Effects of bisphosphonates on bone metabolism and serum matrix metalloproteinase level in patients with ankylosing spondylitis secondary osteoporosis

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The aim of the study is to investigate the effects of bisphosphonates on bone metabolism and serum matrix metalloproteinase (MMP) levels in patients with ankylosing spondylitis (AS) secondary osteoporosis. 60 patients with AS secondary osteoporosis were divided into treatment group and control group. The control group was given conventional treatment of oral calcium D-dimensional, while the treatment group was given combination therapy of conventional treatment, technetium methylene bisphosphonate and alendronate. The MMP-2, MMP-3, bone alkaline phosphatase (BALP), tartrate resistant acid phosphatase 5b (TRACP-5b) and Vitamin D receptors (VDR) levels were measured. After administration, the serum MMP-2, MMP-3 and TRACP-5b levels in treatment group significantly decreased, while compared with pretreatment, the difference were also significant, respectively (t = 7.371, 7.197 and 4.984, p<0.05). Compared with the control group, the serum MMP-2, MMP-3 and TRACP-5b levels in treatment group significantly decreased (t=5.745, 5.311 and 3.761, p<0.05). After administration, the serum BALP and VDR levels in treatment group significantly increased, while compared with pretreatment, the differences were significant, respectively (t=4.890 and 4.376, p<0.05). Compared with the control group, the serum BALP and VDR levels in treatment group significantly increased (t=3.490 and 3.634, P<0.05). The pretreatment serum MMP-2, MMP-3 and TRACP-5b levels had significant positive correlations (r=0.478 and 0.513, p<0.05), while BALP and VDR levels had negative correlations (r=-0.512, -0.492 and -0.563, -0.495, p<0.05). Conclusively, bisphosphonates can inhibit bone resorption and promote bone formation in AS secondary osteoporosis patients by decreasing MMP-2, MMP-3 and TRACP-5b levels and increasing BALP and VDR levels.

Key words: Bisphosphonates, ankylosing spondylitis, osteoporosis, matrix metalloproteinase.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily involves the spine and the enthesis sites. The majority of patients with AS secondary osteoporosis have continued disease activity on long follow up (Santra et al., 2010). However, its mechanism is still unclear. Matrix metalloproteinases (MMPs) and some cytokines might play important roles in its pathogenesis. Anti-tumor necrosis factor (TNF) therapy has been the major advance in the treatment of AS patients. Infliximab, etanecerpet, adalimumab and golimumab are licensed for this indication. Post marketing surveillance has identified many adverse events, including infections, cancer, lymphoma, lupus-like autoimmune disease, liver disease, demyelinating disorders and hematologic abnormalities among others (Azevedo et al., 2011).

In recent years, the effects of bisphosphonates on bone metabolism became popular with the increasing studies about bisphosphonates. In our present work, we investigated the effects of...
bisphosphonates on serum matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-3 (MMP-3), bone alkaline phosphatase (BALP), tartrate resistant acid phosphatase 5b (TRACP-5b) and vitamin D receptor (VDR) levels in patients with AS secondary osteoporosis to clarify its pathogenesis and provide theories for clinic therapy.

MATERIALS AND METHODS

Patients

60 AS patients from the Department of Orthopedics, Fengxian Central Hospital, China were taken as the objects of study. Which were strictly according to diagnostic criteria of AS (Lu and Zhong, 2008). The clinic study was approved by the Ethical Committee of Fengxian Central Hospital, China. Among 60 patients who volunteered to participate in the intervention treatment, there are 42 men and 18 women with a proportion of 2.33: 1. The age ranks and average ages were 20 to 48 and 32.14 ± 5.77, respectively. 60 AS secondary osteoporosis patients were averagely randomized into two groups: Treatment group (30) and control group (30). Their height, weight, gender, age and average course of disease between groups were comparable.

Drug intervention

Random, open and self control test are adopted in drug intervention treatment, in which 30 patients in treatment group were given combination therapy of conventional treatment, technetium (99Tc) methylene bisphosphonate and alendronate. 30 patients in control group were given conventional treatment of oral calcium D-dimensional. Patients with severe adverse reactions must discontinue the administration.

Evaluation of efficacy

At pretreatment and protreatment, the serum MMP-2, MMP-3, BALP TRACP-5b and VDR levels were measured by ABC-ELISA methods in all the patients.

Statistical analysis

The database was set up with the SPSS 16.0 software package for analysis. Data were represented as Mean ± S.D. The means of different groups were compared with Student’s t-test. The relationship among the different was analyzed by using the Spearman correlation test; p<0.05 was considered as statistically significant.

RESULTS

The comparisons of serum MMP-2 and MMP-3 levels

After treatment, the serum MMP-2 and MMP-3 levels of treatment group significantly decreased; compared with pretreatment the difference were significant (t=7.371 and 4.984, p<0.05). Compared with the control group, the serum MMP-2 and MMP-3 levels of treatment group also significantly decreased (t=5.745 and 3.761, p<0.05). All the results were shown in Table 1.

The comparisons of serum BALP, TRACP-5b and VDR levels

After treatment, the serum BALP and VDR levels of treatment group significantly increased; compared with pretreatment, the difference was significant (t=4.890 and 4.376, p<0.05), while TRACP-5b level decreased (t=4.984, p<0.05). Compared with the control group, the serum BALP and VDR levels of treatment group was significantly increased (t=3.490 and 3.634, p<0.05), while TRACP-5b level decreased (t=3.761, p<0.05). In control group, the serum BALP, TRACP-5b and VDR levels have no significant differences among pretreament and protreatment (t=2.956, 2.899 and 2.671, p>0.05). All the results were shown in Table 2.

Correlation analysis

The pretreatment serum MMP-2, MMP-3 and TRACP-5b levels was a significant positive correlation (r=0.478 and 0.513, p<0.05), while BALP and VDR levels a negative correlation (r=-0.512, -0.492 and -0.563, -0.495, p<0.05).

DISCUSSION

AS is the prototype of spondyloarthritides. It affects the

Table 1. The comparisons of serum MMP-2 and MMP-3 levels in treatment group and control group (\(\bar{x} \pm s\)).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MMP-2 (μg/ml) Pretreatment</th>
<th>Protreatment</th>
<th>MMP-3 (ng/ml) Pretreatment</th>
<th>Protreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>30</td>
<td>11.29</td>
<td>3.31</td>
<td>39.30</td>
<td>11.80</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>11.28</td>
<td>8.80</td>
<td>40.10</td>
<td>29.00</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>2.163</td>
<td>5.745</td>
<td>2.205</td>
<td>5.311</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Table 2. The comparisons of serum BALP, TRACP-5b and VDR levels in treatment group and control group ( $\bar{x} \pm s $ ).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>BALP (μg/ml) Pretreatment</th>
<th>Pretreatment</th>
<th>TRACP-5b (ng/ml) Protreatment</th>
<th>Protreatment</th>
<th>VDR (nmol/L) Protreatment</th>
<th>Protreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>30</td>
<td>3.69</td>
<td>8.35</td>
<td>48.90</td>
<td>21.20</td>
<td>265.78</td>
<td>538.82</td>
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<tr>
<td>Control</td>
<td>30</td>
<td>3.78</td>
<td>5.17</td>
<td>49.50</td>
<td>36.90</td>
<td>258.86</td>
<td>320.61</td>
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<tr>
<td>t</td>
<td></td>
<td>2.109</td>
<td>3.490</td>
<td>2.187</td>
<td>3.761</td>
<td>2.219</td>
<td>3.634</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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axial skeleton, peripheral joints and extraarticular structures. Although the pathogenesis of AS is immune-mediated. The treatment of AS is based on peripheral joint or axial involvement.

The matrix metalloproteinase family is indispensable for the recruitment of osteoclasts in developing metatarsals, and this role is distinct from synergy with cysteine proteinases in solubilizing alcified matrix in the resorption zone. The specific MMP(s) responsible for these osteoclastic activities, and its (their) mode of action have not been determined. Meanwhile, some studies found that the serum MMP-2 and MMP-3 levels are higher in some AS patients (Engsig et al., 2009; Uchibori et al., 2004). Therefore, MMP-2 and MMP-3 were used to evaluate the clinical efficacy of bisphosphonates in treating AS secondary osteoporosis.

TRACP-5b is a novel mark for AS, which could reflect the bone resorption and the activities of osteoclasts. Determining the TRACP-5b in the serum also be helpful to understand the situation of bone metabolism (Duque et al., 2008). VDR participates in the regulation of calcium homeostasis by increasing active entry of calcium into blood from bone stores and dietary sources. These processes are mediated by 1,25−(OH)2 Vitamin D (VD). After being taken up by target cells it is bound to the intracellular binding protein. Subsequently it interacts with the 1,25−(OH)2. VDR and induces heterodimerization of the VDR with retinoic X receptor (RXR) (Abrams et al., 2008; Liesegang et al., 2007).

Bisphosphonates have major beneficial effects on the skeleton and are one of the most potent classes of antiresorptive agents used in the treatment of osteoporosis. These compounds have a high affinity for calcium, and therefore target to bone mineral, where they appear to be internalized selectively by bone-resorbing osteoclasts and inhibit their function, promote apoptosis, and, thus, reduce bone resorption and bone loss (Viereck et al., 2002). Since bisphosphonates reduce biochemical markers of bone; resorptedon induce osteoclast apoptosis in vitro and vivo; their beneficial osteotropic effect has mainly been attributed to their inhibitory effects on osteoclasts.

In the present work, we investigated the effects of bisphosphonates on serum MMP-2, MMP-3 and bone metabolism levels in patients with AS secondary osteoporosis to clarify its pathogenesis and provide theories for clinic therapy. After adminstration, the serum MMP-2, MMP-3 and TRACP-5b levels of treatment group were significantly decreased, while the serum BALP and VDR levels significantly increased. The pretreatment serum MMP-2, MMP-3 and TRACP-5b levels were significant positive correlations while BALP and VDR levels were negative.

Conclusion

In conclusion, the data of the present study indicate that bisphosphonates could decrease the serum MMP-2, MMP-3 and TRACP-5b levels and increase the serum BALP and VDR levels in AS secondary osteoporosis patients, which indicated that bisphosphonates plays important roles in the bone metabolism. However, the real mechanisms of bisphosphonates for AS need future studies.

REFERENCES


