

Sarcopenia as a manifestation of systemic energetic failure with ageing

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Sarcopenia remains underdiagnosed and undertreated, partly because it continues to be mainly conceptualised as a disorder intrinsic to skeletal muscle. Although current definitions incorporate muscle strength and physical performance, they are not intended to explain the integrated physiological processes that underlie age-related impairment of muscle function. In this Personal View, we propose that sarcopenia is more appropriately understood as a manifestation of systemic energetic failure. In this framework, muscle function is considered an emergent property of integrated physiology that progressively deteriorates as ageing disrupts the coordination among energetic demand (determined by neural activation), the delivery of oxygen and metabolic substrates, their mitochondrial transformation into ATP, and their efficient utilisation. The resulting mismatch between physiological demand and available energy manifests clinically as reduced strength in physical performances, increased fatigability, impaired recovery, and mobility disability. Independent lines of evidence have shown that muscle dysfunction reflects a failure of integrated physiological systems rather than isolated tissue degeneration. First, epidemiological data show that muscle strength is more closely linked to disability and mortality than muscle mass. Second, interventional studies show that increasing muscle mass does not reliably improve function. Third, emerging findings indicate that mitochondrial performance is constrained by upstream physiological processes that regulate oxygen and substrate delivery. Reframing sarcopenia considering the failure of these integrated physiological systems has important clinical implications. Fatigability and recovery can provide early indicators of dysfunction, risk stratification should account for multisystem impairment, and effective interventions should focus on restoring coordinated physiological function rather than targeting muscle tissue recovery alone. This framework should be viewed as a physiological hypothesis that integrates current evidence and generates testable predictions regarding the mechanisms, assessment, and treatment of sarcopenia.

Introduction

Sarcopenia was originally described as an age-associated loss of skeletal muscle mass;¹ however, its conceptualisation has evolved substantially over recent decades.² Early definitions have primarily focused on quantitative reductions in lean tissue mass and assumed that muscle mass is a valid surrogate marker of muscle health. However, increasing evidence has shown that muscle function, particularly muscle strength, is strongly associated with clinically relevant outcomes, such as mobility limitation, disability, and mortality.³ This increasing evidence has led to a shift towards multidimensional definitions, such as the European Working Group on Sarcopenia in Older People 2 and the Global Leadership Initiative on Sarcopenia,^{4,5} that incorporate muscle strength, mass, and physical performance. These definitions remain largely muscle centric and highlight skeletal muscle as the primary site of muscle dysfunction. Although a multidimensional definition for sarcopenia has improved clinical characterisation, it does not explain why individuals with similar muscle mass or strength have markedly different functional trajectories, nor does it adequately account for the multisystem physiological processes that ultimately constrain muscle function.

This challenge is compounded by how determinants of mobility are measured. Clinical assessment relies on muscle strength assessments (eg, grip strength), muscle quantity estimates (eg, dual-energy x-ray absorptiometry or bioelectrical impedance analysis), and physical performance tests

(eg, gait speed, Short Physical Performance Battery, and Timed Up and Go),⁶ all of which primarily characterise the clinical phenotype rather than underlying mechanisms. Quantitative measures are also hampered by technical limitations; dual-energy x-ray absorptiometry quantifies lean soft tissue rather than contractile muscle and cannot distinguish functional fibres from non-contractile components such as intramuscular fat or connective tissue,⁷ whereas bioelectrical impedance analysis relies on assumptions that are sensitive to hydration status and population characteristics. Consistent with the fact that structural quantity is an imperfect indicator of function, the decline in muscle strength is only weakly correlated with the reduction in muscle mass.⁸ Moreover, the D3-creatine dilution method, which accurately quantifies contractile mass, shows only modest associations with muscle strength.⁹

These observations point to a simple conclusion: muscle function cannot be explained by structural quantity alone but reflects the integrated contribution of neuromuscular activation, muscle composition, contractile properties, and other physiological processes often grouped under muscle quality. Therefore, we propose that sarcopenia is best understood as a manifestation of progressive systemic energetic failure: a state that emerges when integrated physiological systems can no longer match energetic demand with the delivery of oxygen and metabolic substrates, their mitochondrial transformation into ATP, and the efficient utilisation of the produced energy.¹⁰ The contribution of this Personal View is not a new biological

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mechanism but a physiological framework through which existing biological and clinical observations can be understood as converging on impaired muscle function.

Within this framework, energetic failure spans four interacting domains (figure 1). Neural activation establishes energetic demand by setting the pattern for motor unit recruitment and rate coding and indirectly setting the energetic cost of a given output. The cardiac and vascular systems regulate the delivery of oxygen and substrates and their distribution across the capillary network. Mitochondria transform the substrates into usable chemical energy (ATP) while maintaining metabolic flexibility and redox homeostasis. The ability of the muscle to use the energy reflects the efficiency of ATP consumption during work and recovery. Finally, systemic regulatory pathways (ie, endocrine, immune, inflammatory, and metabolic pathways), many of which remain incompletely understood, coordinate these four domains, enabling physiological adaptation to changing demands (figure 1). Progressive loss of physiological coordination between such regulatory pathways causes an energetic mismatch that initially manifests as impaired recovery and reduced fatigue resistance. Based on this perspective, muscle function is an emergent physiological property arising from the coordinated interaction of different systems rather than a property of muscle tissue alone. Therefore, we predict that these early manifestations can precede measurable declines in maximal muscle strength and later muscle mass. This system-level perspective helps to explain the dissociation among muscle mass, strength, and power; heterogeneity of functional trajectories; and restricted functional impact of interventions targeting muscle mass alone.¹¹ Broadly, this framework integrates diverse observations into a coherent physiological hypothesis and generates testable predictions without replacing existing diagnostic definitions (figure 1).

Interventional studies provide important physiological insights. If muscle mass is the dominant determinant of muscle function, interventions that selectively increase muscle mass would be expected to produce corresponding improvements in strength and physical performance. Instead, substantial increases in muscle mass often translate into only modest or inconsistent functional benefits. Pharmacological approaches targeting skeletal muscle mass, such as myostatin or activin pathway inhibitors, anabolic therapies, and nutritional supplementation, often improve body composition while yielding only modest or inconsistent functional benefits. Bimagrumab substantially increases lean body mass but does not meaningfully improve physical performance in older adults with sarcopenia.¹² Similar dissociations have been reported in chronic obstructive pulmonary disease.¹³ Myostatin inhibition (LY2495655),¹⁴ testosterone, selective androgen receptor modulators, growth hormone, and protein supplementation likewise affect muscle mass more than they affect muscle function.^{15,16} In contrast, exercise remains the most effective intervention, likely because it simultaneously improves neural activation, vascular function, mitochondrial quality

control, and coordination among them. Moreover, the marked interindividual variability in response to exercise further indicates that muscle adaptation depends on the integrity of the integrated energetic network rather than on skeletal muscle alone.^{17,18}

Sarcopenia as a multisystem and convergent phenotype of chronic conditions

Sarcopenia rarely occurs in isolation; instead, it emerges across a wide spectrum of chronic diseases and conditions, suggesting that different pathological processes impair a common set of physiological functions required for normal muscle performance. Accordingly, sarcopenia clusters with cardiovascular disease, type 2 diabetes, chronic kidney disease, chronic obstructive pulmonary disease, cancer, neurodegenerative disorders, and increasing multimorbidity burden.¹⁹ This overlap likely contributes to the inadequate inclusion of patients with sarcopenia in randomised controlled trials because identifying individuals with pure sarcopenia in the absence of comorbidities is challenging.²⁰ Even subclinical impairments, such as cognitive decline, depressive symptoms, and reduced physical activity, are closely associated with sarcopenia and likely contribute to its clinical expression.⁴

Rather than being defined solely by loss of muscle mass, sarcopenia is more accurately characterised by reduced muscle strength, impaired physical performance, fatty infiltration of muscle, and diminished physiological reserve, often accompanied by broader functional decline.^{4,21} Importantly, no single disease fully explains age-related sarcopenia. Instead, poor physical conditioning, diverse chronic diseases, or both, impair different components of the integrated physiological network that sustains muscle function. We propose that the cumulative burden of these distributed physiological impairments progressively reduces physiological network coordination, ultimately reducing muscle function and leading to the common clinical phenotype of sarcopenia. From this perspective, muscle dysfunction is best understood as the clinical expression of the progressive loss of coordination among the physiological systems that sustain muscle function. Being an emergent physiological property of this network, muscle function is particularly sensitive to even modest disturbances distributed across multiple physiological domains. Because the network integrates inputs multiplicatively, impairments arising from unrelated diseases are transmitted through the same restricted physiological functions, thus highlighting that aetiologies produce overlapping functional deficits.²² Consistent with this framework, declines in muscle strength and physical performance might emerge early, serving as a functional indicator of systemic physiological deterioration. In this context, skeletal muscle acts as a sensitive integrator of organismal function, where the cumulative effects of multisystem dysregulation become clinically apparent.

A phenotype characterised by reduced muscle strength, impaired physical performance, and altered muscle mass

and quality is not unique to ageing but emerges consistently across a wide spectrum of chronic conditions, including cancer, chronic infections, organ failure, and inadequate nutritional states, overlapping with features of cachexia.²³ Although sarcopenia overlaps clinically with cachexia, frailty, and malnutrition, these conditions are not synonymous because they arise from different primary biological processes. Nevertheless, these conditions perturb the same physiological functions necessary for maintaining muscle performance. Despite different proximal triggers, these conditions share common downstream features in skeletal muscle. In cancer cachexia, muscle wasting and weakness develop even in the presence of adequate caloric intake owing to tumour and host-derived factors that disrupt systemic metabolism and anabolic signalling.²⁴ Chronic infections and inflammatory diseases induce muscle loss through sustained immune activation and altered energy balance.²⁵ In chronic kidney disease, heart failure, and chronic obstructive pulmonary disease, muscle decline reflects a combination of reduced perfusion, metabolic dysfunction, hormonal resistance, and inflammation.^{26,27} Even prolonged nutritional deficiency leads to a phenotype with overlapping functional features.²⁸ The convergence of these diverse chronic diseases towards a common muscle phenotype reflects the activation of shared biological mechanisms. Chronic inflammation, mediated by cytokines, such as interleukin-6 and tumour necrosis factor, promotes catabolism and interferes with anabolic signalling,²⁹ whereas resistance to anabolic hormones, including insulin, insulin-like growth factor 1, and testosterone, further constrains muscle repair and adaptation.³⁰ Circulating stress signals such as growth differentiation factor 15, linked to mitochondrial dysfunction and systemic energy imbalance, have also emerged as mediators of muscle wasting, with the inhibition of growth differentiation factor 15–glial cell line-derived neurotrophic factor family receptor alpha-like signalling attenuating weight and muscle loss in preclinical models and entering clinical investigation.³¹ Across these conditions, diverse downstream processes converge to impair muscle function, including metabolic dysregulation, anabolic resistance, and stress response pathway activation. These shared biological mechanisms provide a common physiological framework linking chronic disease and ageing.³² This convergence suggests that sarcopenia is a final common pathway of systemic physiological stress rather than a process that is intrinsic to muscle tissue.

Chronic conditions can therefore be viewed as models of accelerated disruption of the coordinated physiological network that sustains muscle function, in which the mechanisms contributing to sarcopenia become readily apparent. In physiological ageing, similar processes likely operate at lower intensity, accumulate gradually over time, and remain clinically undetected until functional thresholds are crossed.

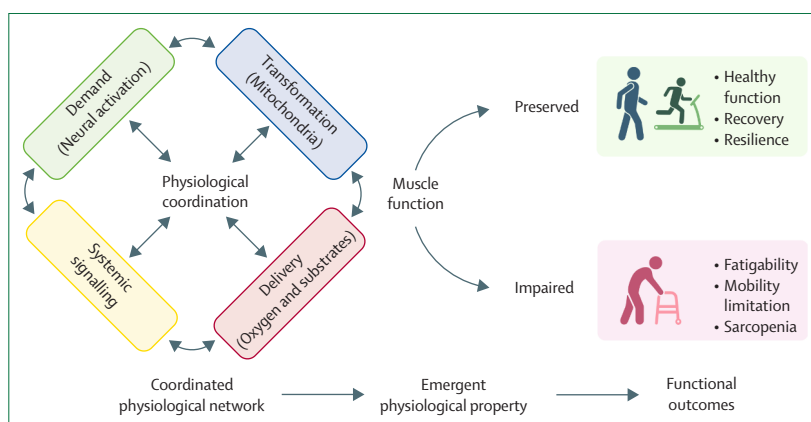


Figure 1: Muscle function as an emergent physiological property

Muscle function occurs because of the coordinated interaction of four physiological domains: energetic demand (neural activation), oxygen and substrate delivery (cardiovascular and vascular systems), energy transformation (mitochondria), and systemic signalling (endocrine, immune, inflammatory, and metabolic pathways). Rather than operating independently, these domains continuously interact to match physiological demand with energy availability and utilisation. When this physiological coordination is maintained, muscle function supports resilience, recovery, and mobility. We propose that with ageing, progressive loss of physiological coordination results in an energetic mismatch that manifests clinically as increased fatigability, impaired mobility, and ultimately sarcopenia.

Age-related biological processes underlying sarcopenia

At the cellular and molecular level, sarcopenia is commonly interpreted within the framework of the hallmarks of ageing, which include among others mitochondrial dysfunction, altered nutrient sensing, impaired proteostasis, and disrupted intercellular communication.³³ The framework discussed here complements rather than replaces these biological mechanisms. Specifically, the framework provides a physiological context through which the functional consequences of these diverse biological processes can be understood and integrated. The coordinated physiological network required to sustain normal muscle function depends on the integrity of multiple cellular processes. Alterations in proteostasis, autophagy, nutrient sensing, mitochondrial adaptive capacity, and intercellular communication progressively reduce the capacity of skeletal muscle to adapt to physiological stress, maintain energetic homeostasis, and effectively coordinate with neural, vascular, and systemic regulatory processes.³⁴

As illustrated in figure 2, diverse hallmarks of ageing converge on the mitochondria, not because they transform oxygen and metabolic substrates into usable chemical energy but because mitochondria serve as cellular integrators of physiological function.^{35,36} Mitochondria continuously integrate physiological signals related to energetic demand and oxygen and substrate availability with intracellular cues regulating calcium homeostasis, redox balance, amino acid metabolism, and cellular stress responses. Through this integrative role, mitochondria regulate energy transformation and cellular adaptation. Consequently, diverse age-related biological alterations converge on the mitochondria, where they are translated into persistent energetic stress, impaired metabolic flexibility,

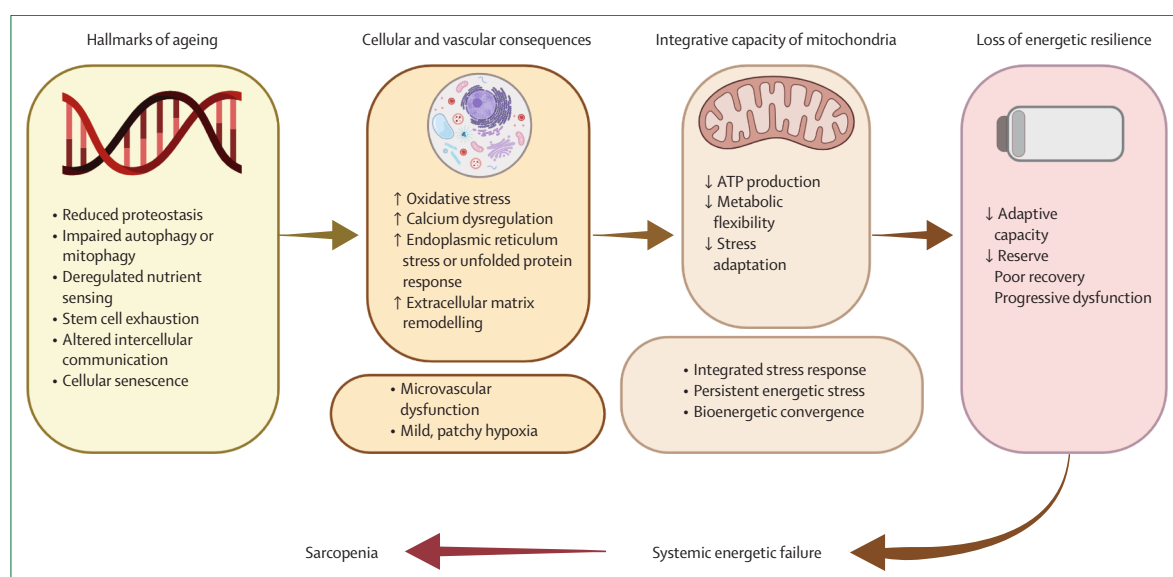


Figure 2: From the hallmarks of ageing to loss of energetic resilience

Multiple hallmarks of ageing converge on the mitochondria by progressively impairing their integrative capacity. Through interconnected cellular and vascular processes, including disrupted proteostasis, deregulated nutrient sensing, chronic inflammation, extracellular matrix remodelling, microvascular dysfunction, and localised hypoxia, this convergence impairs mitochondrial energy transformation, metabolic flexibility, and stress adaptation. The resulting loss of energetic resilience impairs recovery, functional reserve, and adaptive capacity, providing the biological basis for the systemic energetic failure proposed in this Personal View.

reduced adaptive capacity, and disrupted coordination of cellular functions.

Importantly, functional decline does not occur due to a single molecular or cellular defect, but rather because of the progressive disruption of the integrated cellular networks required to sustain physiological function with ageing. As these interacting cellular processes become progressively disrupted, the capacity of skeletal muscle to adapt to physiological stress diminishes, leading to a gradual loss of adaptive capacity. Although mechanistic evidence from experimental models supports causal roles for several of these pathways, human data remain largely associative. However, the consistency of these findings across species and conditions supports the concept that sarcopenia emerges owing to the convergence of multiple ageing-related processes that progressively impair the coordinated physiological network required to sustain normal muscle function.³⁷

Vascular and autonomic constraints on muscle energetics

In-vivo oxidative metabolism results from the integration of the oxygen and substrate delivery cascade, which includes central haemodynamics, autonomic regulation, vascular tone, microvascular perfusion, and mitochondrial oxidative capacity.³⁸ Within this system, the integrative capacity of the mitochondria can be fully expressed when sufficient oxygen and substrates are delivered in sufficient magnitude and with appropriate spatial distribution to match metabolic demand. Ageing disrupts multiple components of this cascade. Declines in cardiac output are relatively modest in healthy individuals, whereas vascular and

autonomic alterations become pronounced. Endothelial dysfunction reduces nitric oxide bioavailability and impairs vasodilatory capacity. Arterial stiffening alters central haemodynamics and compromises efficient flow transmission to the microcirculation.^{39,40} Increased sympathetic vasoconstrictor tone and impaired functional sympatholysis further limit the ability to redistribute blood flow to active muscles during contraction.⁴¹ At the microvascular level, structural and functional changes, including altered capillary density relative to muscle fibre size, impaired capillary geometry, and increased flow heterogeneity, limit oxygen diffusion and extraction. Importantly, effective oxygen delivery depends not only on total blood flow but also on its distribution across the capillary network. Consequently, heterogeneity in ageing-related perfusion can impair oxygen utilisation even when limb-level blood flow appears preserved.⁴²

Collectively, these alterations create a persistent energetic mismatch between physiological demand and oxygen and substrate delivery. At the microvascular level, heterogeneous perfusion produces regions of relative, localised hypoxia that constrain mitochondrial oxidative metabolism despite apparently adequate limb-level blood flow. This mismatch becomes particularly evident during exercise and recovery, when mitochondrial energy transformation should rapidly adapt to changing energetic demands. Under these conditions, impaired substrate and oxygen delivery results in greater energetic stress, increased fatigability, and delayed recovery.⁴³

These delivery constraints are heterogeneous and influenced by physical activity or conditioning, metabolic health, and vascular integrity. In some individuals, vascular

function remains relatively preserved, whereas in others, particularly those with inactivity or cardiometabolic disease, vascular dysfunction becomes a dominant limitation.⁴⁴ Within the proposed framework, vascular ageing limits muscle function, not simply by reducing perfusion but by constraining the coordinated physiological processes required to match oxygen and substrate delivery with energetic demand.

Neural control of muscle energetics: the neuro-vascular-muscle unit

Muscle function emerges from the coordinated interaction among the nervous, vascular, and skeletal muscle systems, forming an integrated neuro-vascular-muscle unit. Within this system, neural activation specifies the temporal and spatial pattern of motor unit recruitment, thereby anticipating the energetic requirements of the intended movement, whereas the vascular and metabolic systems coordinate oxygen and substrate delivery accordingly. Each component of this integrated system is disrupted by ageing. Loss and remodelling of upper and lower motor neurons reduce neural drive and alter motor unit recruitment patterns, while incomplete reinnervation results in the recruitment of fewer, larger motor units, diminished fine motor control, and less efficient matching between neural activation and the energetic requirements of movement.^{45–47} At the neuromuscular junction, structural and functional alterations impair signal transmission, thus reducing the efficiency of activation.^{47,48}

These neural changes have direct energetic consequences. Impaired recruitment and altered firing patterns not only reduce force generation but also increase the energetic cost required to achieve a given mechanical output.⁴⁹ Simultaneously, denervation and reinnervation processes contribute to fibre-type remodelling and selective loss of fast-twitch fibres, which are crucial for power generation.⁴⁵ Neural dysfunction contributes to muscle weakness independent of muscle mass,⁵⁰ reinforcing the concept that muscle strength reflects system-level function rather than structural quantity alone. Furthermore, reduced neural activation has indirect systemic effects. Lower volitional motor drive leads to decreased physical activity, which subsequently accelerates vascular dysfunction, impairs endothelial signalling and insulin sensitivity, and reduces mitochondrial quality control and biogenesis. Thus, reduced physiological demand progressively deconditions the systems required to meet future energetic demands, creating a self-reinforcing cycle of declining physiological capacity and energetic resilience.⁵¹

These interactions are bidirectional. Impaired vascular delivery and mitochondrial energetics increase fatigability and delay recovery and can alter afferent signalling, further limiting motor output. Collectively, these reciprocal interactions create a self-reinforcing cycle in which reduced functional capacity leads to low physical activity and consequent physiological unloading, characterised by diminished neural, vascular, and metabolic stimulation. This

reduced physiological stimulation further impairs mitochondrial integrative capacity, exacerbating energetic mismatch, fatigability, and delayed recovery and further reducing functional capacity. Exercise can interrupt this cycle by simultaneously stimulating neural activation, vascular function, mitochondrial quality control, and systemic energetic adaptation, thereby preserving energetic resilience. Thus, loss of physiological coordination, rather than failure of any single component, can drive the progression of functional decline and the emergence of sarcopenia (figure 3).

The energetic failure framework

The physiological consequences of these processes become most apparent when they are considered an integrated system. Mitochondria serve as the central integrative node of this framework. Because mitochondrial integrative capacity depends on oxygen availability, substrate delivery, redox balance, and intracellular signalling, upstream constraints can be translated into energetic stress, even when the oxidative machinery is intact.⁵² This integrative role positions mitochondria as the principal cellular interface through which distributed physiological constraints are translated into energetic stress and impaired muscle function. Muscle contraction is fundamentally an energy-dependent process, requiring continuous ATP production to match rapidly changing energetic demands.^{53,54} Therefore, energetic failure cannot be reduced to low ATP output. Energetic failure involves the progressive deterioration of the balance among demand, supply, and utilisation, and the first measurable signs of energetic failure are impaired recovery and reduced fatigue resistance, rather than reduced maximal capacity.⁵⁵

Impairment in the integrative capacity of mitochondria is a common feature of ageing across multiple organ systems, including the skeletal muscle, brain, heart, liver, and kidneys.⁵⁶ In the skeletal muscle, studies using ³¹P-magnetic resonance spectroscopy have shown reduced oxidative phosphorylation capacity with ageing,^{57,58} and proteomic analyses have shown declines in mitochondrial protein abundance even in otherwise healthy individuals.⁵⁹ Importantly, reduced mitochondrial integrative capacity is associated with future mobility decline in older adults, supporting its relevance to functional ageing.⁵⁷ Emerging evidence has further linked lower oxidative capacity of muscle with an increased risk of cognitive impairment and neurodegenerative pathology, suggesting shared energetic vulnerability across tissues.^{60–62}

A crucial consequence of impaired integrative capacity of the mitochondria is the emergence of energetic stress, defined as the progressive inability to match energetic demand with energy transformation and utilisation. This state activates conserved stress response pathways, including the integrated stress and unfolded protein responses, which shift cellular priorities from growth and maintenance towards survival.⁶³ These responses suppress protein synthesis, limit energetically costly processes,

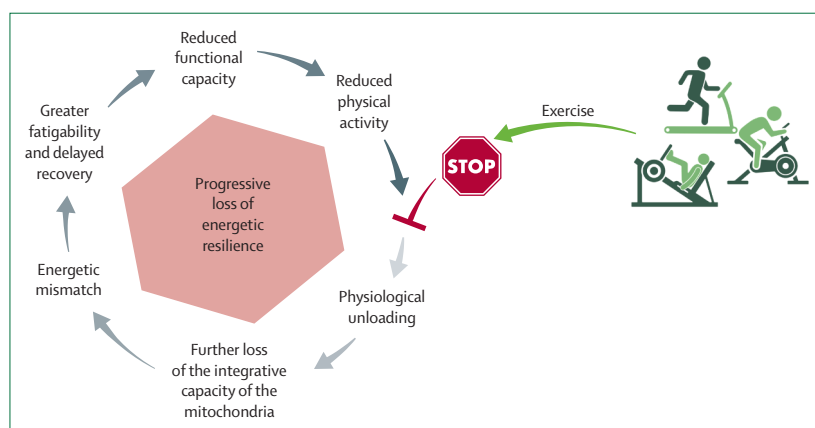


Figure 3: Self-reinforcing cycle linking energetic resilience and functional decline

Declining energetic resilience with age initiates a positive feedback loop in which reduced functional capacity limits physical activity, leading to physiological unloading characterised by diminished neural, vascular, and metabolic stimulation. This reduction in physiological stimulation further impairs the integrative capacity of the mitochondria, increasing the mismatch between energetic demand and energy availability during exertion. The resulting increase in fatigability and delayed recovery further reduces functional capacity, perpetuating the cycle. Physical activity and exercise interrupt this cycle by simultaneously improving neural activation, vascular function, mitochondrial quality control, and systemic energetic adaptation, thereby preserving energetic resilience.

and promote adaptive programmes. Although initially protective, the chronic activation of stress response pathways contributes to impaired proteostasis, reduced synthesis of contractile proteins, and progressive deterioration of muscle structure and function.^{64,65} Beyond the role of mitochondria in energy transformation, they also function as major signalling hubs that coordinate inflammatory and innate stress responses, further supporting their role as cellular integrators of physiological function. This signalling role provides an additional mechanism through which energetic stress can propagate from the cellular level to tissue and organism dysfunction.⁶⁶

In parallel, ageing-related declines in autophagy and proteasomal function impair the clearance of damaged proteins and organelles, leading to the accumulation of dysfunctional cellular components.^{67,68} Collectively, these processes establish a mechanistic link between energetic stress and structural decline, whereby persistent failure to maintain energetic homeostasis progressively compromises muscle quality, adaptive capacity, and ultimately muscle function.⁶⁹

Interventional data reinforce the central but context-dependent role of the integrative capacity of the mitochondria in determining muscle function.⁷⁰ Exercise remains the most effective strategy because it simultaneously enhances neural activation, vascular function, mitochondrial quality control, and systemic metabolic regulation, thereby restoring the coordinated physiological processes required to sustain muscle function.¹⁰ Emerging pharmacological approaches targeting mitochondrial turnover, such as mitophagy activators, show promising but variable effects in humans, with improvements in mitochondrial biomarkers often exceeding gains in functional outcomes.⁷¹ By contrast, interventions that increase

metabolic intermediates without restoring mitochondrial quality control have shown partial functional benefit, underscoring the importance of coordinated regulation.⁷² Because mitochondria integrate diverse physiological and cellular signals, reductions in their integrative capacity provide a mechanistic bridge between cellular alterations and system-level functional decline. Energetic deficits impair excitation–contraction coupling through altered ion homeostasis and calcium handling, thereby increasing fatigability.⁷³ Simultaneously, mitochondrial-derived signals and reactive oxygen species activate inflammatory and senescence pathways, contributing to tissue and systemic dysfunction.⁷⁴

Rather than acting solely as primary drivers, mitochondria represent the point at which upstream neural, vascular, and metabolic constraints converge. Therefore, mitochondrial dysfunction might represent either a primary limitation or a downstream consequence, depending on the prevailing physiological constraint. This dual role explains why mitochondrial function is both highly sensitive to ageing processes and strongly predictive of clinical outcomes. In this framework, sarcopenia emerges when the coordinated regulation of energy demand, delivery, and utilisation is disrupted. Mitochondria integrate these signals, translating distributed physiological impairments into functional decline observed as reduced muscle strength, increased fatigability, and impaired recovery.

Clinical implications of energetic failure

Reconceptualising sarcopenia as a systemic disorder of energetic failure has important implications for clinical practice. From a diagnostic perspective, current measures of muscle strength, muscle mass, and physical performance remain essential but primarily capture downstream clinical manifestations of biological dysfunction. We argue that greater emphasis should be placed on physiological measures that reflect the ability to sustain and recover muscle function under energetic demand. In daily life, muscle performance depends less on the maximal force generated during a single effort than on the capacity to repeatedly produce coordinated submaximal contractions, resist fatigability, and recover efficiently after exertion. However, fatigability is notably not a unitary phenomenon; the physiological mechanisms that limit performance vary according to the specific demands of the task, including contraction intensity and duration, balance between contraction and recovery time during repeated contractions, muscle group, neural control requirements, and metabolic stress.⁷⁵ Thus, different task paradigms might not simply be useful for quantifying fatigability, but also for probing distinct mechanisms of energetic and neuromuscular failure. Measures such as fatigability, recovery kinetics, oxidative capacity, and energetic phenotyping can provide earlier and more mechanistically informative indicators of declining muscle physiological function than those observed with maximal strength or muscle mass alone. However, these measures should be considered primarily

as research-oriented assessments that require further validation before routine clinical use.

The available evidence also supports a shift towards risk stratification based on energetic phenotypes. Individuals with similar muscle mass might show markedly different functional trajectories depending on the integrity of the vascular, neural, and metabolic systems. Identifying these differences can help to explain variability in clinical outcomes and improve prognostic accuracy beyond traditional structural measures.

These differences also have important therapeutic implications. The modest functional gains achieved by interventions targeting muscle mass alone likely occur because the dominant physiological constraints on muscle function differ among individuals and often remain unaddressed. Consequently, interventions that restore coordination among the neural, vascular, metabolic, and mitochondrial systems are more likely to improve functional performance than that observed with interventions targeting skeletal muscle in isolation.

Exercise precisely illustrates the energetic failure framework because it simultaneously engages all domains, and its well known variability in response^{51,76,77} plausibly reflects the dominant physiological constraint in each individual. Accordingly, effective treatment strategies will likely require individualised, system-level approaches targeting the dominant physiological constraint rather than skeletal muscle in isolation, an approach that aligns closely with the principles of geroscience.

Future directions

The energetic failure framework leads to several testable predictions. First, impairments in energetic recovery reflected by delayed phosphocreatine resynthesis or reduced mitochondrial oxidative capacity should precede measurable declines in muscle mass or strength, consistent with evidence linking mitochondrial energetics to mobility and frailty.¹⁰ Second, interventions that restore coordination between energy delivery and transformation (including mitochondrial-targeted therapies or metabolic modulators) should improve functional performance disproportionately to changes in muscle size, as suggested by agents such as elamipretide and sodium–glucose cotransporter-2 inhibitors.^{78,79} Interventions that improve microvascular perfusion and oxygen delivery, including those that increase nitric oxide bioavailability (eg, dietary nitrate supplementation such as beetroot juice), might similarly enhance muscle energetics and functional performance, particularly in older adults.^{80,81} Third, individuals with comparable muscle mass but differing energetic phenotypes should have markedly different risks of functional decline, consistent with findings that muscle strength predicts mortality more robustly than structural measures.³ Testing these predictions will require longitudinal, multidimensional studies that simultaneously assess physiological function across neural, vascular, mitochondrial, and metabolic domains, rather than evaluating these

systems in isolation. Integrating functional assessments with biomarkers of these interacting physiological processes will be essential for defining energetic phenotypes, predicting functional trajectories, and developing personalised interventions.

Conclusion

Along these lines of evidence, we propose that sarcopenia is best understood as a manifestation of progressive systemic energetic failure arising from the loss of coordination among the physiological systems that regulate energetic demand, delivery, transformation, and utilisation. In this framework, skeletal muscle serves as a sentinel organ, with its strength and endurance reflecting the state of an integrated physiology rather than the mass of the tissue itself. This perspective provides a unifying explanation for key features of sarcopenia, including the dissociation between muscle mass and function, heterogeneity of clinical trajectories, and inadequate efficacy of interventions targeting muscle mass alone. Evidence has supported a shift towards multidimensional assessment strategies and system-level therapeutic approaches aimed at restoring energetic balance.

Ultimately, progress in understanding and treating sarcopenia will require moving beyond reductionist, muscle-centric models towards a new paradigm of ageing in which muscle function is recognised as an emergent property of coordinated organismal physiology.

Contributors

LF conceptualised and drafted the manuscript and developed the overall framework. LF, SD, AP, MC-RB, YR, BCC, and MCG-C contributed to literature review, interpretation of the evidence, and development of the concepts presented in the manuscript. All authors critically revised the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

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