Question #5: Does aging change how joint tissues respond to joint injury and thus alter PTOA outcomes?

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Recommendation: Yes. Aging changes how joint tissues respond to injury, and these age-related differences can substantially alter PTOA outcomes.

Level of Evidence: Moderate/Strong

Posttraumatic osteoarthritis (**PTOA**) is a type of osteoarthritis that develops following a joint injury. It is characterized by the degeneration of articular cartilage and subchondral bone, as well as increased inflammation of the surrounding tissues. Unlike primary osteoarthritis (OA), which occurs gradually over time, PTOA is triggered by a specific traumatic event. Traumatic joint injuries, such as meniscus or ligament tears or damage to articular cartilage and bone, increase the susceptibility of developing the PTOA. Their severity is critical in influencing the speed of PTOA[1]. Following trauma, a complex interplay of biological and mechanical factors determines whether the articular surface is preserved or cartilage degenerates, leading to PTOA.

Aging of the musculoskeletal (MSK) system is a natural process characterized by progressive loss of function in muscles, bones, cartilage, and synovium driven by factors such as decreased bone density, muscle mass loss (sarcopenia), fibrosis, and cartilage degeneration.[2] There are several mechanisms that potentially contribute to the aging joint tissues' response to trauma.

1) Cell senescence and mitochondrial dysfunction. Aging has been shown to increase senescence burden in many tissues. Senescent cells secrete pro-catabolic and pro-inflammatory factors (termed senescence-associated secretory phenotype SASPs) that amplify tissue damage and impair natural processes of tissue repair.[3, 4] The majority of joint tissues contain senescent cells that increase in numbers with age and disease progression.[5-7] One of the major drivers of cell senescence in joint tissues is oxidative stress, mainly driven by reactive oxygen species (ROS). Findings suggest oxidative stress induces chondrocyte dysfunction and cartilage degeneration in OA.[8] Furthermore, DNA damage[9, 10] and mitochondrial dysfunction have been associated with tissue degeneration after injury.[11]

2) Altered mechanical responsiveness. It has been shown that aging chondrocytes,[12] meniscal cells,[13, 14] and bone cells[15] exhibit altered mechanotransduction, associated with impaired responsiveness to proanabolic factors such as IGF1 and TGFβ.[16] These results suggest that aging cells within the joint have a reduced ability to repair matrix damage after injury. Furthermore, it has been shown that there is an age-related accumulation of advanced glycation end products (AGEs), leading to decreased cartilage stiffness.[17, 18] Cells within the joint with an impaired ability to respond to loading are more susceptible to injury and less capable of dissipating mechanical stimuli, which can lead to worse post-joint injury outcomes. Furthermore, aging alters bone remodeling dynamics, often leading to maladaptive subchondral bone sclerosis after injury.

3) Inflammaging. Another important mechanism that has been shown to affect tissues during aging is a disturbance in immune system dynamics termed “inflammaging”. Inflammaging is defined as a chronic, low-grade inflammation state driven by endogenous signals in the absence of infections, occurring with aging. [19, 20] The role of immune cells in mitigating PTOA has been previously established in mice and humans.[21, 22] Interestingly, although not directly tested in PTOA, there is a

well-established phenomenon of myeloid skewing in many tissues during aging, which impairs immune cell dynamics and disrupts tissue homeostasis.[23] Others reported an important contribution of other immune cells, such as T cells, in the progression of PTOA.[24, 25] Furthermore, studies reported serum levels of IL-6 and TNF-α to be associated with knee cartilage loss in older people suggesting that low level inflammation plays a role in the pathogenesis of knee OA.[26] In many joint tissues, aging is associated with reduced inflammation resolution and impairment of pro-resolving pathways. Furthermore, other immune cells accumulate age-associated damage, and their response to injury is decreased.

Animal models: In non-injured animals age was shown to cause mild knee OA, mechanical sensitization, and changes to immune cell populations in the dorsal root ganglia in male and female mice.[27] Furthermore, knee joints of older mice (95 weeks old) showed increased expression of inflammatory-response genes and decreased expression of cartilage-metabolism genes with aging as well as age-associated changes in cartilage matrix protein content.[28] Several studies examined differences in PTOA outcomes between young and aged animals. For instance, older (12-month-old) mice exhibited more severe histologic OA after a joint injury that destabilized the medial meniscus (DMM) than younger (12-week-old) mice with an age-related decrease in matrix gene expression and an increase in immune and defense response reported.[32] Furthermore, others showed that 62-week-old mice six weeks post-anterior cruciate ligament injury (ACL) showed increased cartilage degeneration and osteophyte formation compared to 10-week-old mice.[29] Both age groups showed similar transcriptional responses to injury, but older mice had higher inflammatory cytokine activation, while younger mice had greater expression of cartilage/bone metabolism genes. Other studies reported that older rats displayed larger cartilage lesion areas following meniscus transection when compared to younger animals.[30] Furthermore, when destabilization of the medial meniscus (DMM) was performed on 12- and 19-month-old mice, they developed more cartilage erosion and a thicker subchondral bone plate than when DMM was performed on 4-month-old mice.[31]

Summary: Injuries sustained at older ages are more likely to progress rapidly to PTOA. Structural damage is more severe, symptoms may develop sooner, and disease progression is often faster compared to younger individuals. These differences suggest that *age at injury* is a critical biological modifier of PTOA risk and trajectory.

Implications: PTOA mechanisms and interventions may need to be age-specific.

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