Introduction: Distraction osteogenesis is a principle mechanism of the limb lengthening method. Many successful cases of limb lengthening have been reported in the clinical literature. Every effort has been made to improve bone healing in limb lengthening. Previous studies on the basic aspects of distraction osteogenesis have focused on the mechanism of new bone formation in response to mechanical tension-stimuli. Bone resorption and remodeling during distraction have been overlooked, though we demonstrated in a rabbit experiment that the lengthened segment had three characteristic zone structures, consisting of not only a central radiolucent zone (zone of growth) and adjacent scerotic zones (zones of bone formation) but also subsequent osteopenic zones (zones of bone resorption). Newly formed bone trabeculae in the sclerotic zones are rapidly absorbed by highly activated osteoclasts, producing the osteopenic zones. Our objectives were to disclose the effect of inhibition of high turn-over remodeling by administering a third-generation bisphosphonate, YM529/ONO5920, in a rabbit tibial lengthening model.

Materials and Methods: All experimental procedures were approved by the local animal protection and ethics committee. Left tibiae of 34 immature rabbits were lengthened for 3 weeks at a rate of 0.35 mm every 12 hours (0.7 mm/day) after a 1-week lag by using the external fixator. After achieving 15 mm lengthening, a 4-week consolidation phase was instituted, during which the external fixator remained in situ for bone consolidation. Three groups of animals received either vehicle or YM529/ONO5920 at doses of 0.004 mg/kg/w or 0.4 mg/kg/w for 6 weeks. Radiographic bone densities along a longitudinal axis of the lengthened segments were pursued in vivo every other week. Bone histomorphometry was investigated in osteopenic zones at two time points; 4 weeks (at the end of distraction) and 8 weeks (at the end of bone consolidation) postoperation. Eventually the mechanical properties of the bilateral tibiae at 8 weeks postoperation were examined by three-point-bending testing. Statistical analyses to detect differences among respective groups were performed by one-way analysis of variance (ANOVA) and between the two time points by unpaired t-test or Mann-Whitney U-test using a statistical package StatView.

Results: Lengthened segments of the vehicle group showed characteristic zone structures with osteopenic zones. This osteopenic zones expanded from the original osteotomized bones, demonstrating a minimal 3-mm aluminum thickness of bone density. Those of the 0.4-mg/kg/w group showed no osteopenic zone during the course and eventually homogeneously radiodense feature, demonstrating altogether over a 5-mm aluminum thickness. The 0.004-mg/kg/w group also demonstrated same zone structures, but less absorption in the osteopenic zones. The sclerotic zones in all groups consisted of abundant linearly arranged trabeculae. Bone volume in the lengthened segment of the 0.4-mg/kg/w group was preserved at both 4 weeks postoperation (2-fold) and 8 weeks (5.6-fold) through retention of the trabecular number, compared with the vehicle group. Both osteoclast number (N.Oc/B.Pm) (less than half) and osteoclast surface (Oc.S/BS) (less than one-third) were significantly lower in the 0.4-mg/kg/w group compared with the other groups at 4 weeks. The ultimate force of the 0.4-mg/kg/w group was 3.3-fold greater than that of the vehicle group and equivalent to the contralateral tibia. There were no significant differences between the 0.004-mg/kg/w group and the vehicle.

Discussion: The current study focused on consecutive events in the lengthened segment and bone remodeling during distraction osteogenesis. Inhibition of bone remodeling by YM529/ONO5920 caused dramatic modulations in structural and mechanical properties of the lengthened segment, projecting beneficial effects on limb lengthening. Abundant newly formed trabeculae eventually result in fragile bone during distraction osteogenesis by unexpected activated bone resorption before attainment of radiological bony continuity in distraction osteogenesis. Tension-stimuli, which promote bone formation at the center of distraction segment, have adverse effect on preservation of the trabeculae. Inhibition of bone remodeling should be maintained temporarily until attainment of bony continuity and removal of the external fixator. The current results have important implications for development and beneficial effects in distraction osteogenesis.

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Figure 1.: Radiographs of the lengthened segments of the vehicle group (upper), the 0.004-mg/kg/w group (middle), and the 0.4-mg/kg/w group (lower) at 6 weeks postoperation (at the middle of consolidation phase). Note osteopenic zones expanded from the original osteotomized bones in the vehicle group, the 0.004-mg/kg/w group, whereas no osteopenic zones in the 0.4-mg/kg/w group.

Figure 2.: Ultimate force of the lengthened tibiae (left columns) and the untreated contralateral tibiae (right columns) in three-point bending strength. Data are shown for the vehicle group (white), the 0.004-mg/kg/w group (gray), and the 0.4-mg/kg/w group (black). On the lengthened tibiae, the 0.4-mg/kg/w group was significantly stronger (p < 0.0001) as compared to the vehicle group.