**Osteogenic and Chondrogenic Differentiation Defects in Geriatric Human Skeletal Stem Cells from Acute Fractures**

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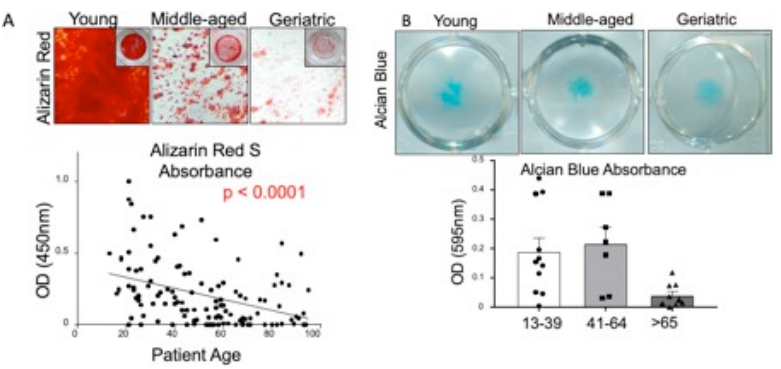
**Purpose:** Geriatric fragility fractures are increasingly prevalent, with significant rates of implant complications, reoperation, and mortality. Evidence suggests aging is associated with impaired stem cell function in human tissues undergoing regeneration. In human fractures, the effect of aging on human skeletal stem cells (hSSCs) in fractures is unknown. We hypothesized that hSSCs prospectively purified from geriatric fragility fractures demonstrate intrinsic functional defects, which can be traced to underlying hSSC signaling defects.

**Methods:** We isolated hSSCs (Podoplanin+, CD146- CD73+ CD164+) by fluorescence-activated cell sorting (FACS) from human fractures. Purified SSCs from geriatric fractures were analyzed subsequently for clonogenicity by colony-forming unit formation (CFU-F) (n = 151 <65 years; n = 55 >65 years). After osteogenic and chondrogenic differentiation, cell staining for Alizarin red and Alcian blue was quantified by spectrophotometry. SSC frequency, CFU-F, and Alizarin red / Alcian blue staining were compared to patient age by linear regression for continuous variables or $\chi 2$ for categorical variables.

**Results:** There was no association between patient age and SSC frequency at the fracture site. There was also no association on CFU-F% or CFU size. However, there was a significant decrease in osteogenic and chondrogenic differentiation associated with increased patient age ($P < 0.05$).

**Conclusion:** SSCs from geriatric fractures retain their proliferative ability but demonstrate differentiation defects potentially contributing to adverse healing outcomes. Our results could open avenues for patient-specific therapeutic strategies to improve healing in geriatric fragility fractures.




A) hSSC from geriatric patients demonstrate significantly diminished alizarin red staining (A) and alcian blue staining (B) after osteogenic differentiation (A) or micromass culture (B) compared to young patients. OD, optical density at specified wavelength.

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