OPEN ACCESS Freely available online

Journal of Bone Research

ISSN: 2572-4916

Perspective

Mitochondrial Dysfunction and Its Impact on Bone Aging

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ABOVE THE STUDY

Mitochondria are often described as the "powerhouses" of the cell, but in the context of bone biology, they are far more than energy-producing organelles. They are central regulators of cellular metabolism, redox balance, and apoptosis, all of which are essential for maintaining skeletal integrity. In my view, mitochondrial dysfunction represents one of the most critical yet underrecognized drivers of bone aging, influencing the gradual decline in bone formation, the increase in resorption, and the overall deterioration of bone quality seen in elderly populations.

Bone is a highly metabolically active tissue that relies on continuous remodeling by osteoblasts and osteoclasts. Osteoblasts, in particular, require substantial energy to synthesize and mineralize bone matrix. This energy demand is largely met by mitochondrial oxidative phosphorylation. When mitochondrial function declines with age, osteoblasts experience reduced ATP production, leading to impaired differentiation, decreased matrix synthesis, and ultimately diminished bone formation. This energy deficit alone can significantly weaken skeletal regeneration capacity over time.

At the same time, aging mitochondria generate increased levels of reactive oxygen species (ROS). While physiological ROS levels are important for signaling, excessive production leads to oxidative stress, damaging cellular proteins, lipids, and DNA. In osteoblasts and osteocytes, this oxidative damage accelerates cellular senescence and apoptosis, further contributing to bone loss. In my opinion, the accumulation of mitochondrial oxidative damage acts as a molecular "timer" of skeletal aging, progressively eroding the regenerative potential of bone tissue.

Osteoclasts are also influenced by mitochondrial function, but in a somewhat paradoxical manner. Unlike osteoblasts, osteoclasts depend on both glycolysis and mitochondrial metabolism to sustain their bone-resorbing activity. In aging, mitochondrial changes can sometimes enhance osteoclast differentiation and activity, tipping the balance toward excessive bone resorption. This imbalance between decreased bone formation and increased bone breakdown is a hallmark of age-related osteoporosis.

Mitochondrial dysfunction is not limited to energy and ROS imbalance; it also affects signaling pathways that regulate bone cell fate. Mitochondria interact closely with key regulatory networks such as AMPK, mTOR, and sirtuins, which are known to control cellular aging and metabolism. For example, reduced activity of SIRT1 and SIRT3 both mitochondrial-associated deacetylases has been linked to impaired osteoblast function and increased bone fragility. These pathways highlight how mitochondrial health is deeply integrated with broader cellular aging mechanisms.

Another important aspect is mitochondrial dynamics, including fission, fusion, and mitophagy (the selective removal of damaged mitochondria). In healthy bone cells, these processes maintain mitochondrial quality control. However, with aging, mitophagy becomes less efficient, leading to the accumulation of dysfunctional mitochondria. This not only reduces cellular efficiency but also amplifies inflammatory signaling, further accelerating bone degeneration. In my opinion, defective mitochondrial quality control may be one of the earliest and most fundamental changes driving skeletal aging.

The role of mitochondria in stem cell aging is equally important. Mesenchymal Stem Cells (MSCs), which give rise to osteoblasts, show a decline in regenerative capacity with age, partly due to mitochondrial dysfunction. Aging MSCs tend to shift from osteogenic to adipogenic differentiation, contributing to increased marrow fat and reduced bone formation. This shift is strongly linked to altered mitochondrial metabolism and reduced oxidative capacity.

From a therapeutic perspective, targeting mitochondrial dysfunction offers a promising strategy for combating bone aging. Approaches such as antioxidants, mitochondrial biogenesis activators, and agents that enhance mitophagy are being explored. Compounds like resveratrol, NAD+ precursors, and exercise mimetics have shown potential in improving mitochondrial function and supporting bone health. However, in my opinion, these interventions must be carefully optimized, as excessive antioxidant use may disrupt essential ROS signaling required for normal bone remodeling. Emerging technologies, including mitochondrial gene therapy and targeted drug delivery systems, may further enhance the

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Received: 25-Jun-2025, Manuscript No. BMRJ-25-41406; **Editor assigned:** 27-Jun-2025, PreQC No. BMRJ-25-41406 (PQ); **Reviewed:** 11-Jul-2025, QC No. BMRJ-25-41406; **Revised:** 18-Jul-2025, Manuscript No. BMRJ-25-41406 (R); **Published:** 25-Jul-2025. DOI: 10.35841/2572-4916.25.13.349.

Citation: Tanaka K (2025). Mitochondrial Dysfunction and Its Impact on Bone Aging. J Bone Res. 13:349.

ability to restore mitochondrial function in bone cells. Additionally, lifestyle interventions such as physical exercise and caloric regulation remain powerful modulators of mitochondrial health and skeletal aging.

In conclusion, mitochondrial dysfunction plays a central and multifaceted role in bone aging by impairing energy production, increasing oxidative stress, disrupting signaling pathways, and altering stem cell fate. In my view, understanding and targeting mitochondrial health may be one of the most effective strategies for preserving skeletal integrity and preventing age-related bone diseases in the future.