IBANDRONATE DOES NOT BLOCK THE ANABOLIC EFFECTS OF PTH IN OVARIECTOMIZED RAT TIBIAE: A MICROARCHITECTURAL AND MECHANICAL STUDY

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SUMMARY
We compared the changes in OVX rat tibiae response to ibandronate or PTH and its combination treatment. This study revealed that the concurrent use of ibandronate did not reduce the anabolic effects of PTH. $F_{\text{max}}$, $\text{SSI}_y$ and $\text{P1NP}$ of concurrent group were significant higher than both of the mono groups, showing partial additive effect. The beneficial effect may be attributed to the proper ratio and course of the treatment.

INTRODUCTION
Osteoporosis is a progressive debilitating disorder associated with reduction in bone mass often leading to fractures. Commonly used anabolic drug is the recombinant human parathyroid hormone (PTH) [1]. The third generation nitrogen-containing bisphosphonates (Ibandronate) is being used as an anti-resorptive agent [2]. Whether the use of both bisphosphonate and PTH would have a synergistic effect on osteoporosis is still controversial [3]. We aim to investigate the effect of individual and combined administration of ibandronate and PTH on the ovariectomized (OVX) rat models in terms of structural and mechanical analyses.

METHODS
A total of 60 female Sprague-Dawley rats of age 10 to 12 weeks were divided into 5 groups (SHAM, OVX+VEH, OVX+PTH, OVX+IBAN, OVX+PTH+IBAN) and subjected to ovariectomy or sham surgery accordingly. Low dose parathyroid hormone (PTH) and/or ibandronate or its vehicle was administered subcutaneously to the respective groups starting from 4th week post surgery at weekly intervals. Three rats from each group were euthanized every 2 weeks and their tibiae were harvested. The tibiae were subjected to metaphyseal 3-point bending, pQCT and μCT analysis. Serum biomarkers for both bone formation ($\text{P1NP}$) and resorption ($\text{CTX}$) were studied.

RESULTS AND DISCUSSION
A total of 11 indices showed a significant difference between SHAM and OVX+VEH groups, suggesting the successful establishment of osteoporosis in the rat model. pQCT analysis showed that the treatment groups had significantly higher bone mineral density (BMD) than OVX+VEH, with OVX+IBAN and OVX+PTH+IBAN groups showing significantly higher BMD than OVX+PTH. Maximum load ($F_{\text{max}}$), Y axis Strength-Strain Indices ($\text{SSI}_y$) and serum bone formation marker ($\text{P1NP}$) of OVX+PTH+IBAN group are significantly higher than both mono therapy groups, showing a partial additive effect. Micro-CT analysis showed OVX+PTH+IBAN has significant beneficial effects on trabecular bone at 6 weeks after OVX surgery compared to OVX+PTH.

CONCLUSIONS
Compared to the previous studies which showed impedance from bisphosphonates in combination therapy with PTH, our study suggested that ibandronate does not block the anabolic effects of PTH in ovariectomized rat tibiae. Maximum load, Strength-Strain Indices and bone formation serum markers of OVX+PTH+IBAN group are significantly higher compared to both mono therapy groups. The effect may be attributed to the proper ratio of anabolic and anti-resorptive drugs combined with the appropriate course of treatment. Further exploration of these findings would allow us to optimize the ratio between PTH and ibandronate and maximize the beneficial effects of the concurrent administration of the two drugs in the treatment of osteoporosis.
ACKNOWLEDGEMENTS
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REFERENCES

Table 1: Mechanical property changes of animal groups measured by 3-point bending test. Group averages are represented as mean ± SD.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Fmax (N)</th>
<th>Weeks after surgery</th>
<th>0</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAM</td>
<td>61.2 ± 21.7</td>
<td>101.5 ± 5.7</td>
<td>117.0 ± 25.3</td>
<td>115.5 ± 6.8</td>
<td>104.0 ± 11.0</td>
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<tr>
<td>OVX+VEH</td>
<td>44.2 ± 9.0</td>
<td>59.1 ± 15.3</td>
<td>50.5 ± 11.9</td>
<td>63.1 ± 12.5</td>
<td>48.9 ± 12.1</td>
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<tr>
<td>OVX+PTH</td>
<td>64.4 ± 6.7</td>
<td>57.3 ± 12.0</td>
<td>67.4 ± 10.1</td>
<td>77.9 ± 17.6</td>
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<tr>
<td>OVX+IBAN</td>
<td>65.0 ± 13.0</td>
<td>85.3 ± 3.6</td>
<td>80.3 ± 9.6</td>
<td>86.4 ± 17.4</td>
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<tr>
<td>OVX+PTH+IBAN</td>
<td>81.8 ± 3.4</td>
<td>121.5 ± 11.5</td>
<td>107.1 ± 19.2</td>
<td>131.1 ± 18.1</td>
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a. Significant difference from SHAM (p<0.05)
b. Significant difference from OVX+VEH (p<0.05)
c. Significant difference from OVX+PTH (p<0.05)
d. Significant difference from OVX+IBAN (p<0.05)