Restoring implant fixation strength in osteoporotic bone with a hydrogel locally delivering zoledronic acid and Bone Morphogenetic Protein 2. A longitudinal *in vivo* microCT study in rats.

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INTRODUCTION: Osteoporosis is a major public health concern that is responsible for more than 9 million fractures annually. Due to the reduction in both cortical and trabecular bone mass in osteoporotic patients the fixation of osteoporotic bones is particularly challenging, mainly regarding screw implantation. Local loads at the bone-implant interface can exceed bone's yield point and result in microfracture and eventually failure of fixation. Systemic treatments for osteoporosis aim to restore bone mass but cannot ensure high efficiency and high quality for improving local bone mass and strength at the screw location. Instead, the use of local drug delivery methods allows an elevated concentration of the chosen agents. The aims of this work were first to demonstrate the safety of a thermoresponsive hyaluronan gel (HA-pNIPAM) in a rat model of screw fixation and the second to test the efficacy of HA-pNIPAM hydrogel to locally deliver bisphosphonate zoledronic acid (ZOL), a potent anti-resorptive drug and bone morphogenetic 2 (BMP2) the bone inducing protein, in an osteoporotic rat model of screw fixation and evaluate its influence on implant fixation strength.

METHODS: Female Wistar rats (n=36) were divided into 2 treatment groups: one group of sham-operated animals (n=16) and a further group that received an ovariectomy (OVX) at 13 weeks to induce an osteoporotic state (n=20). The animal study was approved by the local ethical committee and performed in an AAALAC accredited facility. All animals received a polyetheretherketone (PEEK) screw in the proximal tibia at 25 weeks (i.e., 12 weeks post-OVX). In addition, subgroups of healthy (SHAM) or OVX animals received either HA-pNIPAM hydrogel alone or HA-pNIPAM-ZOL/BMP2 hydrogel, placed into the defect site prior to screw implantation. Drug released analyses was performed on the HA-pNIPAM- ZOL/BMP2 hydrogel over for 5 days and release ZOL and BMP2 were quantified spectrophotometric analysis and ELISA, respectively. Periprosthetic bone and implant fixation were monitored using longitudinal *in vivo* microCT scanning post-operatively and at 3, 6, 9, 14, 20 and 28 days. Analyses of bone implant contact (BIC), periprosthetic bone fraction (BV/TV), implant integration stiffness and bone formation/resorption (BF/BR) were performed using EasyIPL (easyipl.com), a high-level library of macros using the scanner software (SCANCO Image Processing Language and OpenVMS Digital Command Language). At the end of the study, a semiquantitative histological assessment on bone morphology, bone ingrowth and bone implant contact was performed on the Gimsa-Eosin stained sections.

RESULTS SECTION: The *in vitro* release data show that 80% of the ZOL and 20% of BMP2 were released after 120 hours. The *in vivo* data showed that pure HA-pNIPAM hydrogel is bio-inert in terms of implant fixation which was demonstrated by the natural implant integration process in SHAM animals with HA-pNIPAM hydrogel, comparable to the SHAM animals without. As expected, the OVX animals had dramatically reduced trabecular bone and there was almost no bone reaction to the implant. Quantitatively, there were no significant differences in BIC, BV/TV, or implant integration stiffness between animals with and without HA-pNIPAM hydrogel in either the SHAM or OVX conditions. Conversely, the HA-pNIPAM-ZOL/BMP2 hydrogel induced from day 14 a significant increase in BIC, BV/TV and stiffness compared to OVX animals and on day 28 also a significant increase in BIC and stiffness compared to SHAM animals. These findings are connected to the reduced resorption (BF/BR) in the OVX animals with HA-pNIPAM-ZOL/BMP2 hydrogel compared to all the other groups (Figure 1). The semiquantitative histological assessment also confirmed the significantly increased BIC and callus formation of the OVX animals with HA-pNIPAM-ZOL/BMP2 hydrogel compared to the other animals.

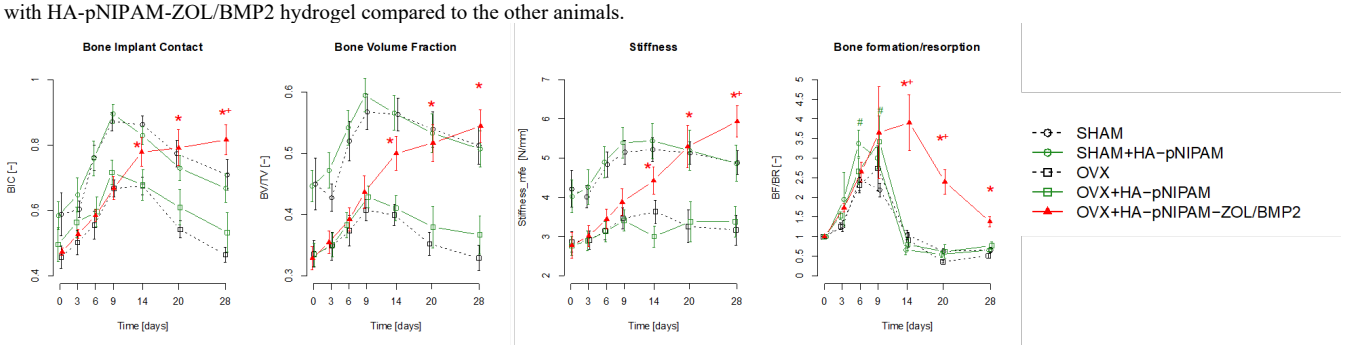

Figure 1. Quantitative findings from longitudinal *in vivo* time lapsed microCT. Shaded areas represent the 95% confidence intervals (CI) of the data fitted with general mixed models; significance with p<0.05 are represented as follow: *: higher than OVX; +: higher than SHAM; and #: higher than without gel.

DISCUSSION: Implant fixation in osteoporotic bone remains a challenge due to reduced and weakened bone and impaired healing capacity. To make matters worse, osteoporosis also alters the establishment of early and maintenance of late-stage implant fixation as well as bone architecture leading to loss of fixation. This study showed that the local delivery of resorption-preventing bisphosphonate and bone-forming BMP2 could improve implant stability in a well-established model of screw fixation in osteoporotic rats.

SIGNIFICANCE/CLINICAL RELEVANCE: Local delivery of ZOL and BMP2 using a biocompatible hyaluronan hydrogel proved to improve implant stability in osteoporotic bone. This approach could constitute a potent alternative to systemic drug administration and may be useful in avoiding implant loosening in clinical settings.

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