Evaluation of the Bisphosphonate-triggered Bone Remodeling Around a Bone Screw Based on Time-lapsed MicroCT Scans

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Disclosures:

Introduction: Revision surgery due to screw-cutout is a frequent complication after the fixation of osteoporotic fractures. Therefore many strategies have been developed to improve screw fixation by reinforcing the bone structure with cement-like materials or a local release of anti-osteoporotic drugs. Our approach is the release of zoledronic acid, the most potent bisphosphonate used in clinics today, from a hydrogel matrix in the bone stock around a screw. With this strong bone resorption inhibitor, we are able to enhance in a rat femoral model locally the bone density in order to improve the anchorage of a miniature screw. Most of the recently published studies evaluate the improved implant fixation with mechanical tests or based on an analysis of the bone density at the end of in vivo experiments (Li, Feng et al. 2010; Agholme, Andersson et al. 2011; Back, Pauly et al. 2012). Those studies give only little information about the mode and range of action of locally delivered bisphosphonates. Nevertheless this information is crucial for the successful development of drug-implant combination products. In order to overcome those limitations, we designed an in vivo model where artefact-free miniature screws are implanted in combination with the drug loaded hydrogels in the femoral condyles of rats. A series of time-lapsed in vivo microCT scans that starts directly after the implantation of the screws allows us to closely monitor the bone remodeling around the implant. A registration of the images from different time points helps to identify resorption and formation sites as well as quiescent bone.

Methods: Zoledronic acid was incorporated in a hyaluronic acid hydrogel matrix with a concentration of 1 mg/ml. 7 µl of the prepared gel was injected in holes presenting a diameter of 1.2 mm that were predrilled in both lateral femoral condyles of female Wistar rats. PEEK miniature screw with a diameter of 1.4 mm and a length of 2.5 mm were implanted following injection of drug-loaded and unloaded gel. MicroCT scans of both hind limbs of the rats with a resolution of 9 µm were performed at day 3 after screw implantation and then every 2 weeks during 2 months (Fig. 1). The microCT datasets acquired from one animal at different time points were automatically aligned and analysed using specific image processing software. Static and dynamic bone parameters were determined following the nomenclature of Schulte et al. (Schulte, Lambers et al. 2011) in a hollow cylinder around the screw with a diameter of 2.4 mm that included trabecular bone only.

Results: Preliminary results from 4 implantation sites show a high bone formation rate (BFRBS, normalized with original bone surface) immediately after surgery that is identical for the Zoledronate and control animals and drops significantly during the following 4 weeks (Fig. 2, 3). The bone resorption rate (BRRBS) is initially very low and increases during the 2 months following surgery. As expected it stays lower for the Zoledronate group compared to the control group throughout the whole experiment. In the Zoledronate group, the BRRBS does not exceed the BFRBS during the experimental time unlike in the control group, where the BRRBS exceeds clearly the BFRBS. This dynamic bone behaviour is also reflected in the static parameters of the bone, the trabecular thickness (Tb.Th) is given as an example in Fig. 3. The control group shows a peak in Tb.Th after 4 weeks whereas the Tb.Th increases in the Zoledronate treated animal during the whole experiment. A 3D visualization of the bone remodeling also confirms those results (Fig. 2).

Discussion: This pilot study allows us to confirm that the local delivery of Zoledronate around screws affects in a favourable way the surrounding bone remodeling. In the untreated group, the bone reaction to the harm caused by the screw is characterized by an initially very high formation of bone around the screw up to 4 weeks followed by a resorption of the superfluous bone. This results in bone parameters similar to the situation before screw implantation. In contrary, in the Zoledronate treated group the bone resorption is reduced throughout the whole experiment and never exceeds the bone formation. Significantly enhanced static bone parameters around the screw at the end of the study are the corresponding consequence. An in vivo study with more animals is needed to confirm these results.

Significance: The local delivery of bisphosphonate around screw is a potentially interesting solution to increase secondary stability of screw inserted in osteoporotic bone. Based on a powerful time-lapsed in vivo microCT technique used for the evaluation of the bone remodeling around an implant, the dynamical aspects of bone remodelling can be analysed and can allow to optimize the drug delivery.
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Fig. 1  MicroCT scan and 3D reconstruction of a Zoledronate treated femoral condyle showing a high bone density and callus formation around the screw 8 weeks after implantation.
Fig. 2  3D visualization of the bone remodeling in cancellous bone around a bone screw that was implanted in the femoral condyle of an untreated rat (upper row) and a Zoledronate treated rat (lower row).

Fig. 3  Left: Bone formation rate and bone resorption rate normalized with the original bone surface of the control and the Zoledronate treated animal (n=2, data expressed as mean ± standard deviation). These parameters are determined by comparing pairs of microCT scans acquired in intervals of 2 weeks.
Right: Trabecular thickness monitored during 8 months in a control and a Zoledronate treated animal (n=2, data expressed as mean ± standard deviation.)

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