MECHANOREGULATION OF BONE FORMATION DURING NON-UNIONS IN PREMATURELY AGEING MICE

Jack J. Kendall[1], Valentin Baumann[1], Neashan Mathavan[1], Esther Wehrle[1,2] , Ralph Müller[1]

[1]Institute for Biomechanics, ETH Zurich, Zurich, Switzerland, [2]AO Research Institute Davos, Davos Platz, Switzerland

Introduction

Soft tissue mechanics plays a vital role in bone regeneration and yet, the local mechanical environment leading to compromised regeneration i.e., delayed- or non-union, remains to be elucidated. [1] Bone regeneration can be studied using time-lapse micro-computed tomography (micro-CT) enabling *in vivo* longitudinal experiments. Combined with micro-finite element (micro-FE) analysis, morphological changes of the bone architecture can be associated with strains at the tissue-level. [2] The PolgA mouse model of premature aging exhibits age-associated impaired bone regeneration in femur osteotomies studies. [3] Thus, we aim to study the mechanoregulation of bone formation during non-unions and/compared to unions in PolgA mice by leveraging micro-FE analysis.

Methods

In vivo time-lapse micro-CT images of femur osteotomies in 12-week-old "young" (n=8) and 35-week-old "old" (n=8) female mice of a prematurely ageing PolgA mouse model were used. [3] The femur osteotomies were stabilised with a PEEK external fixator and mechanical stimulus was provided via ambulatory loading. At 3 week post-op, the young and old groups both presented 4 non-unions. Linear-elastic micro-FE models (Fig. 1a) were generated at each time point by converting mineral density values above 395 mg HA/cm^3 linearly to Young's modulus (4-12 GPa, ν=0.3) to compute the effective strain (EFF). [3] Volumes of formation were obtained by the overlay of registered binary time-lapsed images. The modelling performance of EFF was determined via receiver operator characteristic (ROC) analysis. The computed area under the ROC curve (AUC) summarises the modelling performance of EFF as a predictor for bone formation during regeneration. The AUC ROC was computed within the osteotomy gap (OG) at increasing tissue mineral density thresholds, starting at 395 mg HA/cm^3 and increased by steps of 25 mg HA/cm^3 until the maximum threshold of 720 mg HA/cm^3. Significance ($p < 0.05$) was determined via repeated-measures 3-way ANOVA with Bonferroni correction.

Results

The prediction of bone formation using EFF was significantly higher for both the union (p=0.014) and old (p=0.003) groups than for young and non-union groups (Fig. 1b). Significant differences in bone formation emerged (Fig. 1c) between union and non-union groups (p=0.010) within the osteotomy gap and also between young and old (p=0.043).

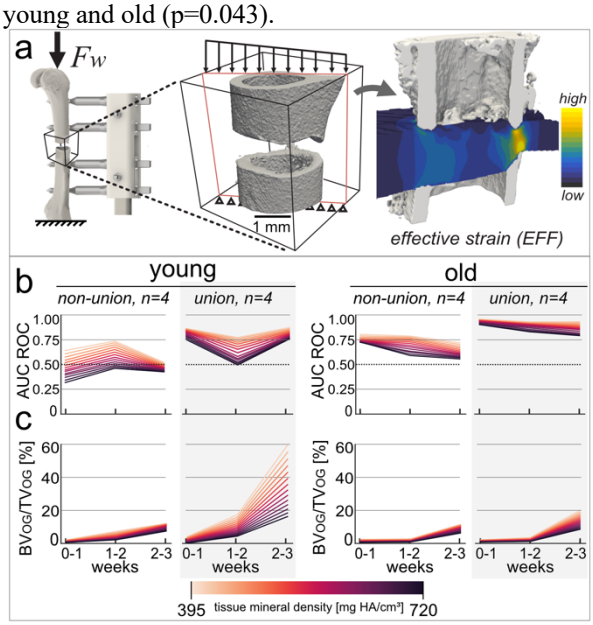

Fig. 1: (a) Micro-FE analysis of EFF in the OG. (b) Mean ROC AUC of EFF as for (c) bone formation in young and aged mice for both unions and non-unions.

Discussion

Bone formation in soft tissue during regeneration is mechanically regulated, with old mice being more sensitive to EFF than young mice. Not only was bone formation in the non-union groups insufficient to bridge the OG, but also the deposition of bone was not mechanically regulated, especially in the young group. Whereas bone formation in both the old and young union groups could be predicted by the EFF in the soft tissue. However, it remains unclear whether the strains across the OG *in vivo* were too large to permit bone formation or if the femur was never effectively loaded by the mice of the non-union group. We conclude that bone formation during unions is mechanically regulated since it can be predicted by EFF whereas poor mechanoregulation in soft tissue in the OG is associated with non-unions.

References

1. Morgan et al., Clin. Rev. Bone Miner. Metab., 13:256-265, 2015.
2. Tourolle né Betts et al., Sci Rep, 10:1100, 2020.
3. Mathavan et al., JBMR, 37:339-340, 2022.

Acknowledgements

Support from EU (MechAGE ERC-2016-ADG-741883)