THE EFFECT OF ATORVASTATIN CALCIUM ON THE CORTICAL BONE STRENGTH OF CORTICOSTEROID TREATED RABBITS

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INTRODUCTION
Corticosteroid therapy is a well known etiological factor for the development of osteoporosis (“secondary” osteoporosis) and femoral head osteonecrosis. Recently, HMG-CoA reductase inhibitors (popularly known as statins) have been suggested as a treatment option to prevent the development of corticosteroid induced femoral head osteonecrosis [1-2]. The exact mechanism by which statins prevent the development of osteonecrosis is unknown. Patients on corticosteroids may also develop hyperlipidemia and require treatment with statins.

Although statins have been shown to have an anabolic effect on bones [3], the effect of the combination of corticosteroid and statin treatment on cortical bones is unknown. In this study, the effect of atorvastatin calcium on the mechanical strength of corticosteroid treated rabbit femurs was evaluated. The results of the mechanical testing were also compared with bone histology sections.

METHODS
25 New Zealand white rabbits were used for this study. The animal protocol was approved by IACUC. Six rabbits were used as controls; the other nineteen rabbits received a weekly 2-3 mg/kg intramuscular injection of methylprednisolone acetate (Depo Medrol). Ten of these nineteen rabbits also received a daily 10 mg oral dose of powdered atorvastatin calcium (Lipitor, Pfizer Inc., NY) mixed with a teaspoon of baby food. The control rabbits also received a teaspoon of baby food daily. The rabbits were sacrificed at the end of 10 weeks.

After removing the surrounding soft tissues, the harvested femurs were wrapped in saline soaked gauze and stored at –20°C until further use. The femurs were tested in 3-point bending mode using an electro mechanical testing machine (800LE4 Dynamic Test System, Test Resources Inc., Shakopee, MN) at a crosshead speed of 1 mm/min until failure. The load-deformation curve and anatomic data was used to calculate the flexural

Figure 1: Most of the corticosteroid treated rabbits exhibited excessive cortical tunneling (A) when compared to the control rabbits (B).
strength and modulus [4]. The flexural strength and modulus of contralateral limbs were averaged before analyzing the differences between the treatment groups. ANOVA was used to analyze the differences between the treatment groups. After mechanical testing and anatomic measurement, one femur from each rabbit was fixed in buffered formalin, decalcified and processed for histology.

RESULTS AND DISCUSSION

The results showed that the average flexural strength and modulus of femurs decreased with corticosteroid treatment (Table 1). However, surprisingly the flexural strength of femurs in the corticosteroid plus statin treated rabbit group was significantly lower when compared to just the corticosteroid treatment group (p<0.05). Both the flexural strength and modulus differences were statistically significant between control and corticosteroid plus statin treated rabbit group (p<0.05) but was not statistically significant between control and corticosteroid treatment group (p>0.05). A very similar trend was seen in the tibias too (results not shown).

The histology slides showed extensive cortical thinning and tunneling of the cortex by fibroblasts and osteoclasts in all the corticosteroid treated bones (Figure 1). There was some reduction in hematopoetic marrow cells and foci of fat necrosis. There was some reduction in hematopoetic marrow cells and foci of fat necrosis. Although the cortical thickness was maintained in corticosteroid plus statin treated rabbits, the strength was nevertheless lower.

It is well known that rabbits are more susceptible to the adverse effects of corticosteroid treatment than other animal species. For example, corticosteroid treated rabbits are more prone to severe weight loss, muscle atrophy, infection, elevated lipid levels and elevated glucose levels. Therefore, the results of this study needs to be taken in perspective. Even though statins seems to maintain cortical thickness, it somehow affects the bone quality of these rabbits. More studies are needed to evaluate the micro-architecture and collagen quality of the corticosteroid plus statin treated rabbit femurs. The study results also warrant at least a retrospective chart review to make sure that the same trend does not happen in human patients.

CONCLUSIONS

Our findings suggest that the introduction of statins in corticosteroid treated rabbits may actually decrease bone strength despite the current impression that statins usually improve bone strength (or at least bone mineral density) when given alone through their anabolic effect. If this finding is substantiated on other species and humans the results can extremely important given the prevalence of steroid and statin use in the general population.

REFERENCES


ACKNOWLEDGEMENTS

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Table 1: The flexural strength and modulus of femurs (average ± SD) from each treatment group measured using 3-point bending test. The number of animals used per group is shown in brackets.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Flexural Strength MPa</th>
<th>Flexural modulus GPa</th>
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<tbody>
<tr>
<td>Control</td>
<td>149 ± 12 (6)</td>
<td>15.98 ± 1.95</td>
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<tr>
<td>Corticosteroid</td>
<td>130.4 ± 22.8 (9)</td>
<td>13.4 ± 3.2</td>
</tr>
<tr>
<td>Corticosteroid + Atorvastatin</td>
<td>109.4 ± 17.5 (10)</td>
<td>11.8 ±1.9</td>
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