

Minding the gap: sex differences influence bone fracture healing

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Bone regeneration involves the (inter)action of cells, regulated by biochemical and mechanical factors. After fracture, successful healing is usually achieved within weeks. However, fracture severity, anatomical location and host factors can lead to delayed- or non-healing. Among the host factors, the role of sex differences is still poorly investigated, and experiments report contradictory findings. Evidence suggests a less efficient bone healing in females [1] due to a sexually dimorphic inflammatory response [2]. Indeed, M1 macrophages predominate in males, and M2 in females; leading to a not-fully-understood, sex-based macrophages-stem cells crosstalk in osteogenesis [3]. In the repair phase, sex hormones regulate stem cell differentiation and proliferation [4]. A stronger repair response is often found in males due to a higher skeletal stem cell [4] and osteoblast [5] activity, and a more prominent cartilaginous callus [5]; but some studies observed the opposite: higher bone formation in females [3]. It is thus not clear how sex disparities integrate in an emergent outcome.

In this study, we used a macrophage-mediated bone healing model [6] to investigate how sex differences influence the healing progress in different fracture types. A sensitivity analysis selected a reduced parameter set: a one-at-a-time approach identified the impactful parameters, and a design of experiments analyzed the joint effect of these. The reduced set was crossed with literature data to create male and female parameter sets. The model was validated with literature data.

The predicted union cases revealed no significant sex-specific differences in the bone outcome, but different cell activities were observed. The non-union cases showed that sex differences further amplify impaired healing. This study contributes to an improved understanding of the role of sex differences in fracture healing.

References: [1] Ortona et al., *Biology*, 2023; [2] Kurapaty & Hsu, *C Reviews Musculo Med*, 2022; [3] Nathan et al., *Bone & Joint R*, 2019; [4] Andrew et al., *Nat Commun*, 2022; [5] Haffner-Luntzer et al., *F Physiology*, 2021; [6] Trejo et al., *Math Comput Appl*, 2019.

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