Bioactive Calcium Sulfate/Hydroxyapatite Augmentation with Systemic Zoledronic Acid for Pedicle Screw Fixation in an Osteoporotic Minipig Model

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INTRODUCTION: Pedicle screws are the gold standard for posterior spinal fixation; however, achieving stable fixation in osteoporotic bone remains challenging due to compromised bone quality, often necessitating cement augmentation. Current FDA-approved PMMA-based cements provide immediate stability but are bioinert, pose risk for adjacent vertebral body fractures and lack the capacity to promote osseointegration [1]. Thus, alternatives to biologically activate biomaterials are required. In our previous proof-of-concept study, calcium sulfate/hydroxyapatite (CaS/HA) composites improved the initial anchorage of pedicle screws in human osteoporotic vertebrae [2], particularly when using the a specialized "prefilling" material augmentation technique to increase the cement-screw interface volume[3]. Moreover, systemically administered bisphosphonates such as zoledronic acid (ZA) have been shown to biologically activate peri-implant HA particles, promoting bone formation and osteointegration in osteoporotic models [4]. Therefore, this study aimed to investigate whether systemic ZA administration could enhance the biofixation strength of pedicle screws augmented with CaS/HA using the prefilling technique.

METHODS: We conducted a study with 11 healthy, primiparous female Göttingen miniature pigs (age range 13-16 months at start). Following an established protocol for osteoporosis induction in minipigs, ovariectomy (OVX) was combined with a protocol of oral prednisolone for glucocorticoid-induced osteoporosis (GIO) and a calcium-restricted diet. Ten animals underwent bilateral laparoscopic ovariectomy (OVX), while one animal underwent a sham procedure (OVX: n=10; sham: n=1). Six months post-OVX, one OVX and the sham animal were sacrificed to positively confirm osteoporotic changes. The remaining nine animals had dorsal spinal surgery of five lumbar vertebrae with 4.5 × 25 mm pedicle screws. As our focus lay primarily on the bone surrounding the implant, we only implanted pedicle screws without further stabilization with rods or additional implants. The right pedicles were augmented with approximately 0.5 mL CaS/HA using a prefilling technique, while contralateral pedicles served as unaugmented controls (screw only). One week later, systemic ZA was administered and diet was changed to a normal calcium intake. Animals were sacrificed at 2, 6, or 12 weeks (n=3/timepoint). Lumbar vertebrae were harvested and subjected to µCT scanning with screws in situ. For biomechanical testing, torsional force was measured using a calibrated Nm screwdriver, leaving vertebrae intact for subsequent µCT and synchrotron CT after screw removal. Bone volume fraction (BV/TV) and bone mineral density (BMD) were quantified from µCT datasets using Dragonfly software, with ROIs placed adjacent to the screw tips and in the center of each vertebral body. Statistical analysis included Shapiro-Wilk normality testing and paired t-tests. Histology was performed with H&E and Goldner's staining. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC, ethics number 2022-11-09 Nr. G2-224 **(Fig. 1)**).

RESULTS: µCT confirmed successful induction of osteoporosis, with significantly reduced BV/TV and BMD in OVX animals compared with sham controls at 6 months **(Fig. 2A)**. Synchrotron CT after screw removal demonstrated bone tissue along the screw threads. Bone substitute was evident at screw tips at 2 and 6 weeks, but was largely integrated by 12 weeks **(Fig. 2B)**. Quantitative µCT showed BV/TV was significantly higher on the augmented side versus screw only side at 2, 6, and 12 weeks ($p<0.05$, **Fig. 2C**). The pull-out torque strength did not differ **(Fig. 3A)**. Histology confirmed bone cement remnants with localized woven bone at 6 weeks. At 12 weeks the CaS had resorbed with no additional new bone formation on either side **(Fig. 3B)**.

DISCUSSION: The OVX + steroid treatment based minipig model effectively mimicked postmenopausal osteoporosis. Systemic ZA with CaS/HA augmentation increased peri-screw bone volume, and imaging confirmed localized bone response around CaS/HA. The narrow pedicles in this mini pig model complicate both cement injection and screw insertion in direct contact with the relatively larger cortical bone mass bone. A reduced bioactivity of systemic ZA on cortical bone contrary to spongious bone is known. Therefore, future studies should employ models that more closely replicate human surgical anatomy and loading conditions to better evaluate the translational potential of bioactive augmentation strategies.

SIGNIFICANCE/CLINICAL RELEVANCE: Pedicle screw fixation in osteoporotic bone remains clinically challenging. This study demonstrates that while bioactive CaS/HA combined with systemic ZA transiently increased peri-screw bone volume, the biomechanical fixation in this mini pig model is not improved, highlighting the need for further validation of bioactive augmentation strategies in more clinically relevant models.

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IMAGES AND TABLES:

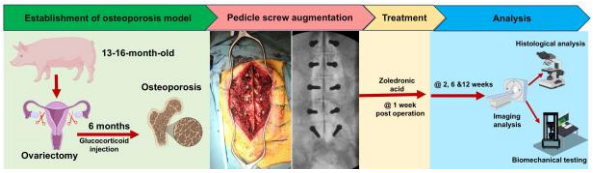

Fig. 1. Study design. Osteoporotic minipig model with ovariectomy (OVX) and glucocorticoid induction (GI), pedicle screw augmentation with calcium sulfate/hydroxyapatite, systemic zoledronic acid treatment, and analysis at 2, 6, and 12 weeks.

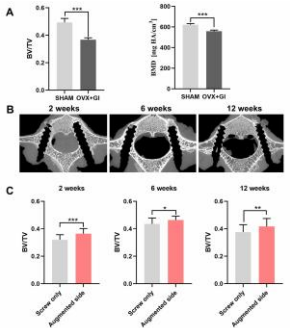

Fig. 2. Micro-CT and synchrotron CT analysis. (A) µCT analysis confirmed osteoporosis induction. **(B)** Synchrotron CT images at 2-, 6-, and 12-weeks showing pedicle screws with visible CaS/HA cement at early time points and degradation by 12 weeks. **(C)** Quantitative µCT analysis revealed significantly higher BV/TV on the augmented side compared with screw-only controls at 2, 6, and 12 weeks (*p<0.05, **p<0.01, ***p<0.001).

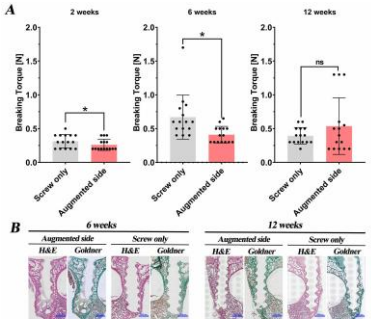

Fig. 3. Biomechanical testing and histological evaluation. (A) Breaking torque measurements at 2, 6, and 12 weeks (*p<0.05, ns = no significance). **(B)** Histological sections stained with H&E and Goldner at 6 and 12 weeks.