Time Course of Bone Screw Fixation Following a Local Delivery of Zoledronate in a Rat Femoral Model

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Introduction: The success of orthopedic implants is highly depending on their anchorage in surrounding bone. A good implant fixation requires a good structural integration between bone and implant surface as well as a strong bone structure around the implant that can resist the loads that are transferred from the implant to the bone [1]. Many successful strategies have been developed to improve the implant osteointegration such as surface topography changing treatments, osteoconductive coatings or surface functionalization with biological molecules [2, 3]. An improvement of the second aspect, the peri-implant bone quality, is however much more difficult to achieve. One of the most promising approaches that came up during the last years is the local delivery of anti-resorptive drugs such as bisphosphonates in the peri-implant bone. Several studies have shown that this strategy can locally enhance the bone density and therefore increase the mechanical stability of implants in animals and humans [4-7]. The temporal effect of the delivered drug is however a very important aspect regarding the fact that osteosynthesis implants are placed to stabilize bone fractures. In this study, a microFE analysis was used to investigate the temporal effect of a locally delivered bisphosphonate (Zoledronate in the present study) on the fixation of miniature screws in a rat femoral model of postmenopausal osteoporosis. The goal of this analysis was to determine if the local bisphosphonate delivery can achieve the fast and durable enhancement of implant fixation that is needed for osteosynthesis implants in osteoporotic bone.

Methods: Eight ovariectomized rats were implanted with radiopaque polyetheretherketone screws in both femoral condyles. In the 4 animals of a first group (Zol-Gel-group), the pre-drilled screw holes (diameter 1.2 mm, depth 3.5 mm) were filled with 5 µl of a commercially available hyaluronic acid hydrogel (Termira AuxiGel™, Stockholm, Sweden) containing 1 µg/ml of Zoledronate (Art.-Nr. ALX-430-153-0000, Enzo Life Sciences, Farmingdale, USA). The 4 rats of the second group (control-group) received only screws. Both femurs of all animals were scanned with a special in vivo microCT for small rodents (Skyscan 1076, Bruker microCT, Kontich, Belgium) at day 3, 10, 17, 31, 45, and 58 after screw implantation.

After image processing, linear elastic microFE models for all microCT scans were created by converting image voxels to linear isotropic hexahedral finite elements [8]. A cube of the same size as a microCT stack was created in the commercially available simulation software Abaqus (Simulia). The cube was meshed with hexahedral elements whereas the edge length of one element in the model was equal to the edge length of one voxel in the pre-processed microCT datasets (55.2 µm). An in-house Matlab (Mathworks, Natick, USA) script was used to assign mechanical properties to the elements according on the grey values in the microCT datasets. To validate the numerical study, experimental pull-out tests were compared to numerical analysis and failure criteria were defined (data not shown).
Results: The initial predicted force at yield was 16.4±1.1 N in the control-group and 16.1±1.0 N in the Zol-Gel-group (Fig. 1 left). In the control-group it increased by 9% to 17.8±1.3 N between day 3 and day 10 and then didn’t show any marked changes until day 58. For the Zol-Gel-group, however, a total increase in the predicted force at yield of 50% to 24.1±1.4 N was found between day 3 and day 31 followed by a slight decrease by 4% until day 58. The difference between the two groups was highly statistically significant starting from day 17.

A similar time course was also found for the force at pull-out (Fig. 1 right). The force at pullout increased in the Control-group from 23.4±1.7 N at day 3 by 10% to a maximum of 25.8±2.2 N at day 10 and did not change significantly any more until the end of the study. The Zol-Gel-group started with a force at pullout of 23.0±1.6 N that increased in total by 57% up to 36.0±0.8 at day 31 followed by slight decrease of 3% until day 58.

Discussion: The combination of in vivo microCT with microFE analysis revealed insights in the time course of the Zoledronate effect showing that a significant enhancement of screw fixation can be expected in rats as early as 17 days after implantation and can persist for minimum 6 weeks after onset. One limitation that affects microCT based studies in general is the fact that computed tomography can detect the degree of mineralization of the bone but is unable to differentiate between mature lamellar bone and unstructured woven bone [9]. The microFE approach considers all bone parts that exceed a certain mineralization degree (grey value threshold for bone segmentation) as equally mechanical competent. This might be a disadvantage in the current study, as the bone trauma caused by the insertion of an implant is known to cause a rapid formation of woven bone in direct proximity of the implant. Despite this limitation, the good correlations between the results of the present study and published experimental and numerical data confirm the great potential of microFE analysis to predict the time course of implant fixation in vivo and how it is altered by the presence of the locally delivered Zoledronate.

Significance: With the present study, we were able to show the time course of the Zoledronate effect on implant fixation in vivo based on microFE analysis. The locally delivered bisphosphonate was predicted by the microFE model to significantly improve force at yield and pullout already 2 weeks after screw implantation in a femoral rat model of postmenopausal osteoporosis. The difference between the groups persisted until the end of the study after 8 weeks. Those results indicate that the local delivery of bisphosphonates from a hydrogel matrix can improve the fixation of implants in impaired bone rapidly and over a long time period. These are very important aspects considering the fact that the bisphosphonate delivery system is intended to stabilize osteosynthesis implant systems in osteoporotic bone.

References
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