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Citation for published version (APA):

Document status and date:
Published: 01/01/2016

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Download date: 03. Mar. 2019
In vivo micro-CT based approach for discrimination of physiological and impaired healing patterns in mouse femur defect models

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INTRODUCTION: Longitudinal non-invasive monitoring of the healing process is crucial in preclinical fracture healing studies. We recently described an in vivo micro-computed tomography (micro-CT) protocol, which was found to show no significant radiation-associated effects on callus properties [1]. In a second step, we now want to assess, whether the protocol is suitable for healing phase-specific detection of physiological vs. impaired fracture healing. For this purpose we monitored the healing process in femoral defect models with different gap sizes.

METHODS: Female 20 week-old C57BL/6J mice received a femur defect of either 1.2mm±0.1 (group 1, n=5) or 2mm±0.1 (group2, n=7), stabilised with an external fixator (MouseExFix, RISystem, Davos, Switzerland). During the healing period the animals received weekly scans of the osteotomy area (vivaCT 40, ScancoMedical, Brüttisellen, Switzerland, for detailed protocol see [1]). In order to assess dynamic callus parameters the scans from later weeks were registered onto earlier scans from the same animal. Statistics: Data were tested for normal distribution (Shapiro-Wilk-Test) and homogeneity of variance (Levene-Test). Comparisons of the two groups were done by Student’s t-test or Mann-Whitney U-test. The level of significance was set at p≤0.05.

RESULTS: In the 1.2 mm defect group a physiological healing pattern was observed with distinct characteristics of the different healing phases (Figs. 1+2): In postoperative week 2 a significant 26x increase in bone formation was detected, indicating progression from the inflammation to the reparative phase. This led to a significant gain in bone volume in the defect with maximum osseous callus volumes being detected by week 3 (BV: 1mm³±0.4) and complete cortical bridging in 80% of animals at this time point. Subsequently, decreasing osseous callus dimensions in combination with increasing resorptive activities indicated the onset of the remodelling phase in postoperative week 4.

In contrast, in the 2mm defect group, both bone formation (week 3) and resorption rates (week 4) were significantly reduced by >50% with steady levels from weeks 2-4 and weeks 3-5, respectively (Fig. 2). Lack of characteristic peak values and only moderate onset of callus mineralization (BVweek3: 0.5mm³±0.2) indicated an impaired and delayed healing pattern.

DISCUSSION & CONCLUSIONS: Using the previously described scanning protocol with subsequent analyses of structural and dynamic callus parameters, we were able to detect callus properties indicative of the different fracture healing phases under physiological conditions. This method also allowed longitudinal characterization of the impaired and delayed healing process associated with increased defect size. In future studies this micro-CT-based approach will also be applicable to assess the healing potential of biomaterials in this preclinical femur defect model in mice.


ACKNOWLEDGEMENTS: The authors acknowledge financial support from the EU (BIODESIGN FP7-NMP-2012-262948).

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