Strontium Loaded Macroporous Xerogel-scaffold Enhances Bone Formation In Critical-size Metaphyseal Osteoporotic Fracture Defects In Rats

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Disclosures:

Introduction: Impaired fracture healing with subsequent implant failure is a dramatic problem in osteoporotic fractures(1). Biomaterials are of interest to stimulate fracture healing in osteoporotic defects and the objective of the current study is to investigate the effects of strontium-enriched macroporous silica/collagen scaffold (ScB30Sr20) in a critical-size metaphyseal fracture defect of osteoporotic rats compared to a plain scaffold (ScB30) and a compact silica/collagen xerogel (B30).

Methods: 45 female Sprague-Dawley rats were randomized into 3 groups: ScB30, ScB30Sr20 and B30 (n=15 for each). A combinatorial approach of multi-deficiency diet for 3 months after bilateral ovariectomy was used for induction of osteoporosis. Left femur of all animals underwent a 4mm wedge-shaped metaphyseal osteotomy that was internally fixed with a T-shaped plate. The defect was then either filled with ScB30, ScB30Sr20 or B30 and internally stabilized with a T shaped mini-plate. After 6 weeks femora were harvested followed by histological, histomorphometrical, immunohistochemical (BMP2; bone-morphogenic protein 2, OPG; osteoprotegerin, RANKL; Receptor activator of nuclear factor kappa-B ligand, ASMA; alpha smooth muscle actin), and molecular biology (alkaline phosphatase, collagen1α1 and RANKL) to demonstrate the effects of the biomaterials on new bone formation. Time of flight secondary ion mass spectrometry (TOF-SIMS) technology was used to assess the distribution of released strontium ions and the biomaterial degradability.

Results: Histomorphometric analysis showed a statistically significant increase in the bone formation in the entire defect region in ScB30Sr20 when compared to B30 (p=0.0001) and ScB30 (p<0.05), respectively. The decreased bone formation in case of B30 was compensated by increased osteoid formation when compared to ScB30 (p=0.0001) and ScB30Sr20 (p=0.0001). In addition B30 also exhibited a higher biomaterial retention when compared to the other two groups (p=0.0001). With respect to biomaterial degradation, in B30 the material was nearly intact (p=0.0001) compared to the other two subgroups, where it was almost dissolved. ED1 positive cells were found to be the highest in the ScB30 group followed by the B30 group (p=0.0001), the least being in the ScB30Sr20 group (p=0.0001). These data were confirmed by the immunohistochemistry results which revealed an increase in bone-morphogenic protein 2, osteoprotegerin and α-smooth muscle actin in ScB30Sr20 when compared to the other two groups. Also the high ED1 count in case of ScB30 was supported by the increased RANKL expression in the same. The gene expression analysis revealed an increase in expression of genes responsible for bone formation viz. alkaline phosphatase, collagen1α1 and RANKL in ScB30 when compared to B30. Whereas no differences were seen between the ScB30Sr20 and ScB30 group. TOF-SIMS analysis also showed a complete degradation of ScB30 and ScB30Sr20 with negligible strontium count in case of the later.

Discussion: ScB30Sr20 treated group showed enhanced new bone formation in a metaphyseal osteoporotic fracture defect of rats after 6 weeks compared to ScB30 and B30 as revealed by the histomorphometry and immunohistochemistry analysis. The no show of differences in gene expression between ScB30Sr20 and ScB30 or B30 could be explained on the basis of the rapid degradation of the scaffolds which led to attenuated impact of strontium. However, generated osteoanabolic enzymes were still detectable by immunohistochemistry. The macroporous scaffold exhibited fast degradation whereas the xerogels showed only marginal resorption after six weeks. Prolongation of the degradation process of the ScB30Sr20 and maintenance of the structural integrity during the preliminary stages of new bone bone formation would not only improve the release kinetics of Sr but also enhance the rate of new bone formation.

Significance: The present study demonstrates the beneficial effects of strontium (Sr) enriched silica collagen scaffold to improve new bone formation in a metaphyseal osteoporotic fracture defects in osteoporotic rats. In addition, also brings out the importance of gradual biomaterial degradation which should be proportional to the rate of tissue repair.

Acknowledgments: This work is supported by the grant of the German Research Foundation (DFG-SFB-TRR 79)

References: 1) Amy Hoang-Kim, a Letizia Gelsomini, a Deianira Luciani, a Antonio Moroni, b and Sandro Giannini: Clinical cases in mineral and bone metabolism Clin Cases Miner Bone Metablv.6(2); May-Aug 2009PMC2781225