Original Article

Effect of risedronate on high-dose corticosteroid-induced bone loss in patients with glomerular disease

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Abstract

Background. Corticosteroids are often used for the treatment of glomerular diseases. We examined whether bisphosphonate or vitamin D3 has beneficial effects on bone mineral density (BMD) in patients with glomerular diseases being treated with high-dose corticosteroids, including pulse therapy.

Methods. Thirty-eight patients (19 men and 19 women, aged 42 ± 16 years) were randomized into three groups: bisphosphonate alone (risedronate 2.5 mg/day, group R, n = 12), vitamin D3 alone (alfacalcidol 0.5 μg/day, group A, n = 15) and the combination of both agents (group R+A, n = 11). BMD at the lumbar spine was measured before and 12 months after treatment. The biochemical parameters of bone metabolism were assessed before and 3, 6 and 12 months after treatment.

Results. In group R+A, BMD was significantly increased (+2.0%), whereas BMD was significantly decreased in group A (−5.6%). The BMD in group R did not show a significant change. In patients treated with steroid-pulse, BMD was decreased in groups R and A. In group R+A, BMD was significantly increased (+2.1%). Serum osteocalcin and alkaline phosphatase levels, markers of bone formation, were significantly decreased in all groups. Urinary crosslinked N-telopeptide of type I collagen (NTx) levels, a marker of bone resorption, were decreased in groups R and R+A. In patients with decreased BMD, the urinary NTx levels at baseline were significantly higher than the patients with increased BMD.

Conclusions. Bisphosphonate might be beneficial for the prevention of steroid-induced bone loss in patients with glomerular diseases compared with vitamin D3. The combined therapy may be more effective, especially in patients treated with high-dose corticosteroids, including pulse therapy. A high urinary NTx level before receiving corticosteroids might be a predictive marker of the loss of BMD.

Keywords: bisphosphonate; bone mineral density; corticosteroid; kidney disease; vitamin D

Introduction

Corticosteroids are often used in treatment in a variety of glomerular diseases, including IgA nephropathy (IgAN), membranous nephropathy (MN), minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Many patients with MN or FSGS have refractory nephrotic syndrome. However, the reduction of proteinuria by treatment with corticosteroids induces a good renal prognosis in these patients [1,2]. Even in the patients with IgAN, that shows gradual progression, steroid-pulse therapy improves renal outcome [3,4]. MCNS is a disease showing a good response with corticosteroids, but relapse is frequent. The cumulative dose of corticosteroid for MCNS tends to be high. Although corticosteroids are approved as the first choice of drugs for these diseases, high-dose and long-term corticosteroid treatment may be required. The prevention of the adverse effects of steroids is a very important issue. Although the adverse effects of corticosteroids are diverse, osteoporosis and bone fractures are frequently seen and are difficult to predict. Even with low doses of corticosteroids, steroid-induced bone fracture may occur [5]. Therefore, the prevention of the loss of bone mineral density (BMD) is important when corticosteroids are used.

Glucocorticoids suppress the differentiation of osteoblastic cells, enhance the apoptosis of mature osteoblasts and activate osteoclasts [6]. As a result, the suppression of bone formation and the activation...
of bone resorption, resulting in loss of BMD, are induced. Bisphosphonates inhibit bone resorption by facilitating the apoptosis of osteoclasts. In many clinical trials [7–10], the efficacy of bisphosphonates for the prevention of corticosteroid-induced bone loss has been proven. Based on these results, the use of bisphosphonates may be recommended as the first choice for preventing steroid-induced osteoporosis [11]. However, there have been few reports on the protective effect of bisphosphonates against steroid-induced bone loss focused on patients with kidney diseases.

Yonemura et al. [12] reported that vitamin D3 or vitamin K2 prevented the reduction of BMD by corticosteroids in patients with chronic kidney diseases, although the follow-up period in this study was short. Corticosteroids and immunosuppressive agents are invariably used for the prevention of rejection in renal transplant patients. In these patients, both bisphosphonate and alfacalcidol, an active vitamin D3 analogue, prevented the post-transplant or steroid-induced bone loss to the same degree [13]. These findings suggest that vitamin D3 is also effective for the prevention of steroid-induced osteoporosis in patients with renal diseases. Active vitamin D3 compounds may recover the inhibition of bone formation by corticosteroids [14]. Indeed, the efficacy of vitamin D3 on steroid-induced osteoporosis has been proven by meta-analysis [15].

We investigated the efficacy of risendronate, a bisphosphonate; alfacalcidol or the combined therapy on steroid-induced bone loss in patients with glomerular diseases in a randomized, open-labelled, prospective study. In addition, we assessed whether these drugs were effective in patients who received steroid-pulse therapy, because steroid-pulse therapy is often used for kidney diseases and the protective effects of bisphosphonates and active vitamin D3 analogues on osteoporosis in steroid-pulse therapy are still unknown.

Methods

Patients

A total of 47 patients with glomerulonephritis and initiated on high-dose corticosteroid therapy (more than 30 mg/day of prednisolone, including steroid pulse therapy) from March 2003 to May 2005 in our hospital were assessed. Prednisolone at a daily dose of 0.6–0.8 mg/kg was administrated for 4–8 weeks and gradually tapered. When the effect of oral prednisolone was insufficient, steroid pulse or immunosuppressive agents were added. Nine patients were excluded for the following reasons: four patients had severe renal dysfunction due to rapidly progressive glomerulonephritis, three patients had very high (more than 130% of the young adult mean) or low (less than 80%) BMD levels of the lumbar spine, one young patient had markedly increased markers of bone metabolism, perhaps reflecting his body growth and one patient had already been given a bisphosphonate for the treatment of osteoporosis. Finally, 38 patients were enrolled in this study after obtaining informed consent. The patients included 19 men and 19 women with a mean age of 42 ± 16 years (range, 18–74 years). There were 23 patients with IgAN, eight MN, three MCNS, two FSGS, one membranoproliferative glomerulonephritis and one lupus nephritis. These diagnoses were confirmed by renal biopsy. There were no patients with previous treatment with steroids or with a past history of bone fracture, hormonal diseases or carcinoma.

Study design

This study was conducted as a randomized, open-labelled, prospective control trial for 1 year. This study was approved by the institutional ethics committee in our hospital. The patients were randomized into three groups, receiving 2.5 mg/day of risendronate (group R, n = 12), 2.5 mg/day of risendronate and 0.5 μg/day of alfacalcidol (group R + A, n = 11) or 0.5 μg/day of alfacalcidol (group A, n = 15), using an envelope randomization method. These drugs were simultaneously started with the initiation of steroid therapy. No patients were given calcium supplementation. The tapering of corticosteroids, or the addition of other immunosuppressive agents, was entrusted to each physician. In the case any adverse effects due to risendronate or alfacalcidol, including hypercalcaemia, hyperphosphataemia, hypocalcaemia or dyspepsia, those medications were quickly stopped.

Bone mineral density and laboratory analyses

BMD of the lumbar spine (L2–4) was assessed by dual energy X-ray absorbiometry (DEXA) using a Hologic QDR-4500A (Hologic Inc., Waltham, WA), before and 12 months after treatment. The change in BMD (ΔBMD) was calculated as (BMD at 12 months – BMD at baseline)/BMD at baseline.

The glomerular filtration rate (GFR), urinary protein, serum blood urea nitrogen (BUN) and creatinine were assayed as markers of renal damage at baseline and 12 months after treatment. GFR was calculated according to the creatinine clearance. As biochemical markers of bone metabolism, serum calcium, phosphorus, alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), osteocalcin and urinary crosslinked N-telopeptide of type I collagen (NTx) were examined at baseline and 3, 6 and 12 months after treatment. Serum samples were obtained in the morning after fasting. The assay of GFR, urinary protein and NTx were performed by 24 h urine collection. Serum BUN, creatinine, calcium, phosphorus, ALP, albumin and urinary creatinine and protein were measured by standard methods using an automatic analyser. The serum calcium levels were corrected according to the serum albumin levels. Serum iPTH was measured using a chemiluminescent immunoassay (Lumico PTH kit, Nichols Institute Diagnostic, San Clemente, CA; normal range, 10–65 pg/ml), serum osteocalcin was measured by immunoradiometric assay (Mitsubishi BGP-IRMA kit, Mitsubishi Chemical Co., Tokyo, Japan; normal range, 2.5–13 ng/ml) and urinary NTx was measured by enzyme-linked immunosorbent assay (Osteomark, Ostex International Inc., Seattle, WA; normal range, 9.3–89.0 nmol BCE:mmol creatinine). Urinary NTx levels were corrected according to the urinary creatinine levels.
Effect of risedronate on steroid-induced bone loss

Statistical analyses

Results are expressed as the mean ± SD. Comparison of the data among the groups at each point was achieved by Kruskal–Wallis test and Mann–Whitney U-test. Changes within the groups between before and after treatment were analysed using the Wilcoxon matched-pairs signed-rank test. The correlation between the changes in BMD and the cumulative doses of prednisolone was assessed by Spearman’s correlation test. A P-value of <0.05 was considered significant.

Results

Characteristics of patients

The baseline characteristics of all patients are summarized in Table 1. There were no significant differences in sex, age or body mass index (BMI) among the groups. Two, one and two post-menopausal women were included in group R, R+A and A, respectively. Although the urinary protein level in group R+A was higher than that in group R or A, the difference was not significant. The renal function was similar among the groups. The mean stages of chronic kidney disease in group R, R+A and A were 1.8 ± 0.9, 2.0 ± 0.9 and 1.9 ± 0.9, respectively (P = 0.90). There were also no significant differences in BMD or the biochemical markers of bone metabolism among the groups.

All patients were able to be followed up for 1 year and received prednisolone throughout the follow-up period. No patients had any episode of bone fracture or had to be excluded because of adverse effects during the follow-up period. The cumulative doses of steroids in group R were significantly lower than that in group R+A. The steroid pulse therapy was added in nine, seven and eight patients in groups R, R+A and A, respectively. All patients with steroid-pulse therapy were subsequently given oral high-dose prednisolone. The immunosuppressive agent, mainly ciclosporin A, was used in one, three and two patients in group R, R+A and A, respectively. According to these treatments, urinary protein was significantly decreased and the renal function was stable in all groups (Table 2).

Changes in bone mineral density

At 12 months after treatment, the BMD in groups R, R+A and A was 1.03, 1.08 and 0.96 g/cm², respectively. The change in BMD in the three groups is shown in Figure 1. Although the BMD at 12 months in group R did not show a significant change compared with that at the baseline, the BMD in group A was significantly decreased by 5.6% and that in group R+A was significantly increased by 2.0%. In each group, there were no significant differences of the change in BMD between men and women.

In patients treated with steroid-pulse therapy, BMD at the end of the study was decreased in groups R and A. In group R+A, BMD was significantly increased by 2.1% (Figure 2).

Changes of biochemical markers of bone metabolism

Serum osteocalcin levels at all points after treatment, were significantly decreased compared with those at

<table>
<thead>
<tr>
<th>Causes (n)</th>
<th>Risedronate (n = 12)</th>
<th>Risedronate + Alfacalcidol (n = 11)</th>
<th>Alfacalcidol (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>9</td>
<td>6</td>
<td>8</td>
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<td>Membranous nephropathy</td>
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<td>3</td>
<td>3</td>
<td>0.14</td>
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<td>MCNS</td>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>FSGS</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MPGN</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>6/6</td>
<td>5/6</td>
<td>8/7</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex (man/woman)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.9 ± 18.0</td>
<td>43.7 ± 16.7</td>
<td>41.5 ± 15.4</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 4.2</td>
<td>23.0 ± 2.9</td>
<td>21.1 ± 3.0</td>
<td>0.14</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>17.8 ± 6.8</td>
<td>20.5 ± 12.8</td>
<td>19.5 ± 10.0</td>
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<td>Serum creatinine (mg/dl)</td>
<td>0.96 ± 0.25</td>
<td>0.97 ± 0.27</td>
<td>0.91 ± 0.32</td>
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<tr>
<td>GFR (ml/min)</td>
<td>78.4 ± 23.9</td>
<td>73.6 ± 24.1</td>
<td>81.2 ± 29.5</td>
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<td>Urinary protein (g/day)</td>
<td>2.10 ± 2.07</td>
<td>4.53 ± 3.80</td>
<td>2.29 ± 2.51</td>
<td>0.10</td>
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<tr>
<td>iPTH (pmol/l)</td>
<td>44.5 ± 21.7</td>
<td>35.3 ± 18.9</td>
<td>43.0 ± 17.4</td>
<td>0.39</td>
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<tr>
<td>Osteocalcin (ng/ml)</td>
<td>6.01 ± 2.67</td>
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<td>6.62 ± 1.99</td>
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<td>ALP (IU/l)</td>
<td>180.9 ± 47.4</td>
<td>208.4 ± 87.1</td>
<td>195.6 ± 54.7</td>
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<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.05 ± 0.36</td>
<td>9.16 ± 0.37</td>
<td>9.17 ± 0.36</td>
<td>0.62</td>
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<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>3.56 ± 0.47</td>
<td>3.72 ± 0.77</td>
<td>3.72 ± 0.56</td>
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<tr>
<td>Urinary NTx (nmolBCE/mmolCr)</td>
<td>29.4 ± 14.8</td>
<td>24.6 ± 11.8</td>
<td>29.0 ± 11.0</td>
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<tr>
<td>Bone mineral density (g/cm²)</td>
<td>1.04 ± 0.10</td>
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<td>1.02 ± 0.10</td>
<td>0.48</td>
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<td>T-score</td>
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<td>0.13 ± 0.71</td>
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</tr>
<tr>
<td>Z-score</td>
<td>0.63 ± 1.13</td>
<td>0.73 ± 0.71</td>
<td>0.29 ± 0.70</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. MCNS, minimal change nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; NTx, crosslinked N-telopeptide of type I collagen.
The serum ALP levels also showed similar changes to osteocalcin in all groups (Figure 3B). Urinary NTx was significantly decreased at all points compared with that at baseline in groups R and R + A. The urinary NTx in group A did not change during the follow-up period (Figure 3C). The serum iPTH was mildly deceased in group R, but it did not reach statistical significance. Serum iPTH at 3 and 6 months in group A was significantly decreased compared with that at baseline. Also, in group R + A, serum iPTH was significantly decreased at 6 months (Figure 3D). Serum calcium levels were mildly increased in all groups, but the differences were not significant (Figure 3E). Serum phosphorus levels were mildly decreased in all groups. Serum phosphorus levels at 3 and 6 months in group A and at 12 months in group R + A were significantly decreased compared with those at baseline (Figure 3F).

The predictive factors for the loss of BMD

We classified the patients into three groups according to the change in BMD during the study period; increased more than 1.1% in BMD (group I, n = 12), mild change (−3.2 to +1.1%) (group II, n = 13) or decreased more than 3.2% (group III, n = 13), and assessed the predictive factors for the loss of BMD (Table 3). There were no significant differences in sex, age, BMI or renal function at baseline among the groups. The BMD at baseline was also the same among the groups. However, urinary NTx in groups II or III was significantly high compared with that in group I. Serum osteocalcin and ALP levels in groups II or III were also higher than those in group I, although the difference did not reach the level of statistical significance. The daily dose and cumulative dose of prednisolone, or the addition of steroid-pulse therapy, were not related to the change in BMD. In regression analysis, there was no association between the cumulative dose of prednisolone and the change in BMD (R = 0.08, P = 0.63).

Discussion

Osteoporosis and bone fracture are one of the major adverse effects of corticosteroids. Glucocorticoids, suppress the differentiation of osteoblastic cells and enhance the apoptosis of mature osteoblasts, resulting in the decrease of bone formation [6]. In our study, both serum osteocalcin and ALP at the initial phase of steroid therapy were significantly decreased compared
with those at baseline. Osteocalcin, a bone gla protein, is a non-collagenous bone matrix protein and is synthesized and secreted by cells with an osteoblastic phenotype. Therefore, serum osteocalcin levels are often used as a marker of osteoblastic activity, equal to bone formation. The reduction of serum osteocalcin levels in our patients during the study might suggest that bone formation was suppressed by the administration of corticosteroids. This suggestion may be supported by the finding that serum ALP levels were also decreased at the same time, because ALP is synthesized in poorly differentiated osteoblastic cells. Active vitamin D3 compounds increase the serum osteocalcin level. The administration of both 1, 25-dihydroxyvitamin D3 and low-dose prednisolone (10 mg) prevented the decrease of osteocalcin by steroids in humans [14]. This result suggested that vitamin D3 might prevent steroid-induced osteoporosis.
The prevention of steroid-induced osteoporosis with vitamin D3 has also been proven by meta-analysis [15]. In patients with glomerular diseases, vitamin D3 had protective effects on the steroid-induced loss of BMD at 8 weeks after the treatment [12]. In our study, BMD at 12 months in the patients treated with vitamin D3 alone was significantly decreased compared with that at baseline, despite the study design being similar to the previous report [12]. We think that this discrepancy could be explained by the differences of cumulative dose of prednisolone and follow-up period. There is a report that calcitriol could not improve the decrease of serum osteocalcin levels caused by high-dose prednisolone (40 mg) [16]. We did not have a placebo-control group without either bisphosphonates or vitamin D3 analogues in this study. In the previous reports [7–9,15], the change in BMD at the lumbar spine by DEXA in steroid-treated patients without any supportive drugs was −0.3 to −2.3% for 1 year. These results could not be directly compared with ours, because the diseases and the dose of corticosteroids were diverse and the patients who were already given corticosteroids at baseline were included in these studies. However, we felt that the decrease of BMD in the patients treated with alfacalcidol alone in our study was remarkable. Nakayamada et al. [10] reported that the change in BMD at the lumbar spine in patients with autoimmune diseases treated with high-dose glucocorticoid and 1 μg/day of alfacalcidol for 1 year was −10.3%. Summarizing these findings, vitamin D3 alone may not prevent the loss of BMD caused by the high-dose and long-term use of corticosteroids.

In the patients with nephrotic syndrome, the serum 25-hydroxyvitamin D levels were low and there was an inverse correlation between serum 25-hydroxyvitamin D levels and urinary protein [17]. Since we did not assess serum vitamin D levels in our patients, the effect of proteinuria on the change in BMD could not be completely denied. However, the urinary protein levels among the groups did not show significant differences at either the entry or the end of study. We think that the effect of proteinuria on the change in BMD might not differ among the groups.

Corticosteroids also increase bone resorption, which may be due to the parathyroid hormone-mediated activation of osteoclasts. Glucocorticoids decrease the absorption of calcium in the gastrointestinal system and increase the urinary excretion of calcium [6]. These mechanisms may be related to steroid-induced bone loss. NTx is produced by osteoclasts in the bone as a degradation product of type I collagen. Since NTx reflects the activity of osteoclasts, it is often used as a marker of bone resorption. Bisphosphonates enhance the apoptosis of osteoclasts, resulting in the inhibition of bone resorption. Based on the results of many clinical trials [7–10], bisphosphonates are widely used as the most effective drug to prevent steroid-induced osteoporosis or bone fracture. However, these studies enrolled patients with a variety of diseases, mainly collagen and lung diseases. In the present study, we focused on the patients with renal diseases that may affect the metabolism of bone, and examined whether a bisphosphonate suppressed the steroid-induced loss of BMD in these patients. Urinary NTx was rapidly and significantly reduced, which may indicate the inhibition of bone resorption, in the patients treated with risedronate. As a result, the BMDs in these patients showed no significant differences during the study period, even in the patients with risedronate alone. The finding suggests that bisphosphonates may also be effective for the prevention of steroid-induced osteoporosis.
osteoporosis in the patients with kidney diseases. In many countries, including Japan [11], bisphosphonate is recommended as the first choice of a preventive drug for steroid-induced osteoporosis, and vitamin D or K is the second. Our findings were also compatible with this guideline.

Steroid therapy initiated at higher doses is common in many patients with glomerular diseases, and steroid pulse therapy is often added. In IgAN, the efficacy of steroid pulse therapy has been proven [3,4]. As the pulse therapy, 0.5—1.0 g of methylprednisolone is intravenously administrated for three consecutive days. The glucocorticoid receptor could be almost completely saturated at this dosage. Although the immunosuppressive and anti-inflammatory effects can be expected to be stronger with pulse therapy, the frequency of adverse effects, including bone fracture, may be higher. The effects of steroid-pulse on bone metabolism remain largely unknown. Serum osteocalcin and carboxyterminal propeptide of type I procollagen levels significantly decreased in the patients with active rheumatoid arthritis and treated with steroid-pulse, but this change was transient [18]. Markers of bone resorption were unchanged or decreased, reflecting the decrease of disease activity. Although this study was a short-term observation, the authors concluded that the effect of steroid-pulse on bone metabolism might be mild. On the other hand, Haugeberg et al. [19] reported that the BMD in the patients treated with steroid-pulse, even in the patients without concomitant oral prednisolone, decreased during several months of follow-up. Although it was unclear whether steroid-pulse therapy has the effect on bone metabolism beyond corticosteroids per se from our results, the finding that combined therapy with risedronate and alfalcacidol improved the BMD also in patients treated with pulse therapy was notable. These drugs might correct the imbalances between osteoblasts and osteoclasts induced by corticosteroids. It has been thought that steroid-induced bone fracture may occur without any association with the degree of BMD. However, the decrease in BMD is undoubtedly an important predictive factor of bone fracture. When the steroid-pulse therapy is performed, the combined therapy of bisphosphonate and vitamin D3 may be more effective for the prevention of bone fracture.

We also assessed the factors predictive of the loss of BMD due to corticosteroids. Older age and decreased renal function are thought to be risk factors for osteoporosis. In the present study, however, no relation was found between the decrease in BMD and sex, age or renal function. In a meta-analysis, a strong correlation between the cumulative dose of corticosteroid and the loss of BMD has been reported [20]. However, the dose of corticosteroid was not associated with the change in BMD in patients given protective drugs for osteoporosis. Steroid-pulse therapy did not affect the change in BMD either. The urinary NTx levels in group III were significantly high compared with group I. The serum osteocalcin and ALP levels in group III were also higher than those in group I, although the differences were not significant. This finding suggests that the patients with higher baseline bone turnover, which may be related to genetic factors [21,22], may have a higher risk of loss of BMD by corticosteroids. The high levels of urinary NTx and serum osteocalcin at baseline may be a predictive factor of steroid-induced osteoporosis.

In conclusion, the loss of BMD by the high-dose and long-term use of corticosteroids could be prevented by bisphosphonates, but not vitamin D3 analogues. In the patients with steroid-pulse therapy, the combined therapy with bisphosphonates and vitamin D3 might be recommended. Also, in the patients with high urinary NTx levels at baseline, the combined therapy might be needed.

Conflict of interest statement. None declared.


References


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