Skeletal Muscle as a Metabolic and Endocrine Organ: The Hidden Cost of Muscle Loss for Glycemic Control and Healthy Aging

Dr. Eugene Capitano, DC, MSc (Neuroscience & Psychology of Mental Health, King's College London), Research interests: gut-brain axis, functional nutrition, and translational microbiome science.

Abstract

Skeletal muscle is traditionally viewed as the organ of locomotion, posture, and physical strength. Yet converging evidence from physiology, endocrinology, and gerontology demonstrates that muscle is also a central metabolic and endocrine organ. It accounts for approximately 40–50% of body mass, disposes of most postprandial glucose, and secretes myokines that influence whole-body homeostasis (Schnyder & Handschin, 2015; Hoffmann & Weigert, 2017). Age-related loss of muscle mass and strength, known as sarcopenia, begins in midlife and can progress to a loss of up to 50% of total muscle mass by age 80 (Volpi et al., 2004). This loss is accompanied by greater fat infiltration, insulin resistance, and heightened risk for type 2 diabetes, cardiovascular disease, disability, and mortality (Volpi et al., 2004; De Carvalho et al., 2020; Saner et al., 2023).

Despite this, public health messaging has focused heavily on aerobic activity, while participation in resistance training and adequate protein intake, both of which are essential for preserving muscle remains low (Bhattacharyya et al., 2024; Statistics Canada, 2024). This paper synthesizes evidence on: (1) skeletal muscle as the primary "sponge" for blood glucose and a key endocrine organ; (2) how sarcopenia and "anabolic resistance" drive insulin resistance and cardiometabolic disease; and (3) why resistance training plus sufficient dietary protein are non-negotiable for metabolic health across the lifespan (Merz & Thurmond, 2021; Hodson et al., 2019; Breen & Phillips, 2011). We argue that muscle loss is not an inevitable, benign feature of aging but a modifiable driver of metabolic dysfunction.

Finally, we outline practical, non-prescriptive educational guidance to support individuals and practitioners in prioritizing muscle mass and strength as core targets for healthy aging.

Introduction

Many adults believe they are “doing everything right” for their health because they meet aerobic activity guidelines, logging steps, completing 150 minutes of weekly walking, or attending spin classes (Garber et al., 2011; Bhattacharyya et al., 2024). Yet a parallel and largely silent epidemic of sarcopenia (age-related muscle wasting) is unfolding.

Skeletal muscle mass begins to decline in midlife, decreasing approximately 3–8% per decade after age 30, with the rate of loss accelerating after age 60 (Volpi et al., 2004). Longitudinal and cross-sectional data suggest that by the eighth decade of life, cumulative losses can reach approximately 50% of total muscle mass in the absence of targeted countermeasures (Volpi et al., 2004; Leon, 2015). This is not merely an aesthetic or “strength” issue. Skeletal muscle is the body’s largest metabolic organ and the primary site of insulin-stimulated glucose disposal (Merz & Thurmond, 2021; Sjøberg et al., 2021).

Thus, progressive muscle loss represents an erosion of our capacity to store and use glucose safely. In practical terms, the metabolic engine is shrinking even while the cardiovascular “pump” may be well-trained. Aerobic exercise remains crucial for cardiorespiratory health, but without resistance training and adequate protein, the body’s main buffer for blood sugar, skeletal muscle is slowly dismantled (Leon, 2015; Breen & Phillips, 2011).

National surveillance data from the most recent cycles of the Canadian Health Measures Survey (CHMS), as summarized by both Statistics Canada and ParticipACTION, provide a clear snapshot of how adults in Canada are performing relative to national physical activity guidelines, and they reveal a

consistent pattern: Canadians are doing substantially better on aerobic activity than on strength training, yet both are under-utilized relative to their importance for metabolic health (ParticipACTION, n.d.; Statistics Canada, 2025). Objectively measured accelerometer data show that roughly half of adults aged 18–79 accumulate at least the recommended 150 minutes per week of moderate-to-vigorous physical activity, meaning that a substantial minority engage in little or no higher-intensity movement beyond incidental daily tasks (ParticipACTION, n.d.; Statistics Canada, 2025). When these data are broken down by sex, a clear disparity emerges: men are more likely than women to reach the aerobic target, a pattern that appears consistently in both CHMS technical releases and public-facing summaries (ParticipACTION, n.d.; Statistics Canada, 2025). However, when we shift focus from “how much we move” to “how we move”, that is, whether our activity actually loads skeletal muscle, the national picture becomes more concerning. Only 39% of adults reported engaging in muscle-strengthening activities at least twice per week. The CHMS includes self-reported questions on muscle-strengthening activity, and these indicate that fewer than half of Canadian adults perform strength or resistance exercise (such as lifting weights, using resistance bands, heavy yard work, or body-weight exercises) on at least two days per week, the minimum frequency recommended in national guidelines (Statistics Canada, 2025). In practice, this means that even among those who do meet the aerobic standard, a large proportion are not providing the specific mechanical stimulus required to preserve muscle mass, strength, and metabolic function, despite skeletal muscle being the primary site for insulin-stimulated glucose disposal and an important endocrine organ through its secretion of myokines (Merz & Thurmond, 2021; Schnyder & Handschin, 2015). The CHMS also documents the other side of the energy-balance equation and that is adults in Canada spend, on average, the majority of their waking hours in sedentary postures, with sitting, reclining, and screen-based behaviors occupying much of the day, and this high sedentary load co-exists with only moderate adherence to both aerobic and resistance-training recommendations (Statistics Canada, 2025).

In the United States, recent data from the 2022 National Health Interview Survey reveal that adherence to physical activity guidelines remains below public health targets, with only 24.3% of adults successfully meeting the combined requirements for both aerobic and muscle-strengthening activities (Bhattacharyya et al., 2024). While approximately 47.2% of U.S. adults perform sufficient aerobic activity to gain health benefits, only 30.6% meet the recommended frequency of at least two sessions of muscle-strengthening exercise per week, a participation rate notably lower than the 39% recently reported for Canada (Bhattacharyya et al., 2024; Statistics Canada, 2025). Furthermore, nearly half of the U.S. adult population (46.5%) fails to meet either aerobic or strengthening recommendations, highlighting a widespread gap in engaging the specific stimulus required for long-term muscle preservation, glycemic control, and metabolic health (Bhattacharyya et al., 2024).

Skeletal Muscle as a Central Integrator of Metabolic and Systemic Health

Skeletal Muscle as the Dominant Site of Glucose Disposal

Skeletal muscle constitutes approximately 40–50% of total body mass in healthy adults and represents a major contributor to resting energy expenditure (Volpi et al., 2004; Leon, 2015). Beyond its structural and mechanical roles, it serves as the principal site of insulin-mediated glucose uptake and storage. In the postprandial state, an estimated 70–80% of circulating glucose is cleared by skeletal muscle, primarily through glycogen synthesis and oxidative metabolism (Merz & Thurmond, 2021; Sjøberg et al., 2021).

Following uptake, glucose is either stored as glycogen or oxidized to generate ATP. Although the liver also contributes to glycogen storage, the substantially greater mass of skeletal muscle confers a far larger total storage capacity. Consequently, skeletal muscle functions as the body's primary metabolic reservoir for glucose. When muscle mass or functional quality declines, this reservoir is diminished,

resulting in reduced glycogen storage capacity and prolonged elevation of circulating glucose concentrations. In response, pancreatic β-cells increase insulin secretion to maintain glycemic control, establishing a compensatory hyperinsulinemic state that can, over time, contribute to the development of insulin resistance and type 2 diabetes (Merz & Thurmond, 2021; Shou et al., 2020).

In a metabolically healthy state, skeletal muscle efficiently sequesters glucose following nutrient intake, maintaining blood glucose within tightly regulated physiological limits. However, in conditions such as sarcopenia or physical inactivity, this capacity is significantly impaired. Reduced muscle mass, combined with diminished insulin sensitivity, limits glucose uptake and storage, forcing the pancreas to sustain elevated insulin output. While initially effective in preserving euglycemia, this compensatory mechanism ultimately becomes insufficient as the capacity of skeletal muscle to accommodate incoming substrates is exceeded (Shou et al., 2020).

As glucose disposal becomes impaired, excess energy substrates, including both glucose and fatty acids, are redirected toward ectopic storage sites such as the liver, visceral adipose tissue, and intramuscular lipid depots. This process promotes lipid accumulation in non-adipose tissues, contributing to inflammation, lipotoxicity, and further impairment of insulin signaling pathways (Hong & Choi, 2020; Merz & Thurmond, 2021). This phenomenon, often described as “energy spillover,” represents a critical transition from localized metabolic dysfunction to systemic disease.

The downstream consequences of chronic hyperglycemia extend beyond metabolic dysregulation. Persistently elevated glucose levels promote non-enzymatic glycation reactions, leading to the formation of Advanced Glycation End-products (AGEs), which accumulate in long-lived structural proteins such as collagen (Shou et al., 2020). This accumulation reduces tissue elasticity and contributes to the stiffening of tendons, ligaments, and joint structures. Simultaneously, vascular endothelial cells are exposed to sustained metabolic stress, resulting in oxidative damage,

inflammation, and impaired nitric oxide production, which compromises vascular function (Hong & Choi, 2020). Over time, these vascular changes impair microcirculatory supply to peripheral nerves, contributing to the development of neuropathy commonly observed in metabolic disease (Shou et al., 2020).

Collectively, these processes illustrate that the failure of skeletal muscle to function as an effective metabolic sink initiates a cascade of systemic pathophysiological changes. Maintenance of muscle mass and function is therefore not merely relevant to locomotion or physical performance, but is fundamental to preserving metabolic stability and structural integrity across multiple organ systems (Liu & Zhu, 2023; Merz & Thurmond, 2021).

Skeletal Muscle as an Endocrine Signaling Hub

In addition to its metabolic functions, skeletal muscle is now recognized as a dynamic endocrine organ that secretes a diverse array of signaling molecules, collectively termed myokines. These contraction-induced cytokines and peptides exert autocrine, paracrine, and endocrine effects, enabling skeletal muscle to communicate with distant tissues including adipose tissue, liver, bone, brain, and immune cells (Schnyder & Handschin, 2015; Hoffmann & Weigert, 2017).

Through these signaling pathways, skeletal muscle actively regulates systemic processes such as lipolysis, hepatic glucose production, inflammation, and neuroplasticity. Myokines including interleukin-6 (IL-6), irisin, and brain-derived neurotrophic factor (BDNF) have been implicated in enhancing insulin sensitivity, promoting anti-inflammatory responses, and supporting cognitive function and neural adaptation (Hoffmann & Weigert, 2017; Sandoval & Dueñas Gómez, 2024).

Importantly, skeletal muscle is not merely a passive recipient of hormonal signals but acts as an active regulator of whole-body metabolic homeostasis, particularly during and following exercise. The

endocrine function of muscle allows it to coordinate energy distribution, substrate utilization, and adaptive responses across multiple organ systems. Consequently, loss of muscle mass or function results not only in impaired glucose handling but also in diminished endocrine signaling capacity, amplifying vulnerability to metabolic and chronic disease (Leon, 2015; Sarcopenic Obesity Working Group, 2020).

Loss of Muscle as Loss of Metabolic and Structural Capacity

The progressive deterioration of skeletal muscle associated with aging or disuse extends far beyond reductions in visible mass and strength. It represents the loss of several critical physiological reservoirs, including the body's largest glycogen store, its primary amino acid reserve, and a substantial portion of its oxidative machinery.

Skeletal muscle normally serves as the principal storage site for glycogen and provides a readily mobilizable pool of amino acids during periods of fasting, illness, injury, or insufficient dietary intake. This makes it central to both energy homeostasis and nitrogen balance (Merz & Thurmond, 2020; McKendry et al., 2023). As muscle mass declines, these reservoirs are progressively diminished, reducing the body's capacity to buffer metabolic stress.

At the cellular level, aging and inactivity are associated with marked reductions in mitochondrial content, mitochondrial DNA copy number, and the activity of oxidative and β-oxidative enzymes. Studies indicate that mitochondrial oxidative capacity can decline by approximately 30–40% in older adults compared with younger individuals (Short et al., 2005; Petersen et al., 2003). This reduction impairs the muscle's ability to oxidize fatty acids and generate ATP efficiently through oxidative phosphorylation.

As oxidative capacity diminishes, there is a concomitant accumulation of intramyocellular lipids and lipid intermediates such as diacylglycerols and ceramides. These metabolites are strongly linked to impaired insulin signaling and the development of insulin resistance (Bonnard et al., 2008; Shou et al., 2020). In parallel, the reduced capacity for β-oxidation further limits the muscle's ability to utilize fatty acids as a fuel source.

Under these conditions, skeletal muscle becomes increasingly reliant on glycolysis to meet energy demands, particularly during physical activity. While glycolysis provides a rapid source of ATP, it is less efficient than oxidative metabolism and is associated with increased lactate production. This metabolic shift contributes to earlier fatigue, reduced endurance, and diminished metabolic flexibility (Short et al., 2005; Miotto et al., 2018).

In practical terms, the deterioration of skeletal muscle involves a simultaneous loss of glycogen storage capacity, amino acid reserves, and mitochondrial function. This leaves the organism increasingly dependent on less efficient energy pathways and less capable of responding to metabolic challenges such as physical exertion, excess caloric intake, or acute illness (McKendry et al., 2023; Merz & Thurmond, 2020).

Exercise Modality and the Myokine-Mediated Adaptation Response

The endocrine function of skeletal muscle is highly responsive to the nature of contractile activity, with distinct myokine profiles emerging in response to different forms of exercise. Endurance exercise, characterized by sustained, moderate-to-vigorous activity, promotes a myokine profile associated with metabolic regulation and mitochondrial adaptation. A central mediator of these adaptations is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which drives mitochondrial biogenesis and enhances oxidative capacity. This pathway also stimulates the expression of fibronectin type III domain-containing protein 5 (FNDC5), leading to the secretion of

irisin, which contributes to the browning of white adipose tissue and increased thermogenesis. Endurance exercise also induces substantial increases in IL-6, which acts systemically to enhance insulin sensitivity, stimulate lipolysis, and promote anti-inflammatory signaling. Additionally, exercise-induced increases in BDNF support neurogenesis, synaptic plasticity, and cognitive function.

Beyond classical myokines, metabolites such as lactate play a significant signaling role. Lactate, produced during periods of increased glycolytic flux, functions as a signaling molecule capable of crossing the blood–brain barrier, where it contributes to the upregulation of BDNF and other genes associated with neuroplasticity.

In contrast, resistance training elicits a myokine profile more closely associated with tissue remodeling and structural adaptation. Mechanical loading stimulates the release of IL-7 and IL-15, which are involved in satellite cell activation, muscle repair, and the maintenance of type II muscle fibers. Resistance exercise also promotes the expression of SPARC, a protein associated with bone formation and potential anti-tumor effects.

Although distinct patterns exist, there is considerable overlap between exercise modalities. Both endurance and resistance training stimulate the release of key myokines such as IL-6, IL-15, and BDNF. Endurance exercise primarily enhances mitochondrial and metabolic adaptations, whereas resistance training drives hypertrophy and structural integrity. Together, these modalities provide complementary benefits, supporting both metabolic health and musculoskeletal resilience.

Aging, Sarcopenia, and the Collapse of Glucose Disposal Capacity

The trajectory of muscle and strength loss

Human skeletal muscle mass and strength peak in early adulthood, then decline progressively. Average muscle mass decreases by 3–8% per decade after age 30, with losses accelerating after age 60

(Volpi et al., 2004). Strength declines even more steeply than mass, estimates suggest approximately 1.5% per year after age 50, with further acceleration in later decades (Nałęcz-Luta et al., 2024; Leon, 2015).

Sarcopenia is not merely low muscle mass It combines reduced mass, diminished strength, and impaired physical performance (Volpi et al., 2004; Nałęcz-Luta et al., 2024). These deficits translate into slower gait speed, reduced balance, increased fall risk, loss of independence, and higher mortality (LaMonte et al., 2026; Leong et al., 2015).

Progressive loss of skeletal muscle mass and quality means not only that you have less contractile tissue, but also that you lose a substantial fraction of the body's glycogen storage, amino acid reservoir, and oxidative machinery. Skeletal muscle is the principal site for postprandial glucose disposal and a major regulator of fat oxidation. When mitochondrial content and β-oxidative enzyme capacity decline with aging and disuse, the muscle's ability to oxidize incoming fatty acids is markedly reduced. The excess lipid load is then preferentially stored as triglyceride in adipose tissue and as ectopic fat within myocytes and hepatocytes, where accumulation of intermediates such as diacylglycerols and ceramides activates stress kinases and impairs insulin receptor substrate–PI3K–Akt signaling, promoting insulin resistance, hyperglycemia, and further fat gain (Hwang & Choi, 2020; Merz & Thurmond, 2020; Shou et al., 2020). In this setting, "overnutrition" simply means that habitual energy intake chronically exceeds what a shrunken, mitochondrially compromised muscle mass can oxidize; once limited glycogen stores are replete and oxidative capacity is saturated, additional carbohydrate is increasingly diverted to de novo lipogenesis and dietary fat is stored directly, lowering the caloric threshold at which ectopic fat and metabolic disease develop (Merz & Thurmond, 2020; Short et al., 2005).

Importantly, these deficits are not immutable: moderate-intensity endurance training, conceptually similar to "Zone II" work, robustly increases mitochondrial respiratory capacity, improves

fatty acid oxidation, and preserves or restores mitochondrial function across the adult lifespan, even in older men (Cefis et al., 2025; Gouspillou et al., 2014; Menshikova et al., 2006). Regular aerobic training upregulates PGC-1α-driven programs of mitochondrial biogenesis and oxidative remodeling in skeletal muscle and, when combined with resistance exercise and adequate protein intake, improves insulin sensitivity and attenuates the adverse effects of aging on muscle metabolism (Leon, 2015; Schnyder & Handschin, 2015; Volpi et al., 2014).

Therefore, deterioration of muscle implies a shift toward greater reliance on glycolytic ATP production, earlier fatigue, and a narrower metabolic "buffer" for surplus energy, but these changes can be meaningfully countered by structured endurance and resistance training that expand and enhance the remaining mitochondrial network.

Sarcopenic obesity and insulin resistance

In many older adults, loss of muscle mass is accompanied by an increase in fat mass, especially ectopic fat infiltrating muscle and liver, a condition termed sarcopenic obesity. Myosteatosis (fat infiltration within muscle) is associated with mitochondrial dysfunction, oxidative stress, and impaired insulin signaling, further promoting anabolic resistance and metabolic inflexibility (Shin & Choi, 2020; Shou et al., 2020).

Multiple cohort studies demonstrate that low skeletal muscle mass and its progressive loss are associated with higher incidence of type 2 diabetes. In a population-based Chinese cohort, lower baseline muscle mass and greater decline over time were each independently associated with increased diabetes risk, even after adjusting for adiposity and other risk factors (Xue et al., 2023). Similar cross-sectional data in men show that lower skeletal muscle indices are inversely associated with a metabolically unhealthy phenotype, irrespective of BMI (De Carvalho et al., 2020).

Mechanistically, insulin resistance in aging muscle is characterized by impaired insulin signaling (e.g., reduced IRS–PI3K–Akt activation), diminished GLUT4 translocation, mitochondrial dysfunction, and increased intramuscular lipid intermediates such as diacylglycerols and ceramides (Merz & Thurmond, 2021; Shou et al., 2020). These changes blunt muscle protein synthesis (MPS) in response to both insulin and amino acids a phenomenon termed anabolic resistance (Breen & Phillips, 2011; Wall et al., 2015).

In essence, as muscle mass and quality decline, the body's largest "sponge" for glucose shrinks and stiffens. The same carbohydrate load that was handled easily at age 30 becomes progressively more toxic at 60 or 70, not because the food changed, but because the storage organ did.

Protein, Anabolic Resistance, and the "Self-Cannibalization" of Muscle

No dedicated protein storage—and why muscle is the reservoir

Unlike fat and glycogen, which are stored in relatively inert depots such as adipose tissue and hepatic or myocellular glycogen granules, the human body maintains no dedicated storage form for amino acids. Instead, all body protein is structurally or functionally active, incorporated into enzymes, immune system, contractile elements, transporters, receptors, and the collagen-rich architecture of connective tissues and vascular structures.

Within this context, skeletal muscle comprising approximately 40–50% of total body mass serves as the body's principal reservoir of amino acids. During periods of fasting, acute illness, injury, or inadequate dietary intake, muscle protein is mobilized to sustain essential physiological processes, including gluconeogenesis and the maintenance of vital organ function (Breen & Phillips, 2011; Volpi et al., 2004).

When dietary protein is insufficient or physiological demand is elevated, the body does not reduce its functional requirements. Instead, it prioritizes critical systems, such as the gut epithelium, immune cell proliferation, and hepatic acute-phase protein synthesis, by increasing proteolysis within skeletal muscle (Breen & Phillips, 2011; Kilroe et al., 2023). This process represents a form of metabolic triage, redistributing amino acids to preserve survival at the expense of contractile tissue (Aragon et al., 2022).

This hierarchical allocation ensures that essential processes, including collagen synthesis for tissue repair, neurotransmitter production for cognitive function, and enzymatic activity for metabolic and vascular regulation, are maintained even under conditions of limited dietary supply (Aragon et al., 2022). However, sustained reliance on this mechanism results in a chronic negative net protein balance, contributing to sarcopenia, reduced metabolic capacity, and diminished resilience to physiological stress.

Anabolic Resistance and the Inadequacy of Conventional Protein Targets

The current Recommended Dietary Allowance (RDA) for protein (0.8 $g \cdot kg^{-1} \cdot day^{-1}$), derived from nitrogen balance studies in younger, sedentary individuals, reflects a minimal requirement to prevent deficiency rather than an optimal intake for maintaining muscle mass and function. In contrast, stable isotope and kinetic studies demonstrate that older adults exhibit a blunted muscle protein synthetic response to typical mixed meals and modest protein intakes, a phenomenon termed *anabolic resistance* (Aragon et al., 2022; Wall et al., 2015).

To overcome this reduced anabolic sensitivity and maintain a neutral or positive net protein balance, higher protein intakes are required. Current evidence-based recommendations suggest 1.2–1.6 $g \cdot kg^{-1} \cdot day^{-1}$ for community-dwelling older adults, with intakes of up to 2.0 $g \cdot kg^{-1} \cdot day^{-1}$ often

necessary in the context of acute or chronic illness, frailty, or rehabilitation (Deutz et al., 2014; Layman, 2024).

Importantly, these higher intakes should not be interpreted as performance-oriented targets, but rather as physiological requirements that account for age-related anabolic resistance and the increased catabolic burden associated with illness and inactivity. When protein intake remains insufficient, the body's hierarchical prioritization of amino acid allocation ensures that the needs of the gut, immune system, liver, brain, and cardiovascular system are met at the continued expense of skeletal muscle.

Over time, this results in the progressive erosion of muscle tissue, compromising not only mechanical function, but also metabolic health. As the primary site of insulin-stimulated glucose uptake, skeletal muscle plays a central role in glycemic regulation (Merz & Thurmond, 2021). Consequently, the loss of muscle mass links inadequate protein intake to impaired metabolic control, increased insulin resistance, and heightened vulnerability across multiple organ systems.

Anabolic Resistance and Elevated Protein Requirements with Aging

Per-Meal Protein Requirements and Muscle Activation Thresholds

Aging skeletal muscle exhibits a reduced sensitivity to anaboli c stimuli, including dietary protein intake and exercise. Controlled tracer studies demonstrate that, compared with younger adults, older individuals require a higher per-meal dose of high-quality protein to maximally stimulate muscle protein synthesis (MPS), approximately 0.4 $g \cdot kg^{-1}$ per meal versus approximately 0.24 $g \cdot kg^{-1}$ in younger populations (Wall et al., 2015; Zaromskyte et al., 2021).

This difference reflects a higher "muscle activation threshold," often attributed to a greater leucine requirement needed to sufficiently activate mTORC1 signaling and initiate protein synthesis in older muscle (Zaromskyte et al., 2021).

In line with these findings, expert groups such as PROT-AGE and ESPEN recommend daily protein intakes of 1.0–1.2 $g \cdot kg^{-1}$ for healthy older adults, increasing to 1.2–1.5 $g \cdot kg^{-1}$, and up to 1.6–2.0 $g \cdot kg^{-1}$ in cases of illness, frailty, or high physiological stress (Bauer et al., 2013; Deutz et al., 2014). These values substantially exceed the legacy RDA of 0.8 $g \cdot kg^{-1} \cdot day^{-1}$, which was designed to prevent deficiency rather than preserve muscle mass and functional capacity (Volpi et al., 2013; Martinez et al., 2023).

Importantly, protein distribution across the day appears to be a critical determinant of MPS. Older adults benefit from consuming approximately 0.4 $g \cdot kg^{-1}$ of high-quality protein at least three to four times daily to repeatedly stimulate anabolic signaling (Breen & Phillips, 2011; Zaromskyte et al., 2021).

Anabolic Resistance: Mechanistic Characteristics

In sedentary older adults, skeletal muscle exhibits a blunted increase in MPS following feeding and acute exercise. Notably, basal (fasted) MPS rates are generally comparable between young and older individuals; the age-related effect emerges primarily as a diminished post-prandial response (Breen & Phillips, 2011; Wall et al., 2015).

For example, Wall et al. (2015) reported approximately 16% lower post-prandial MPS rates in older men following ingestion of a 20 g protein bolus, despite a higher relative intake per unit of lean mass. This phenomenon has been described as *anabolic inflexibility*, wherein aging muscle requires larger amino acid stimuli, typically approximately 30–40 g of high-quality protein (~0.4 $g \cdot kg^{-1}$ and ~2.8–3.0 g leucine), to achieve near-maximal MPS (Aragon et al., 2022; Moore et al., 2015).

Disuse as a Primary Driver of Anabolic Resistance

Crucially, anabolic resistance is not an immutable consequence of chronological aging, but is strongly influenced by physical activity levels. Periods of reduced activity, including bed rest, limb immobilization, or even short-term step reduction, rapidly impair MPS and induce anabolic resistance in both young and older adults.

For instance, reducing daily activity for as little as two weeks can decrease post-prandial MPS by approximately 25% in older adults, with incomplete recovery upon resumption of habitual activity (Breen et al., 2013). These findings suggest that sedentarism is a major driver of anabolic resistance, with aging increasing susceptibility rather than acting as the sole cause.

Exercise as a Restorative Anabolic Signal

In contrast, regular physical activity, particularly resistance exercise, can substantially restore anabolic sensitivity. Acute exercise performed prior to protein ingestion enhances amino acid incorporation into muscle, effectively "sensitizing" skeletal muscle to nutrient availability.

Studies demonstrate that older adults consuming rapidly digested protein (e.g., whey) after exercise can achieve MPS responses comparable to younger individuals (Pennings et al., 2011). Over longer time frames, resistance training induces hypertrophy, strength gains, and protein turnover patterns that resemble those of younger, trained individuals rather than sedentary, age-matched peers (Deutz et al., 2014; Morton et al., 2018).

Integrated Perspective

Taken together, these findings indicate that anabolic resistance is best understood as a context-dependent physiological state, driven by the interaction between aging, inactivity, and insufficient protein intake. While advancing age increases vulnerability to anabolic resistance, it is the combination

of sedentarism and inadequate nutrition that accelerates muscle loss. Without sufficient protein intake and regular mechanical loading, the body increasingly relies on endogenous muscle proteolysis to meet systemic amino acid demands. Over time, this contributes to the progressive decline in muscle mass, metabolic health, and functional capacity.

Why Resistance Training Is Non-Negotiable for Metabolic Health

Resistance exercise is one of the most potent stimuli for muscle protein synthesis (MPS) across the lifespan. Even in very old or frail individuals, including nonagenarians, high-intensity resistance training has been shown to induce muscle hypertrophy, increase strength, and significantly improve functional capacity (Melov et al., 2007; Brooks et al., 2007).

Beyond structural adaptations, resistance training exerts profound metabolic effects. It enhances insulin sensitivity, improves glycemic control, and partially reverses anabolic resistance through improvements in muscle perfusion, mitochondrial function, and intracellular signaling pathways, including mTORC1 (Hodson et al., 2019; Shou et al., 2020). In older adults with type 2 diabetes, strength training interventions have demonstrated meaningful improvements in muscle quality and insulin sensitivity, reinforcing the concept that skeletal muscle remains highly plastic even in the presence of metabolic disease (Brooks et al., 2007).

Muscle Mass as Metabolic Infrastructure ("Mitochondrial Real Estate")

A critical but often overlooked concept is that muscle mass itself represents metabolic infrastructure. Because mitochondria reside within muscle fibers, total mitochondrial capacity is partly determined by the amount of muscle tissue available.

With aging, reductions in muscle cross-sectional area are often accompanied by declines in total mitochondrial volume. However, this is largely a consequence of disuse and fiber atrophy rather than

an inevitable effect of chronological aging (Short et al., 2005; Johnson et al., 2013). In physically active older adults, mitochondrial respiration and oxidative capacity are remarkably similar to those observed in younger individuals, indicating that mitochondrial function can be largely preserved when activity is maintained (Distefano et al., 2017; Cefis et al., 2025).

Thus, resistance training plays a foundational role in preserving what can be conceptualized as "mitochondrial real estate", the total volume of metabolically active tissue capable of glucose disposal and oxidative metabolism.

Endurance Training as a Complementary Mitochondrial Stimulus

While resistance training is the primary driver of muscle hypertrophy and strength, endurance-type exercise is the dominant stimulus for mitochondrial biogenesis. Moderate-intensity continuous exercise ("Zone II") and high-intensity interval training (HIIT) both robustly activate PGC-1α and related transcriptional pathways, leading to increases in mitochondrial density, oxidative enzyme activity, and fatty acid oxidation capacity (Schnyder & Handschin, 2015; Cefis et al., 2025). In older adults, endurance training increases mitochondrial DNA content, respiratory chain activity, and overall oxidative capacity to levels approaching those seen in younger individuals (Menshikova et al., 2006; Grevendonk et al., 2021).

Resistance training also contributes to mitochondrial health, particularly when performed with sufficient volume, by enhancing mitochondrial protein turnover, reducing oxidative stress, and improving mitochondrial efficiency, although its primary effect remains on myofibrillar protein synthesis and type II fiber hypertrophy (Holloway et al., 2018; McKendry et al., 2024).

Disuse, Not Age, as the Primary Driver of Mitochondrial Decline

Sedentary aging is consistently associated with reduced mitochondrial volume, impaired oxidative phosphorylation, and increased mitochondrial DNA damage. However, when physical activity levels are matched, many of these differences between young and older individuals diminish substantially (Distefano et al., 2017). Long-term endurance-trained older adults ("master athletes") maintain high mitochondrial content and oxidative enzyme activity, demonstrating that mitochondrial decline is largely preventable (Hawkins et al., 2003; Coggan et al., 1992). Although some loss of muscle fibers and type II fiber size occurs with age, even in active individual, the majority of mitochondrial decline observed in typical aging populations is attributable to inactivity rather than aging per se (Nilwik et al., 2013; Narici & Maffulli, 2010).

Integrated Perspective: Resistance Training as the Foundation

Taken together, resistance training is non-negotiable because it preserves the structural and metabolic foundation upon which all other adaptations depend. By maintaining muscle mass, it sustains the body's primary glucose sink, preserves amino acid reserves, and maximizes total mitochondrial capacity.

Endurance exercise enhances the quality and efficiency of this system, but without sufficient muscle mass, the overall capacity for glucose disposal and oxidative metabolism remains limited. In practical terms, while aging may reduce absolute muscle mass compared to youth, regular resistance and endurance training can maintain high mitochondrial density within existing muscle tissue and preserve metabolic function. Thus, the goal is not merely to slow decline, but to actively maintain both the quantity (muscle mass) and quality (mitochondrial function) of skeletal muscle across the lifespan.

Muscle as a modifiable predictor of morbidity and mortality

Low muscle strength and mass predict disability, falls, hospitalization, and all-cause mortality, independent of body weight (LaMonte et al., 2026; Leong et al., 2015). Observational data suggest that older adults with higher muscle mass and strength have lower rates of diabetes, cardiovascular disease, and mortality, even when adjusted for adiposity (LaMonte et al., 2026; Xue et al., 2023). This underscores that muscle is not merely "nice to have" but a critical determinant of healthspan.

Resistance training 2–3 times per week, targeting major muscle groups, is consistently recommended by expert bodies for older adults, alongside aerobic activity and balance training (Deutz et al., 2014; Leon, 2015). While "heavy" lifting can be intimidating, effective resistance work can be achieved with bodyweight, resistance bands, free weights, or functional tasks (e.g., loaded carries, gardening) scaled to individual capacity.

Practical Implications and Educational Guidance

From the evidence above, three educational messages emerge:

1. Muscle is a metabolic organ, not just a mechanical one.

- It is the primary sink for postprandial glucose and a major endocrine organ via myokine secretion (Merz & Thurmond, 2021; Schnyder & Handschin, 2015; Hoffmann & Weigert, 2017).
- Preserving muscle mass and function is central to preventing insulin resistance, type 2 diabetes, and related cardiometabolic diseases (Shin & Choi, 2020; Xue et al., 2023; De Carvalho et al., 2020).

2. Muscle loss is modifiable.

- Sarcopenia is common but not inevitable; resistance training and adequate protein can substantially attenuate or reverse age-related declines in muscle mass and strength (Volpi et al., 2004; Breen & Phillips, 2011; Melov et al., 2007).
- Even in older or frail adults, relatively short interventions (12–24 weeks) of progressive resistance training improve muscle size, strength, and quality (Brooks et al., 2007; Melov et al., 2007). 29 28

3. Protein and resistance training must be aligned with age-related physiology.

- Older adults generally require higher daily protein intakes (≥1.0–1.2 g/kg/day, often 1.2–1.6 g/kg/day) and higher per-meal doses (~0.4 g/kg) to overcome anabolic resistance (Bauer et al., 2013; Deutz et al., 2014; Wall et al., 2015; Zaromskyte et al., 2021).
- Whole foods should provide the majority of protein; supplemental protein powders are tools for convenience and gap-filling, not stand-alone solutions (Breen & Phillips, 2011; Martinez et al., 2023).

Any educational tools derived from this evidence, such as calculators that estimate daily protein targets from height (as a proxy for lean mass), age, and activity level, and provide per-meal "muscle activation" targets, should be framed carefully. They can raise awareness of how muscle mass, protein intake, and resistance training interact, but they are not medical or dietary prescriptions. Individual needs vary based on health status, medications, comorbidities, and personal goals. Accordingly, any such tool is for educational purposes only and does not constitute medical or nutrition advice. Individuals, especially those with chronic diseases (e.g., diabetes, kidney disease, cardiovascular

disease), should consult a physician or registered dietitian before making substantial changes to diet or exercise.

Conclusion: Protecting the Metabolic Engine

Skeletal muscle is more than a structure that moves us; it is a central regulator of energy balance, glucose handling, and systemic health (Merz & Thurmond, 2021; Sjøberg et al., 2021). As we age, failing to protect and stimulate this tissue through resistance training and sufficient protein intake leads to a progressive loss of our primary glucose "sponge" and amino acid reservoir. The consequences, insulin resistance, sarcopenic obesity, frailty, and cardiometabolic disease, unfold over decades, often silently, until they manifest as disability or a chronic diagnosis (Volpi et al., 2004; Shin & Choi, 2020; Xue et al., 2023).

Reframing muscle as a metabolic and endocrine organ shifts the focus from cardio-only approaches to a more comprehensive view of movement and nutrition. Walking for the heart remains important; but without sufficient muscle, the heart pumps into a metabolically compromised system. Resistance training, scaled appropriately, and age-appropriate protein intake are therefore not optional add-ons but foundational components of metabolic health and healthy aging (Leon, 2015; Breen & Phillips, 2011; Deutz et al., 2014). 12 11 25

The best time to invest in muscle was decades ago; the second-best time is now.

Author Information

Eugene Capitano, BA, BSc, DC, DAc, MSc, ACSM-CPT, ACSM-EIM
Chiropractor | Functional Wellness Specialist | Clinical Researcher
MSc in Psychology & Neuroscience of Mental Health – King's College London
Eugene Capitano is a clinician-scientist integrating musculoskeletal rehabilitation, exercise physiology, and nutritional neuroscience. He holds a *Master of Science in Psychology & Neuroscience of Mental Health* from King's College London, is an ACSM-certified Exercise is Medicine® practitioner and Personal Trainer, and has over 25 years of clinical experience in chiropractic and functional wellness care. His research and professional focus bridge the gut–brain–muscle axis, exploring how targeted nutrition, resistance training, and mitochondrial health strategies optimize metabolic function and healthy aging. **squareonerehabilitation.com** | **tlcpureorigin.com**

References

Aragon, A. A., Tipton, K. D., & Schoenfeld, B. J. (2022). Age-related muscle anabolic resistance: Inevitable or preventable? *Nutrition Reviews, 80*(9), 2048–2067. https://doi.org/10.1093/nutrit/nuac035

Bauer, J., Biolo, G., Cederholm, T., Cesari, M., Cruz-Jentoft, A. J., Morley, J. E., Phillips, S., Sieber, C., Stehle, P., Teta, D., Visvanathan, R., Volpi, E., & Boirie, Y. (2013). Evidence-based recommendations for optimal dietary protein intake in older people: A position paper from the PROT-AGE Study Group. *Journal of the American Medical Directors Association, 14*(8), 542–559. https://pubmed.ncbi.nlm.nih.gov/23867520/

Bhattacharyya, M., Miller, L. E., Miller, A. L., Bhattacharyya, R., & Herbert, W. G. (2024). Disparities in adherence to physical activity guidelines among US adults: A population-based study. *Medicine, 103*(36), e39539. https://pubmed.ncbi.nlm.nih.gov/39252263/

Bonnard, C., Durand, A., Peyrol, S., Chanseaume, E., Chauvin, M.-A., Morio, B., Vidal, H., & Rieusset, J. (2008). Mitochondrial dysfunction results from oxidative stress in the skeletal muscle of diet-induced insulin-resistant mice. *Journal of Clinical Investigation, 118*(2), 789–800. https://pubmed.ncbi.nlm.nih.gov/18188455/

Breen, L., & Phillips, S. M. (2011). Skeletal muscle protein metabolism in the elderly: Interventions to counteract the “anabolic resistance” of ageing. *Nutrition & Metabolism, 8*(1), 68. https://doi.org/10.1186/1743-7075-8-68

Breen, L., Stokes, K. A., Churchward-Venne, T. A., Moore, D. R., Baker, S. K., Smith, K., & Phillips, S. M. (2013). Two weeks of reduced activity decreases leg lean mass and induces “anabolic

resistance" of myofibrillar protein synthesis in healthy elderly. *The Journal of Clinical Endocrinology & Metabolism, 98*(6), 2604–2612. https://doi.org/10.1210/jc.2013-1502

Brooks, N., Layne, J. E., Gordon, P. L., Roubenoff, R., Nelson, M. E., & Castaneda-Sceppa, C. (2007). Strength training improves muscle quality and insulin sensitivity in Hispanic older adults with type 2 diabetes. *International Journal of Medical Sciences, 4*(1), 19–27. https://pubmed.ncbi.nlm.nih.gov/17211497/

Cefis, M., Marcangeli, V., Hammad, R., et al. (2025). Impact of physical activity on physical function, mitochondrial energetics, ROS production, and Ca2+ handling across the adult lifespan in men. *Cell Reports Medicine, 6*, 101968. https://pmc.ncbi.nlm.nih.gov/articles/PMC11866497/pdf/main.pdf

Coggan, A. R., Spina, R. J., King, D. S., et al. (1992). Skeletal muscle adaptations to endurance training in 60- to 70-yr-old men and women. *Journal of Applied Physiology, 72*(5), 1780–1786. https://pubmed.ncbi.nlm.nih.gov/1601786/

De Carvalho, C. J., Longo, G. Z., Kakehasi, A. M., Santos, T. C., Sachetti, A., Santos, A. D., & Peixoto, M. R. G. (2020). Skeletal mass indices are inversely associated with metabolically unhealthy phenotype in overweight/obese and normal-weight men: A population-based cross-sectional study. *British Journal of Nutrition, 124*(4), 498–507. https://pubmed.ncbi.nlm.nih.gov/33143771/

Deutz, N. E. P., Bauer, J. M., Barazzoni, R., Biolo, G., Boirie, Y., Bosy-Westphal, A., Cederholm, T., Cruz-Jentoft, A., Krznarić, Ž., Nair, K. S., Singer, P., Teta, D., Tipton, K., & Calder, P. C. (2014). Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. *Clinical Nutrition, 33*(6), 929–936. https://doi.org/10.1016/j.clnu.2014.04.007

Distefano G, Standley RA, Dubé JJ, Carnero EA, Ritov VB, Stefanovic-Racic M, Toledo FG, Piva SR, Goodpaster BH, Coen PM. Chronological Age Does not Influence Ex-vivo Mitochondrial Respiration and Quality Control in Skeletal Muscle. J Gerontol A Biol Sci Med Sci. 2017 Apr 1;72(4):535-542. doi: 10.1093/gerona/glw102. PMID: 27325231; PMCID: PMC6075361. https://pubmed.ncbi.nlm.nih.gov/27325231/

Gouspillou, G., Sgarioto, N., Kapchinsky, S., et al. (2014). Increased sensitivity to mitochondrial permeability transition and myonuclear translocation of endonuclease G in atrophied muscle of physically active older humans. *FASEB Journal, 28*, 1621–1633. https://pubmed.ncbi.nlm.nih.gov/24371120/

Grevendonk L, Connell NJ, McCrum C, Fealy CE, Bilet L, Bruls YMH, Mevenkamp J, Schrauwen-Hinderling VB, Jörgensen JA, Moonen-Kornips E, Schaart G, Havekes B, de Vogel-van den Bosch J, Bragt MCE, Meijer K, Schrauwen P, Hoeks J. Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. Nat Commun. 2021 Aug 6;12(1):4773. doi: 10.1038/s41467-021-24956-2. PMID: 34362885; PMCID: PMC8346468. https://pubmed.ncbi.nlm.nih.gov/34362885/

Hawkins SA, Wiswell RA, Marcell TJ. Exercise and the master athlete--a model of successful aging? J Gerontol A Biol Sci Med Sci. 2003 Nov;58(11):1009-11. doi: 10.1093/gerona/58.11.m1009. PMID: 14630882. https://pubmed.ncbi.nlm.nih.gov/14630882/

Hodson, N., West, D. W. D., Philp, A., Burd, N. A., & Moore, D. R. (2019). Molecular regulation of human skeletal muscle protein synthesis in response to exercise and nutrients: A compass for overcoming age-related anabolic resistance. *American Journal of Physiology–Cell Physiology, 317*(5), C1061–C1078. https://doi.org/10.1152/ajpcell.00209.2019

Hoffmann C, Weigert C. Skeletal Muscle as an Endocrine Organ: The Role of Myokines in Exercise Adaptations. Cold Spring Harb Perspect Med. 2017 Nov 1;7(11):a029793. doi: 10.1101/cshperspect.a029793. PMID: 28389517; PMCID: PMC5666622. https://pubmed.ncbi.nlm.nih.gov/28389517/

Holloway GP, Holwerda AM, Miotto PM, Dirks ML, Verdijk LB, van Loon LJC. Age-Associated Impairments in Mitochondrial ADP Sensitivity Contribute to Redox Stress in Senescent Human Skeletal Muscle. Cell Rep. 2018 Mar 13;22(11):2837-2848. doi: 10.1016/j.celrep.2018.02.069. PMID: 29539414. https://pubmed.ncbi.nlm.nih.gov/29539414/

Hong SH, Choi KM. Sarcopenic Obesity, Insulin Resistance, and Their Implications in Cardiovascular and Metabolic Consequences. Int J Mol Sci. 2020 Jan 13;21(2):494. doi: 10.3390/ijms21020494. PMID: 31941015; PMCID: PMC7013734. https://pubmed.ncbi.nlm.nih.gov/31941015/

Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, Aubertin-Leheudre M, Bernabei R, Cadore EL, Cesari M, Chen LK, de Souto Barreto P, Duque G, Ferrucci L, Fielding RA, García-Hermoso A, Gutiérrez-Robledo LM, Harridge SDR, Kirk B, Kritchevsky S, Landi F, Lazarus N, Martin FC, Marzetti E, Pahor M, Ramírez-Vélez R, Rodriguez-Mañas L, Rolland Y, Ruiz JG, Theou O, Villareal DT, Waters DL, Won Won C, Woo J, Vellas B, Fiatarone Singh M. International Exercise Recommendations in Older Adults (ICFSR): Expert Consensus Guidelines. J Nutr Health Aging. 2021;25(7):824-853. doi: 10.1007/s12603-021-1665-8. PMID: 34409961; PMCID: PMC12369211. https://pmc.ncbi.nlm.nih.gov/articles/PMC12369211/

Johnson ML, Robinson MM, Nair KS. Skeletal muscle aging and the mitochondrion. Trends Endocrinol Metab. 2013 May;24(5):247-56. doi: 10.1016/j.tem.2012.12.003. Epub 2013 Feb 1. PMID: 23375520; PMCID: PMC3641176. https://pubmed.ncbi.nlm.nih.gov/23375520/

Kilroe, S. P., Fulford, J., Holwerda, A. M., Jackman, S. R., Lee, B. P., Gijsen, A. P., van Loon, L. J. C., & Wall, B. T. (2023). Integrated muscle protein synthesis during disuse and rehabilitation in late-midlife adults. *The Journal of Physiology, 601*(14), 3025–3042. https://pubmed.ncbi.nlm.nih.gov/40908115/

Kumar, V., Selby, A., Rankin, D., Patel, R., Atherton, P., Hildebrandt, W., Williams, J., Smith, K., Seynnes, O., Hiscock, N., & Rennie, M. J. (2009). Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *The Journal of Physiology, 587*(1), 211–217. https://doi.org/10.1113/jphysiol.2008.164483

LaMonte MJ, Hyde ET, Nguyen S, et al. Muscular Strength and Mortality in Women Aged 63 to 99 Years. *JAMA Netw Open.* 2026;9(2):e2559367. doi:10.1001/jamanetworkopen.2025.59367

Layman, D. K. (2024). Impacts of protein quantity and distribution on body composition. *Frontiers in Nutrition, 11*, 1363654. https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2024.1388986/full

Leon AS. Attenuation of Adverse Effects of Aging on Skeletal Muscle by Regular Exercise and Nutritional Support. Am J Lifestyle Med. 2016 Jun 23;11(1):4-16. doi: 10.1177/1559827615589319. PMID: 30202306; PMCID: PMC6124840. https://pmc.ncbi.nlm.nih.gov/articles/PMC6124840/

Leong, D. P., Teo, K. K., Rangarajan, S., et al. (2015). Prognostic value of grip strength: Findings from the Prospective Urban Rural Epidemiology (PURE) study. *The Lancet, 386*(9990), 266–273.

Liu ZJ, Zhu CF. Causal relationship between insulin resistance and sarcopenia. Diabetol Metab Syndr. 2023 Mar 15;15(1):46. doi: 10.1186/s13098-023-01022-z. PMID: 36918975; PMCID: PMC10015682. https://pubmed.ncbi.nlm.nih.gov/36918975/

Martinez, O. T., Witard, O. C., Hector, A. J., Daly, R. M., & Phillips, S. M. (2023). Dietary protein recommendations to support healthy muscle ageing in the 21st century and beyond: Considerations and future directions. *Proceedings of the Nutrition Society, 82*(3), 1–14. https://pubmed.ncbi.nlm.nih.gov/37818636/

McKendry J, Stokes T, Mcleod JC, Phillips SM. Resistance Exercise, Aging, Disuse, and Muscle Protein Metabolism. Compr Physiol. 2021 Jun 30;11(3):2249-2278. doi: 10.1002/cphy.c200029. PMID: 34190341. https://pubmed.ncbi.nlm.nih.gov/34190341/

McKendry J, Coletta G, Nunes EA, Lim C, Phillips SM. Mitigating disuse-induced skeletal muscle atrophy in ageing: Resistance exercise as a critical countermeasure. Exp Physiol. 2024 Oct;109(10):1650-1662. doi: 10.1113/EP091937. Epub 2024 Aug 6. PMID: 39106083; PMCID: PMC11442788. https://pubmed.ncbi.nlm.nih.gov/39106083/\

Melov, S., Tarnopolsky, M. A., Beckman, K., Felkey, K., & Hubbard, A. (2007). Resistance exercise Melov S, Tarnopolsky MA, Beckman K, Felkey K, Hubbard A (2007) Resistance Exercise Reverses Aging in Human Skeletal Muscle. PLOS ONE 2(5): e465. https://doi.org/10.1371/journal.pone.0000465

Menshikova EV, Ritov VB, Fairfull L, Ferrell RE, Kelley DE, Goodpaster BH. Effects of exercise on mitochondrial content and function in aging human skeletal muscle. J Gerontol A Biol Sci Med Sci. 2006 Jun;61(6):534-40. doi: 10.1093/gerona/61.6.534. PMID: 16799133; PMCID: PMC1540458. https://pubmed.ncbi.nlm.nih.gov/16799133/

Merz KE, Thurmond DC. Role of Skeletal Muscle in Insulin Resistance and Glucose Uptake. Compr Physiol. 2020 Jul 8;10(3):785-809. doi: 10.1002/cphy.c190029. PMID: 32940941; PMCID: PMC8074531. https://pmc.ncbi.nlm.nih.gov/articles/PMC8074531/

Miotto PM, LeBlanc PJ, Holloway GP. High-Fat Diet Causes Mitochondrial Dysfunction as a Result of Impaired ADP Sensitivity. Diabetes. 2018 Nov;67(11):2199-2205. doi: 10.2337/db18-0417. Epub 2018 Jul 6. PMID: 29980534. https://pubmed.ncbi.nlm.nih.gov/29980534/

Moore, D. R., Churchward-Venne, T. A., Witard, O., Breen, L., Burd, N. A., Tipton, K. D., & Phillips, S. M. (2015). Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. *The Journals of Gerontology: Series A, 70*(1), 57–62. https://doi.org/10.1093/gerona/glu103

Morton, R. W., Murphy, K. T., McKellar, S. R., Schoenfeld, B. J., Henselmans, M., Helms, E., Aragon, A. A., Devries, M. C., Banfield, L., Krieger, J. W., & Phillips, S. M. (2018). A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. *British Journal of Sports Medicine, 52*(6), 376–384. https://doi.org/10.1136/bjsports-2017-097608

Narici MV, Maffulli N. Sarcopenia: characteristics, mechanisms and functional significance. Br Med Bull. 2010;95:139-59. doi: 10.1093/bmb/ldq008. Epub 2010 Mar 2. PMID: 20200012. https://pubmed.ncbi.nlm.nih.gov/20200012/

ParticipACTION. (n.d.). *Key facts and stats: Physical activity in Canada*. Retrieved from https://www.participaction.com/the-science/key-facts-and-stats/

Nilwik R, Snijders T, Leenders M, Groen BB, van Kranenburg J, Verdijk LB, van Loon LJ. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. Exp Gerontol. 2013 May;48(5):492-8. doi: 10.1016/j.exger.2013.02.012. Epub 2013 Feb 17. PMID: 23425621. https://pubmed.ncbi.nlm.nih.gov/23425621/

Pennings, B., Koopman, R., Beelen, M., Senden, J. M. G., Saris, W. H. M., & van Loon, L. J. C. (2011). Exercising before protein intake allows for greater use of dietary protein–derived amino acids for de novo muscle protein synthesis in both young and elderly men. *The American Journal of Clinical Nutrition, 93*(2), 322–331. https://doi.org/10.3945/ajcn.110.029649

Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science. 2003 May 16;300(5622):1140-2. doi: 10.1126/science.1082889. PMID: 12750520; PMCID: PMC3004429. https://pmc.ncbi.nlm.nih.gov/articles/PMC3004429/

Sandoval EYH, Gómez ZJD. Irisin and neuroinflammation: Challenges and opportunities. Exp Mol Pathol. 2024 Dec;140:104941. doi: 10.1016/j.yexmp.2024.104941. Epub 2024 Oct 28. Erratum in: Exp Mol Pathol. 2024 Dec;140:104943. doi: 10.1016/j.yexmp.2024.104943. PMID: 39467426. https://pubmed.ncbi.nlm.nih.gov/39467426/

Saner C, Senior AM, Zhang H, Eloranta AM, Magnussen CG, Sabin MA, Juonala M, Janner M, Burgner DP, Schwab U, Haapala EA, Heitmann BL, Simpson SJ, Raubenheimer D, Lakka TA. Evidence for protein leverage in a general population sample of children and adolescents. Eur J Clin Nutr. 2023 Jun;77(6):652-659. doi: 10.1038/s41430-023-01276-w. Epub 2023 Feb 16. PMID: 36797489; PMCID: PMC10247372. https://pubmed.ncbi.nlm.nih.gov/36797489/

Schnyder S, Handschin C. Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise. Bone. 2015 Nov;80:115-125. doi: 10.1016/j.bone.2015.02.008. PMID: 26453501; PMCID: PMC4657151. https://pubmed.ncbi.nlm.nih.gov/26453501/

Shin, S.-h., & Choi, K. M. (2020). Sarcopenic obesity, insulin resistance, and their implications in cardiovascular and metabolic consequences. *International Journal of Molecular Sciences, 21*(2), 494. https://pubmed.ncbi.nlm.nih.gov/31941015/

Short KR, Bigelow ML, Kahl J, Singh R, Coenen-Schimke J, Raghavakaimal S, Nair KS. Decline in skeletal muscle mitochondrial function with aging in humans. Proc Natl Acad Sci U S A. 2005 Apr 12;102(15):5618-23. doi: 10.1073/pnas.0501559102. Epub 2005 Mar 30. PMID: 15800038; PMCID: PMC556267. https://pmc.ncbi.nlm.nih.gov/articles/PMC556267/

Shou J, Chen PJ, Xiao WH. Mechanism of increased risk of insulin resistance in aging skeletal muscle. Diabetol Metab Syndr. 2020 Feb 11;12:14. doi: 10.1186/s13098-020-0523-x. PMID: 32082422; PMCID: PMC7014712. https://pubmed.ncbi.nlm.nih.gov/32082422/

Sjøberg, K. A., et al. (2021). The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. *Cell Metabolism, 33*(4), 758–780. https://www.sciencedirect.com/science/article/pii/S1550413121001273

Statistics Canada. (2025, October 17). *Directly measured physical activity and sedentary time in Canada: New results from the Canadian Health Measures Survey, 2022 to 2024*. The Daily. https://www150.statcan.gc.ca/

Volpi, E., Campbell, W. W., Dwyer, J. T., Johnson, M. A., Jensen, G. L., Morley, J. E., & Wolfe, R. R. (2013). Is the optimal level of protein intake for older adults greater than the recommended dietary allowance? *Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 68*(6), 677–681. https://pubmed.ncbi.nlm.nih.gov/23183903/

Volpi, E., Nazemi, R., & Fujita, S. (2004). Muscle tissue changes with aging. *Current Opinion in Clinical Nutrition and Metabolic Care, 7*(4), 405–410. https://pmc.ncbi.nlm.nih.gov/articles/PMC2804956/

Volpi, E., Campbell, W. W., Dwyer, J. T., Johnson, M. A., Jensen, G. L., Morley, J. E., & Wolfe, R. R. (2004). Is the optimal level of protein intake for older adults greater than the recommended dietary allowance? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59*(11), 1192–1199. https://pubmed.ncbi.nlm.nih.gov/23183903/

Volpi E, Mittendorfer B, Rasmussen BB, Wolfe RR. The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. J Clin Endocrinol Metab. 2000 Dec;85(12):4481-90. doi: 10.1210/jcem.85.12.7021. PMID: 11134097; PMCID: PMC3192447. https://pubmed.ncbi.nlm.nih.gov/11134097/

Wall, B. T., Gorissen, S. H. M., Pennings, B., Koopman, R., Groen, B. B. L., Verdijk, L. B., & van Loon, L. J. C. (2015). Aging is accompanied by a blunted muscle protein synthetic response to protein ingestion. *PLoS ONE, 10*(11), e0140903. https://doi.org/10.1371/journal.pone.0140903

Xue, Y., Hu, T., Shi, Y., Wang, Y., Ma, X., & Bao, Y. (2023). Association of skeletal muscle mass and its change with diabetes occurrence: A population-based cohort study. *BMC Public Health, 23*, 466. https://pubmed.ncbi.nlm.nih.gov/36945053/

Zaromskyte, G., Prokopidis, K., Ioannidis, T., Tipton, K. D., & Witard, O. C. (2021). Evaluating the leucine trigger hypothesis to explain the post-prandial regulation of muscle protein synthesis in young and older adults: A systematic review. *Frontiers in Nutrition, 8*, 685165. https://pubmed.ncbi.nlm.nih.gov/34307436/