The Effects of Bone Remodeling Inhibition by Alendronate on 3-D Microarchitecture of Subchondral Bone Tissues in Guinea Pig Primary Osteoarthritis

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Introduction: It has long been a subject of debate whether subchondral bone changes in osteoarthritis (OA) are preceding, concurring with, or following cartilage degeneration. Generally, there are two opposing hypotheses: bone sclerosis is secondary to cartilage loss and is the result of cartilage breakdown; and cartilage degeneration and loss is secondary to bone sclerosis—the Radin hypothesis (1). The Radin hypothesis emphasizes that thickening of subchondral bone increases internal cartilage stress leading to increased hardening of the subchondral bone (sclerosis) and progressive thinning of articular cartilage. The aim of this study was to assess the Radin hypothesis that thickening and hardening of subchondral bone increases cartilage stress during impact loading leading to progressive degeneration of articular cartilage and accelerated OA progression.

Materials and Methods: Sixty-six male Charles River strain outbred Dunkin–Hartley guinea pigs were purchased (HB Lidköpings Kaninfarm, Lidköping, Sweden) and used in this study. The experimental protocol was approved by the Danish Animal Experiment Committee (Study no: J.nr. 2000/561-329). These male guinea pigs were randomly divided into 6 groups. During a 9-week treatment period, 4 groups received twice weekly subcutaneous injections of alendronate (ALN) in 2 doses: 2 groups received 10 mg/kg, and 2 groups received 50 mg/kg. The 2 control groups received vehicle. After 9 weeks, one 10 mg/kg ALN group, one 50 mg/kg ALN group, and one control group were sacrificed. The remaining 3 groups (17-week groups) were left for an additional 8 weeks receiving the same treatment regimen before sacrifice.

The left tibiae were harvested and micro-CT scanned (mCT 40, Scanco Medical AG., Switzerland) to quantify three-dimensional (3-D) microarchitecture of proximal tibial subchondral bone, followed by mechanical testing (MTS Systems Co., USA) and determination of bone collagen and mineral (2). The results were analyzed statistically using SPSS version 10.0.7 (SPSS Inc., USA). One-way ANOVA were performed among the three groups in each of the two experimental periods, and the post hoc multiple comparisons were adjusted using Bonferroni test or Dunnett’s test as appropriate. A p-value <0.05 was considered significant.

Results: The control groups had typical OA-related cartilage degeneration at 9 and 17 weeks, whereas all ALN-treated groups had even worse degeneration with higher Mankin’s score (Fig. 1A). The 9-week ALN group had significantly greater subchondral plate thickness (Fig. 1B). The 9-week and 17-week groups had similar changes of cancellous bone microarchitecture, with significantly greater bone volume fraction, connectivity density, and extremely plate-like structure (Fig. 1C). Likewise, ALN-treated cortical bone had significantly greater thickness at both observation times (Fig. 1D). The 9-week ALN group had greater bone mineral concentration and apparent density (Fig. 1E). The 17-week ALN group had reduced collagen concentration, greater mineral concentration, tissue density and apparent density. Treatment with ALN did not significantly change in the mechanical properties of the cancellous bone, whereas the ALN significantly increased ultimate stress and failure energy of the cortical bone (Fig. 1C&D).

Discussion: The present results on the proximal tibia of guinea pig demonstrate ALN treatment-induced increments in subchondral cancellous and cortical bone volumes. In addition, pronounced microarchitectural changes of cancellous bone, increased densities and mineralization of the subchondral bone, and elevated normalized ultimate stress of subchondral cortical bone shell were found. All these changes to some extent were accompanied by increased articular cartilage degeneration (Mankin’s score). ALN treatment dramatically changed the microarchitecture of the subchondral cancellous bone in both the 9-week and 17-week groups. Thus, ALN increased cancellous bone volume fraction, changed trabecular structure to extremely plate-like, decreased architectural anisotropy, and increased connectivity density (Fig. 1C). The fact that the increased total amount of bone volume could not show parallel increased mechanical properties is likely due to deterioration of OA subchondral bone quality. ALN treatment resulted in significantly greater thickness and cross-sectional area of the subchondral cortical shell with the most marked changes after 17 weeks of treatment (Fig. 1D). However, the importance of the cortical shell in OA progression is not known and has attracted little attention. Recent studies have revealed that accelerated subchondral bone turnover is accompanied by specific structural changes in the cancellous bone of OA joints, abnormal bone mineral content, and several fold increased subchondral bone collagen metabolism in human femoral heads. To what extent ALN directly may affect chondrocytes or the cells in the other tissues is, at present, unknown.

In conclusion, ALN treatment significantly increased the subchondral bone mass, greatly changed the microarchitecture, and increased the bone mineral content and density. Furthermore, ALN treatment caused the articular cartilage degeneration to be accelerated at the medial condyle and, to some extent, also at the lateral condyle. The mechanical properties were only found to increase significantly for the subchondral cortical bone. Thus, the present results suggest that ALN treatment promotes OA progression and call for circumspection in using bone density enhancing drug in intervention of primary OA.


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