [2, 3, 4]. Clodronate is a first generation bisphosphonate, used successfully for treatment of osteolytic tumor-induced bone disease, Paget's disease and non-tumor-induced hypercalcemia [5]. Recent studies showed that oral clodronate 800 mg daily given for three years reduces the new vertebral fracture risk in women with postmenopausal or secondary osteoporosis [6] and is effective in increasing BMD and reducing bone turnover in postmenopausal women [7].

The aim of the present study was to evaluate in a prospective, randomized, double blind and placebo-controlled clinical trial whether clodronate prevents bone loss and decreases bone turnover in healthy, early postmenopausal women with vertebral osteopenia.

MATERIAL AND METHODS

Study subjects

The study was performed on 45 women with vertebral osteopenia. To be eligible they had to be 45 years or more of age and 1-5 years after natural menopause. Women with the concomitant diseases in the history or taking medications that might affect bone metabolism were not enrolled to the study. They had to have a lumbar spine (Spine) BMD value between -1 and -2.5 standard deviation below the mean of healthy young females, according to the WHO classification of osteopenia [8]. The protocol was approved by the ethics committee at each center, and all women gave written informed consent.

Measurements

Height and weight were measured without shoes; height was measured with a single fixed stadiometer, and weight was measured on a standard clinical balance. Body mass index was calculated as weight (kilograms) divided by height squared (meters squared).

BMD of the L1-L4 Spine and the femoral neck (Femur) were measured by dual-energy-x-ray absorptiometry (GE Lunar, Madison, WI) using the medium scan mode. BMD values were expressed in grams per centimeter squared and as t-scores. The coefficient of variation of BMD at our institution determined in perimenopausal women is 1.6 at the lumbar spine and 1.3% at the proximal femur.

Changes in bone turnover were evaluated by monitoring serum osteocalcin (OC), assessed by RIA (Incstar Corporation, Stillwater, MN; normal range: 2.7-11.5 ng/ml). In all the women OC was measured in one batch in serum that had been thawed for the first time. The intra- and interassay CVs were below 10%.

BMD and serum OC were assessed at the baseline, after 12 months of treatment and after 24 and 36 months of the follow-up.

Measurements of the safety of treatment included serum calcium (adjusted for albumin), serum phosphate, and indices of hematological, hepatic, and kidney function at entry and at regular intervals thereafter.

Study design

This was a prospective, double-blind, randomized and placebo controlled study, performed in two centers: Szczecin and Warsaw. Subjects were randomly allocated to treatment groups to receive placebo or 400 mg of clodronate (Bonefos, Leiras Oy, Finland) daily for 12 months. The randomization was done with a random permuted blocks separately for each center and the medication for each patient was supplied by Leiras Oy. Study drugs were given in the evening 2 hours away from meals swallowed with a glass of water, as suggested in earlier report [7]. No other medications, food or drink were allowed to be taken at the same time as the study drug. Calcium supplementation (400 mg of elemental calcium daily) was given to every patient in the morning. Patients who completed the treatment phase continued the 2-year follow-up. In extension period patients from both groups received only calcium supplementation in the same dose.

Statistical analysis

The results were expressed as the mean ± SD, assuming $P < 0.05$ as a significant difference between means. Prospective data were analyzed with the analysis of variance for repeated measurements (ANOVA). The differences between means in both treatment groups were tested by Wilcoxon test or Mann-Whitney non-parametric U test as appropriate.

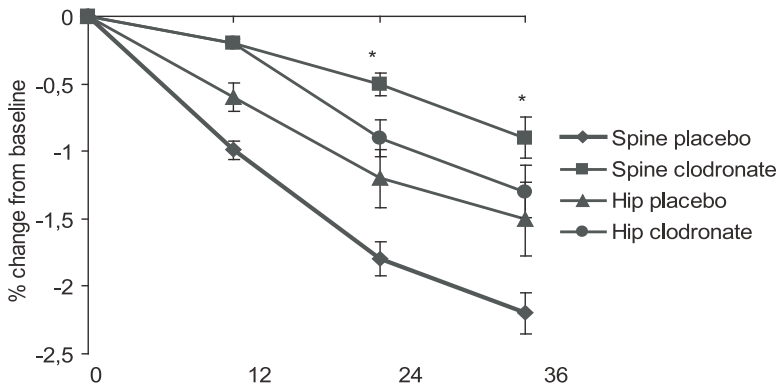
RESULTS

Clinical characteristics, BMD values and serum OC are summarized in Table 1. There were no significant differences between the studied parameters in both treatment groups. During 12 months of treatment, Spine BMD decreased by 0.99% in the placebo group and by 0.2% in the 400 mg clodronate group. During a follow-up period, a further and significant decrease of Spine BMD after 24 months (1.8±0.2%; P<0.05) and after 36 months (2.2±0.3%; P<0.05) in the group receiving placebo was observed. There were no differences of Spine BMD between both groups of women during 12 months of treatment but during the 2-year follow-up the 400 mg clodronate group had significantly higher BMD in comparison with the group receiving placebo (Fig. 1). Femur BMD slightly decreased in both groups but the differences were not statistically significant. During 36 months mean serum OC remained stable in the placebo group (Fig. 2), but significantly decreased after 12 months of treatment with clodronate, and this effect maintained for 12 months after cessation of treatment.

Treatment with clodronate was well tolerated and no serious adverse events occurred during treatment and after treatment withdrawal. Mild gastrointestinal side effects, including abdominal pain and dyspepsia, were reported sporadically. There were no clinically significant effects of clodronate on hematological or biochemical indices of safety.

Tab. 1. Baseline characteristics of women receiving clodronate and placebo

	Clodronate (n = 22)	Placebo (n = 23)
Age (years)	52.38 ± 3.8	51.92 ± 3.7
Weight (kg)	68.65 ± 11.7	66.68 ± 11.7
Height (cm)	158.53 ± 5.8	160.18 ± 5.5
BMI (kg/m^2)	27.49 ± 2.8	26.02 ± 3.2
Years since menopause	2.19 ± 0.4	2.01 ± 0.3
Smokers/non smokers	9/13	9/14
Spine (g/cm^2)	0.997 ± 0.08	1.019 ± 0.06
Femur (g/cm^2)	0.854 ± 0.07	0.863 ± 0.09
Spine t-score (SD)	-1.76 ± 0.44	-1.68 ± 0.49
Femur t-score (SD)	-1.11 ± 0.34	-1.14 ± 0.29
Osteocalcin (ng/ml)	6.83 ± 2.99	6.94 ± 2.73



P<0,05 between groups receiving clodronate and placebo (Spine BMD)

Fig. 1. Changes of bone mineral density in the lumbar spine and femoral neck during treatment with clodronate or placebo (months 0-12) and withdrawal of treatment (months 12-36)

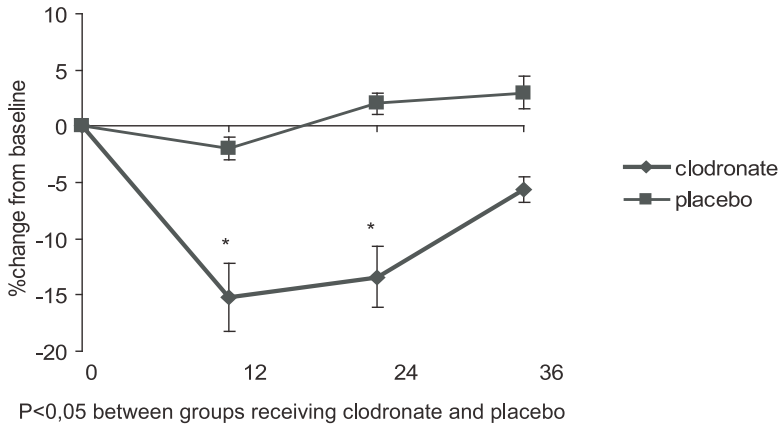


Fig. 2. Changes of serum osteocalcin during treatment with clodronate or placebo

DISCUSSION

Our study demonstrates that in early postmenopausal women with newly identified vertebral osteopenia, clodronate in a daily dose of 400 mg effectively reduce bone turnover as assessed by changes in serum OC. Although the mean BMD increased in the clodronate group and was significantly higher in comparison with the controls, clodronate therapy failed to increase spinal BMD significantly at 12 months of treatment. It has been suggested that one to three years of therapy with clodronate significantly increase spinal BMD [6, 7, 9, 10, 11]. On the contrary, the results of some earlier studies [12, 13, 14, 15] are consistent with our findings that the effect of clodronate on the spine BMD is relatively low, much less than the effects of another BPs – alendronate [12, 16], risedronate [2, 12], pamidronate [3] or ibandronate [17], where bone mass gain reaches approximately 3-7%/year. Some of these discrepancies might be explained, at least partially, by different treatment regimens applied – different cyclical dosing regimens [7, 9, 11, 14], continuous oral administration [6, 10, 14] or clodronate given parentally in varying doses [12, 13, 15]. However, Tsai et al. [14] in a randomized study compared the efficacy of cyclic and continuous oral administration of clodronate in 54 newly identified osteopenic postmenopausal women, and found that clodronate was not effective in decreasing postmenopausal bone loss at various sites, regardless of the treatment regimen.

It has been suggested that the effect of BPs on bone mass depends on the initial BMD [3, 18]. Most of studies on the efficacy of different BPs were performed on postmenopausal women with osteoporosis, according to WHO criteria, and this is much less evident in women with normal or only slightly decreased BMD [18]. Our results are consistent with these observations. On the contrary, McCloskey et al. [6] found that antifracture efficacy and positive effect of clodronate on the bone mass is independent of the underlying BMD, at least in women with established osteoporosis.

Our results indicate that after discontinuation of clodronate treatment, the postmenopausal BMD decrease at the lumbar spine was significantly diminished for a period of the 2-year follow-up in comparison with the placebo group. This finding was clearly demonstrated with other BPs [3, 5, 19], and less investigated with clodronate. The reason of this phenomenon is that BPs have a long residence time in bone and therefore they accumulate in bone up to 30 years [3, 5]. Inhibition of bone resorption is sustained for at least several years after cessation of therapy, illustrating that BPs released from the matrix during bone remodeling effectively inhibit osteoclasts, as it has been well documented for alendronate [19].

In the present study, the clodronate's bone-sparing effects did not differ from placebo at the femoral neck. This finding is consistent with previous reports and seems to be inferior to those obtained with other BPs [5, 7, 13, 14].

There have been no previous studies on the effect of clodronate discontinuation on serum OC in postmenopausal women. Our study demonstrated that serum OC significantly decreased during treatment and this effect maintained for 12 months after discontinuation of clodronate. In the only study assessing the influence of long term treatment with clodronate on serum OC, Morabito et al. [15] reported a slight decrease of OC after 12 and 24 months of 100 mg clodronate given intramuscularly every 10 days in young patients with thalassemia-induced osteoporosis. Together with the results of previous studies reporting

the significant effect of clodronate on markers of bone turnover: urinary excretion of type I collagen aminoterminal (NTX) and carboxyterminal (CTX) telopeptides [7, 14], pyridinoline and deoxypyridinoline [13], serum concentration of procollagen I carboxyterminal propeptide (PICP) [20] or hydroxyproline excretion [20], our results indicate that long-term therapy with clodronate significantly inhibits bone turnover, regardless of dose and route of administration. This is an important finding, since fracture prevention by BPs and other antiresorptive agents is correlated much better with reduction in markers of bone turnover that with gain in BMD [21, 22].

Our results confirm the previous reports that treatment with clodronate is well tolerated, with no significant adverse events attributable to the therapy [6, 7, 9, 11, 14].

CONCLUSION

Clodronate 400 mg daily given postmenopausal women with osteopenia is effective in decreasing OC but an effect on BMD is just detectable and its clinical significance is unclear.

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