Does Locally Delivered Zoledronate Influence Peri-implant Bone Formation? - Spatio-temporal Monitoring Of Bone Remodeling In Vivo

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Introduction: Unlike osteoblasts, osteoclasts can internalize bone mineral bound bisphosphonates (BPs) as they are highly endocytic during the bone resorption process. This is why osteoclasts are considered to be the main target for this potent resorption inhibiting group of drugs. Nevertheless, BP effects on cells of the osteoblast lineage have also been described, that raises the question if BPs can also influence bone formation [1]. Specifically for Zoledronate, the most potent bisphosphonate used in clinics today, an improved mineralization and proliferation of human osteoblast-like cells was demonstrated [2]. However conflicting results can be also found showing that BPs might inhibit mineralization and osteoblast growth, induce osteoblast apoptosis, and inhibit protein prenylation in osteoblasts in a dose-dependent manner [3]. Therefore the aim of the present study is to investigate the spatio-temporal effect of locally delivered Zoledronate on peri-implant bone remodeling using the so-called dynamic histomorphometry, a previously developed microCT-based technique [4]. Hereby we focus specifically on the unclear effect of a locally applied BPs on bone formation.

Methods: Custom-made polymeric miniature screws were implanted bilaterally in the femoral condyles of ovariectomized (OVX) rats. Unlike metal implants, these screws are visible on microCT scans without creating image disturbing artifacts. A hydrogel based drug delivery system was developed that is suitable for release of a precise amount of Zoledronate into the peri-implant bone stock. During surgery the hydrogel was inserted into the predrilled screw-hole before screw implantation. The study included 3 experimental groups. In the first group, the hydrogel was loaded with 5 µg Zoledronate (Zol-Gel-group), in the second group unloaded hydrogel was used (Gel-group) and in the third group no hydrogel was inserted (Control-group) before screw implantation. Time-lapsed in vivo microCT scans of the animals were performed for close monitoring of the bone response to the implantation and how it is altered by the bisphosphonates delivery. In particular, four screw enveloping layers of 368 µm (20 voxels) each were created to assess the dynamic bone parameters (bone formation and resorption rates) depending on the distance from the screw surface.

Results: The analysis of the bone resorption rate clearly confirms the anti-resorptive effect of Zoledronate (Fig. 1). In direct proximity of the screw, a constant low bone resorption rate (BRR) of around 2-3 %/d can be seen for the Zol-Gel-group throughout the whole study. The Control- and Gel-group show initially (day 3-10) an equally low BRR followed by a high peak of around 12 %/d from day 10-17. From then onward the BRR diminishes until the study end point and reaches a value equal to the Zol-Gel-group for the last period analyzed which was from 45-58 days after screw implantation. In the outer three layers, the BRR in the Control- and Gel-group is already initially very high (8-10 %/day) compared to the Zol-Gel-group (3-5 %/day). This difference even out over time and is no longer significant from day 31-58. The analysis of the bone formation rate (BFR) shows that the implantation of the screw induced an early peak in bone formation in the inner two layers in all groups (Fig. 2). The BFR
in the Control- and Gel-group is characterized by a peak of around 20 %/d from day 3 to 10 followed by an almost constant low BFR of 1-2 %/d during the rest of the study. This phenomenon can also be found to a lesser degree in the second layer from 368 - 736 µm where the initial BFR reaches 10 %/d and then decreases to 2-3 %/d. The BFR in the two outer layers is unaffected by the screw implantation and shows a constant value of 3-4 %/d.

**Discussion:** With Zoledronate being an anti-resorptive agent, the drug is expected to mainly influence bone resorption. In the present study, this was clearly reflected by the significantly reduced BRR in the drug treated animals. The strong resorption peak seen in the Control-group was not at all present in the bone-healing-zone of the Zol-Gel-group in which the BRR remained at a constant low level. The original result of this study is an up to 100% increase of the early bone formation rate caused by the locally delivered Zoledronate that accompanies an efficient inhibition of peri-implant bone resorption. In this way, Zoledronate initially boosts bone formation and later on helps to preserve the newly formed bone.

**Significance:** The present study was able to show that Zoledronate delivered from a fast degradable hydrogel can boost early bone formation and later on efficiently inhibit peri-implant bone resorption close to an implant and stabilize the bone loss situation further apart in an OVX rat model. This results in a significantly augmented bone mass and enhanced bone micro-structure in the treated peri-implant bone during minimum 2 months post-implantation.
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