Local Delivery of BP by an Injectable Calcium Phosphate Biomaterial Induce Bone Augmentation in the Proximal Femur Of Osteoporotic Ewes

E. Verron1, O. Gauthier2, P. Janvier3, B. Bujoli2, J. Guicheux1 and J.-M. Bouler1
1INSERM UMR 791 LIOAD, Nantes, France; 2National Veterinary School, Nantes, France
3CNRS UMR 6513 LSO, Nantes, France
Corresponding Author: elise.verron@univ-nantes.fr

Introduction
Osteoporosis has been defined as "a systemic disease characterized by low bone mass and micro architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture"[1]. Resorbable calcium phosphate (CaP) biomaterials have proved a noticeable efficacy in bone reconstruction surgery. Furthermore bisphosphonates (BPs) are well known antiresorptive agents largely used in systemic clinical treatments of osteoporosis. An injectable BP-combined CaP matrix has been developed in order to reinforce locally osteoporotic bone by increasing bone mineral density and improving bone micro architecture [2-3]. The purpose of this study was to implant such a combined device in the proximal femurs of ovariectomized ewes device in ewes’ osteoporotic proximal femurs and to quantify bone structure modifications. The properties of bone reinforcement after implantation of our combined BP-CaP materials were investigated by three-dimensional microtomography (3D-µCT) that was first developed for nondestructive analysis of trabecular bone architecture [4].

Materials and Methods
Calcium deficient apatite was loaded with zoledronate (7%-w/w) and mixed with a sterile cellulosic-derived hydrogel that made it injectable. Eight ewes were ovariecotomized in order to induce osteoporosis. Biomaterial were implanted for 12 weeks in proximal femur of osteoporotic ewes. 3D-µCT analysis was conducted on all implanted and control femurs. Bone volume density (BV/TV), trabecular thickness (TbTh), space between trabeculae (TbSp) and number of trabeculae (TbN) were measured.

Results
Osteoporosis induction is confirmed (figure) by a 40.0% decrease of BV/TV (iliac crest). Comparing treated versus control femurs for µ-CT histomorphometric measurements show significant increases (p<0.05) for bone volume density (+32.3%), trabecular thickness (+15.8%) and trabecular number (+16.8%) and a significant decrease for trabecular space (-12.8%). These modifications were confirmed by histological and SEM observations which revealed CaP granules resorption and new bone trabeculae formation.

Discussion and Conclusions
For the first time to our knowledge, a local combined effect of calcium phosphate particles and bisphosphonate is evidenced on sheep osteoporotic proximal femurs. Those preliminary results can be considered as a first step for a local approach that aims in delaying or even preventing osteoporotic fractures. Reinforcing specific bone sites like proximal femurs, vertebral bodies or wrists by implanting calcium phosphate materials that can promote bone ingrowth and release controlled quantities of bisphosphonates could be considered, in the near future, as an alternative to current systemic injections. Indeed, this combined device allows using small quantities of BPs that present a pure local effect because of the high affinity of BPs for bone apatite. This way of delivery could then decrease described side-effects (e.g. jaw osteonecrosis), due to regular and long-term BPs treatments. Obviously complementary in vivo experiments (mechanical tests, undecalcified histology) have to be conducted in order to better characterize the potential efficacy and eventual limits of such a local approach.

References

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