RISEDRONATE TREATMENT ONLY PARTIALLY PRESERVES CANCELLOUS BONE MASS AND MICROARCHITECTURE AFTER LONG-TERM DISUSE

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INTRODUCTION:
Bone loss in disuse results principally from extremely elevated bone resorption (1-2); thus targeting osteoclasts should be an effective strategy for preventing disuse osteoporosis. Currently, bisphosphonates are the most effective inhibitors of osteoclast activity. They have been shown to effectively prevent bone loss in a range of metabolic disorders (3-4). Their efficacy in preventing long-term disuse osteoporosis is unknown. In the current study, our objective was to determine whether risedronate at high dose can prevent bone loss from long-term disuse osteoporosis.

METHODS:
Right forelimbs of 5-7 years old retired breeder Beagle dogs (N=28) were immobilized (IM) with a jacket-type plastic splint, placing the elbow flexed at 90 degrees and the carpal joint volar-flexed slightly. Age matched, non-immobilized dogs served as controls (Con). Half the animals from each group received risedronate daily (RIS, 1 mg/kg, p.o.) (Con+RIS and IM+RIS), the remaining dogs received only the sterile water vehicle (Con and IM) for the 12 month duration. All animals received anutable bone fluorochrome-labels. All procedures were approved by the Institutional Animal Care Committees of the Bronx, New York VA Hospital and Mount Sinai School of Medicine. MicroCT scans were performed at 13 μm resolution using an EVS MS-8 system. Changes in cancellous bone were assessed by histomorphometry. Trabecular bone area (%Tb.Ar/T.Ar), trabecular number (Tb.N) and trabecular width (Tb.Wi) were measured to examine bone mass and architecture. Osteoclastic activity was assessed from eroded surface (%Er.Pm/B.Pm). Osteoblastic activity was assessed from the labelled surface (%L.Pm/B.Pm), mineral apposition rate (MAR) and area-based bone formation rate (BFR/B.Ar). Differences among groups were tested using ANOVA with Fisher’s PLSD for post-hoc testing; significance is reported at p<0.05.

RESULTS:
Immobilization: After long-term IM, there was a dramatic (Fig 1) reduction of cancellous bone mass (%Tb.Ar/T.Ar -71%), resulting from marked decreases in trabecular thickness (Tb.Th -48%) and number (Tb.N -43%). Bone resorption was greatly elevated (%Er.Pm/B.Pm +328%), indicating that disuse bone loss at this long-term period is a “high turnover” type process.

Immobilization+Risedronate: Risedronate-treatment in IM animals reduced the amount of bone loss, but this effect was incomplete (Fig 1). Even with the RIS treatment, IM animals lost nearly 50% of their cancellous bone mass, while Tb.Th and Tb.N were reduced by 31% and 25%, respectively. Bone formation indices were also significantly higher in IM than in control bones (%L.Pm/B.Pm +328%), indicating that disuse bone loss at this long-term period is a “high turnover” type process.

DISCUSSIONS:
These studies show that high dose risedronate cannot completely protect bone loss resulting from long-term disuse. Bisphosphonate treatment attenuated cancellous bone loss by half compared to non-treated animals. However, even with this attenuation of bone loss, the IM+RIS bones were markedly osteoporotic. This observation stands in stark contrast to the high degree of effectiveness for bisphosphonates in preventing “metabolically-driven” osteoporoses, such as after ovariecotmy, menopause or glucocorticoid administration (5).

Among the most surprising findings of this study was that in RIS-treated IM animals, so much of the bone surface is covered by osteoclasts. Given that RIS the reduced amount of bone loss, these osteoclasts would appear to be diminished in their ability to resorb bone. Together these data suggest a paradoxical scenario wherein disuse may provide a very large stimulus to recruit osteoclasts, a stimulus that is not inhibited by bisphosphonates; however, the ability of those cells to resorb bone once recruited is suppressed by the bisphosphonate.

Recent studies of the effect of bisphosphonates in acute spinal cord injury patients show very similar results to ours. Using different bisphosphonates (tiludronate and pamidronate), these studies found essentially the same result, i.e., that the bisphosphonates attenuate disuse-induced bone loss, but do not prevent it to the degree seen in other osteoporosis. That several different bisphosphonates in different species all show such similar results suggests that disuse is fundamentally different from other osteoporosis in its sensitivity to anti-resorptive drugs.

Figure 1: Coronal µCT Images of Distal Canine Metacarpals

Figure 2: Cancellous Bone Mass and Architectural Changes with Long-term Disuse and Risedronate Treatment

Table 1: Dynamic Parameters in Distal Metacarpal Metaphyses

<table>
<thead>
<tr>
<th>Groups</th>
<th>%L.Pm</th>
<th>MAR</th>
<th>BFR/B.Ar</th>
<th>Er.Pm/B.Pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>1.00 ± 0.84</td>
<td>0.71 ± 0.13</td>
<td>4.60 ± 3.66</td>
<td>2.99 ± 1.56</td>
</tr>
<tr>
<td>Con+RIS</td>
<td>0.54 ± 0.41</td>
<td>0.42 ± 0.3</td>
<td>2.10 ± 2.02</td>
<td>5.76 ± 2.86</td>
</tr>
<tr>
<td>IM</td>
<td>4.25 ± 3.84*</td>
<td>0.75 ± 0.13</td>
<td>40.84 ± 28.86*</td>
<td>15.42 ± 7.93*</td>
</tr>
<tr>
<td>IM+RIS</td>
<td>0.33 ± 0.26*</td>
<td>0.10 ±0.27#</td>
<td>0.57 ± 1.51#</td>
<td>27.36 ± 8.92#</td>
</tr>
</tbody>
</table>

Data shown as means ±SD; *p<0.05 vs. control; #p<0.05 vs. IM.

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References:
4. Eriksen, Bone 31:620-625, 2002

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