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CORR Insights®: Fractures in Geriatric Mice Show Decreased Callus Expansion and Bone Volume

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Where Are We Now?

Most orthopaedic surgeons recognize that the elderly heal their fractures more slowly than younger individuals, but the explanation for why this might be and whether fracture healing in the elderly can be improved has rarely

been investigated. This question is important as after the first fragility fracture the probability of additional fractures is markedly increased [6]. Despite data suggesting that osteoporosis is not an immediate consequence of aging [1], the elderly, in general, have reduced bone mass and more porous bones [10]. This situation leads to a vicious cycle as the elderly have a greater tendency to have fragility fractures and these fractures heal more slowly, causing decreased weight bearing, which leads to bone with even more reduced mass and greater porosity. The elderly also tend to exercise less [9], leading to reduced muscle strength, increased risk of falling, and fragility fractures. While a variety of environmental and inherited factors contribute to fracture risk in all individuals [5], age-related bone loss appears to be an underlying contribu-

tor. Questions related to this observation are two-fold; (1) why is fracture healing retarded in the elderly, and once we understand that (2) how can a healthy bone state be retained or regenerated in the geriatric population? The paper by Lopas et al. [8] begins to address the first question. Fracture healing mimics endochondral ossification and it appears from this paper that the mechanism for endochondral repair still functions in older mice; at least in the species of aged mouse studied, the repair process is slower and less complete. This begins to address the issue of slower fracture healing in the geriatric population. The study, as mentioned by the authors, is limited in that the rodent is not necessarily the best animal model for studying human osteoporosis. To date, however, there are no ideal animal models [4]. Further, the fracture model used, while reproducible, mimics traumatic as opposed to fragility fractures, and it is fragility fractures that contribute to the mortality in the elderly [3]. However, even with these limitations, some important fundamental lessons about fracture healing in the elderly can be gleaned from this paper.

This CORR Insights® is a commentary on the article “Fractures in Geriatric Mice Show Decreased Callus Expansion and Bone Volume” by Lopas and colleagues available at: DOI: [10.1007/s11999-014-3829-x](https://doi.org/10.1007/s11999-014-3829-x)

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Where Do We Need To Go?

The paper [8] demonstrates that in elderly (25 months old) mice provided by National Institute on Aging the fracture healing was delayed (based on microcomputed tomography and histology) relative to adult mice (5 months old) from the same colony. The sex of the animals was unstated, and since there is a known sexual dimorphism of bone properties in these and other mice [2], the question still remains whether these pathways are similarly attenuated in males and females. This question is important in humans because males with fractures are reported to have a worse prognosis than females [3]. Is this due to psychological factors or to gene expression differences between males and females as they age? Further, since the endochondral pathway appeared to be functional in geriatric mice, albeit reacting more slowly, what factors do differ as a function of age? It will be important to look for these factors in the B6 mice (strain of aging mice used) and also in other strains since different strains of mice reach peak bone age at different rates [2], and may, for similar reasons, have different rates of bone healing. As recently pointed out [5], it is also important to understand the biomechanical mechanisms that define how molecular

pathways ultimately impact whole bone fracture resistance.

How Do We Get There?

To address these questions, studies of mechanical, histological, and genetic parameters of fracture healing in a variety of aging animal models will be necessary. Fracture healing involves large numbers of genes [7], only a few of which have been identified to date, and almost none have been shown to vary with age. Microarray analysis or whole genome wide analysis of fracture healing in the adult and elderly mouse might reveal known and new genes associated with the process, and explain why there is an age dependent difference. We also need to know which, if any, of the drugs used to improve bone mass [12], accelerates the fracture healing process in the geriatric population. There is also a perception that the oldest old will not respond to these drugs, yet data shows that diet, fall prevention and certain therapies can act with 12 months to prevent fracture [11]. This can be learned by testing the mechanical strength of the callus in these mouse models or by characterizing the cellular changes as a function of time, as done in the Lopas paper [8].

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