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Acid–Base Dysregulation Links Aging Metabolism to Frailty

Frailty in older adults, modelled either as an accumulation of health deficits or a phenotypic energetic collapse, is characterized by heightened vulnerability and reduced physiological reserve. Despite these established diagnostic frameworks, the fundamental pathophysiology connecting cumulative stress to systemic energy failure remains incompletely understood. We propose that the dysregulation of acid-base balance is a critical, yet underappreciated mechanism driving this collapse. In a narrative review, we examine how aging-related cumulative stress and mitochondrial dysfunction escalate acid load alongside disease and deficit accumulation. This accumulating metabolic acid strongly taxes the diminishing capacity for intracellular and extracellular buffering, renal acid excretion, and ventilatory reserve, causing subtle acidosis. Subtle acidosis further reduces mitochondrial ATP production, driving system-wide inefficiency and accelerating the accumulation of deficits. It also prompts compensatory responses such as fatigue and reduced activity to lower the metabolic acid load. To preserve serum pH, skeletal muscle, bone, liver, and kidneys cooperate to mobilize base reserves and redirect amino acid metabolism for renal acid elimination. However, this critical adaptation occurs at the direct expense of musculoskeletal integrity, driving sarcopenia and osteoporosis. The "shrinking iceberg" metaphor illustrates this frailty progression: repeated stressors silently erode acid buffers and energy reserves, rendering individuals vulnerable to homeostatic and multiorgan failure during acute stress. Crucially, this metabolic acid model bridges Rockwood's deficit accumulation with Fried's phenotype, unifying two foundational concepts of frailty. Recognizing this specific pathophysiology suggests novel therapeutic targets (diet, exercise, buffering) to preserve metabolic reserve and delay frailty.

Keywords: Frailty, Physiolgical reserve, Metabolic buffer, Sarcopenia

Biography

As a clinical geriatric fellow at MacKay Memorial Hospital, I deliver holistic care across both hospital and home-based settings, anchored in a deep passion for the pathophysiology of aging. With a PhD from ETH Zurich, an MD from Poznan University of Medical Sciences, and a foundation in Life Science from NTU, I leverage over a decade of training to bridge the gap between molecular research and clinical practice.

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