



PHYSICAL ACTIVITY AND SKELETAL MUSCLE MITOCHONDRIAL HEALTH ACROSS THE HUMAN LIFESPAN

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Age-related muscle atrophy and functional decline lead to reduced mobility, increased fall risk, and disability in older adults (1). Impaired mitochondrial function is widely considered a hallmark of muscle aging, with reduced mitochondrial respiration and increased mitochondrial reactive oxygen species (ROS) production frequently cited as key contributing mechanisms (2). Disrupted mitochondrial calcium handling, altered mitochondrial permeability transition pore (mPTP) function, and downstream activation of apoptotic and proteolytic pathways have also been implicated in skeletal muscle aging (3,4). However, the confounding influence of physical inactivity has obscured whether skeletal muscle mitochondria accumulate genuine age-related defects (5,6). To disentangle the effects of aging from physical activity-related mitochondrial adaptations, we performed comprehensive functional profiling of skeletal muscle mitochondria in 139 men aged 20-93 years, comprising 51 inactive and 88 physically active individuals (7). Physical activity conferred partial protection against age-related decline in physical performance. In ac-

tive participants, mitochondrial respiratory capacity remained stable across the entire age range, demonstrating that aging per se does not impair mitochondrial respiration. Mitochondrial ROS production was unaffected by age and was elevated in active relative to inactive participants. In striking contrast, mitochondrial calcium retention capacity declined progressively with age regardless of physical activity status. This age-dependent decrease in calcium retention capacity correlated with muscle mass and physical performance. These findings demonstrate that previously reported age-related mitochondrial respiratory deficits reflect physical inactivity rather than intrinsic aging. This interpretation aligns with evidence showing that a few days/weeks of physical (in)activity can substantially alter mitochondrial content and function in older adults (8,9). Conversely, impaired mitochondrial calcium handling emerges as a bona fide aging-related defect independent of activity status (7). Therapeutic strategies targeting mitochondrial calcium regulation may hold promise for mitigating age-related muscle impairments.

Keywords: calcium retention capacity, mitochondria, mitochondrial permeability transition pore, muscle atrophy and weakness, skeletal muscle aging.