

Review in Depth

# Pathophysiological Mechanisms Explaining the Association Between Low Skeletal Muscle Mass and Cognitive Function

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## Abstract

Low skeletal muscle mass is associated with cognitive impairment and dementia in older adults. This review describes the possible underlying pathophysiological mechanisms: systemic inflammation, insulin metabolism, protein metabolism, and mitochondrial function. We hypothesize that the central tenet in this pathophysiology is the dysfunctional myokine secretion consequent to minimal physical activity. Myokines, such as fibronectin type III domain containing 5/irisin and cathepsin B, are released by physically active muscle and cross the blood–brain barrier. These myokines upregulate local neurotrophin expression such as brain-derived neurotrophic factor (BDNF) in the brain microenvironment. BDNF exerts anti-inflammatory effects that may be responsible for neuroprotection. Altered myokine secretion due to physical inactivity exacerbates inflammation and impairs muscle glucose metabolism, potentially affecting the transport of insulin across the blood–brain barrier. Our working model also suggests other underlying mechanisms. A negative systemic protein balance, commonly observed in older adults, contributes to low skeletal muscle mass and may also reflect deficient protein metabolism in brain tissues. As a result of age-related loss in skeletal muscle mass, decrease in the abundance of mitochondria and detriments in their function lead to a decrease in tissue oxidative capacity. Dysfunctional mitochondria in skeletal muscle and brain result in the excessive production of reactive oxygen species, which drives tissue oxidative stress and further perpetuates the dysfunction in mitochondria. Both oxidative stress and accumulation of mitochondrial DNA mutations due to aging drive cellular senescence. A targeted approach in the pathophysiology of low muscle mass and cognition could be to restore myokine balance by physical activity.

**Keywords:** Dementia, Inflammation, Insulin, Myokines

Diagnostic measures of sarcopenia in older adults, that is, low skeletal muscle mass, muscle strength, and physical performance (1), are associated with detrimental health outcomes and morbidity, that

is, falls and fractures (2), caregiver dependence in activities of daily living (3), diabetes (4), and cognitive decline/impairment (5). The prevalence of sarcopenia in older community-dwelling individuals

with dementia is more than 3 times higher than individuals without dementia (4). Diagnostic criteria for sarcopenia (eg, low handgrip strength and muscle mass) are independent risk factors for cognitive decline in community-dwelling older individuals (3,6). Despite such strong epidemiological associations, the underlying pathophysiological mechanisms between measures of sarcopenia and cognitive impairment and dementia are yet to be fully established.

A direct link between the skeletal muscle and brain axis has been demonstrated by the release of exercise-induced myokines (7,8). Similarly, insulin metabolism (9), protein metabolism (10), mitochondrial function (11), and systemic inflammation (12) have been suggested to be altered in individuals with low skeletal muscle mass and may contribute to the development of cognitive impairment. Whether these mechanisms drive the pathophysiology of cognitive impairment and therewith explain the association of sarcopenia and cognitive impairment, or whether these mechanisms are indirect links between sarcopenia and cognitive impairment, is debatable. Sarcopenia may be a neurogenic syndrome, as there is a strong link between the central nervous system and muscle via motor neuron connectivity (13). However, in this review, we will focus on the unidirectional relationship between low skeletal muscle mass and cognition. Identification of the underlying pathophysiology may pave the way for novel treatments and targeted interventions to improve the metabolic and functional quality of skeletal muscle mass to reverse sarcopenia, and possibly also improve cognitive function. This narrative review aims to describe the pathophysiological mechanisms of muscle mass loss that may underlie its association with cognitive impairment.

## Literature Search

The literature search for this narrative review comprised 2 databases (PubMed, Embase) and was executed in collaboration with a medical data specialist. Administered indexing terms (eg, MeSH in PubMed and Emtree in Embase) and free-text search terms included (a) muscle mass and strength, (b) cognitive decline and dementia, and (c) predetermined pathophysiological mechanisms: “insulin resistance,” “mitochondrial function,” “protein metabolism,” and “inflammation” (Supplementary Appendix). Reference lists of relevant articles were screened for additional relevant articles.

In our review, we investigated the unidirectional relationship between low skeletal muscle mass and cognitive impairment, and their possible predetermined mechanisms. We do not exclude the possibility that other mechanisms that govern the coupling of skeletal muscle mass and cognitive dysfunction might exist.

## Understanding Skeletal Muscle Mass Loss

Skeletal muscle mass loss occurs during aging and is caused by atrophy of muscle fibers and a decrease in the number of myofibers. After the age of 30 years, muscle mass declines at a rate of approximately 3%–8% per decade and accelerates from 60 years onwards (14). Skeletal muscle fibers are classified into slow-twitch type I and fast-twitch type II fibers. Type II fibers predominate high glycolytic capacity, whereas type I fibers comprise a higher mitochondrial content and oxidative capacity (15). During skeletal muscle aging, the loss of type II fibers occurs prior to the loss of type I fibers (16).

The decline of immune function caused by aging is characterized by a systemic increase in proinflammatory cytokines, such as interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (16),

resulting in a chronic low inflammatory state. Systemic inflammation and thereby uncontrolled release of inflammatory cytokines result in dysfunction of mitochondria, with a negative spiral in which less energy (ATP) is produced, and reactive oxygen species (ROS) further exacerbates damage to mitochondria (16). In addition, damaged mitochondria lead to metabolic abnormalities such as insulin resistance and the activation of the ubiquitin–proteasome system (UPS), which plays a major role in muscle degradation (17).

Fundamental to muscle fiber atrophy is the occurrence of anabolic resistance, which is the suppression of protein synthesis to anabolic stimuli, such as an increased amino acid availability (16). As a typical response to amino acid availability, signaling pathways for synthesis will be activated by mammalian target of rapamycin (mTOR). However, mTOR activation is reduced in older individuals (18). Given isocaloric amounts of protein, protein synthesis is also reduced in older individuals (16).

As a result of aging, the number of mitochondria is reduced with an increased number of mitochondrial DNA (mtDNA) mutations, which may drive apoptosis (19). Moreover, oxidative stress drives oxidative damage, as the production of ROS increases (19). ROS further exacerbates damage to mitochondria, with a vicious cycle in which dysfunctional mitochondria beget dysfunctional mitochondria (19).

## Understanding Cognitive Dysfunction

Aging is the largest risk factor for loss of muscle mass and cognitive decline. The World Health Organization (WHO) estimated that 55 million individuals worldwide are living with dementia (20). As the number of old adults increases, it is predicted that the number of individuals with dementia will double every 5 years (21).

Age-related changes that correlate with cognitive decline include loss of synapses, dysfunction in neuronal networks, and changes in neuronal structure without neuronal death (22). Neuronal loss that occurs with aging in the central nervous system (CNS) is limited (<10%) and restricted to certain regions (23). The changes that occur to neurons are, for instance, a decrease in the number of axons, loss of synapses, decrease in number and length of dendrites, and a loss of dendritic spines (22). It is suggested that these morphological changes contribute significantly to cognitive decline (22,23). The purported molecular mechanisms that connect loss of muscle mass with cognitive decline include altered myokine secretion, inflammation, insulin resistance, abnormal protein accumulation, oxidative stress, and mitochondrial dysfunction (24).

Neuroinflammation may play a role in cognitive decline. An increase in peripheral proinflammatory cytokines during aging can exert its effects in the brain by directly crossing the blood–brain barrier (BBB), and activate microglia, resulting in neuroinflammation in the CNS (24). In Alzheimer’s disease (AD), the role of neuroinflammation is clearer because A $\beta$  contributes directly to microglial activation (24). Microglia are resident macrophages in the brain, which mediate this inflammatory response. However, it is suggested that altered morphology of microglia leads to altered functions that enhance the production of proinflammatory cytokines (24).

Insulin in the brain is mainly originated from insulin secreted by  $\beta$  cells in the pancreas and transported via a saturable receptor-mediated pathway (25). Insulin becomes active as a tyrosine kinase when bound to its receptor (26). The number of insulin receptors in the brain reduces with aging (26). Aberrant insulin uptake makes the

brain susceptible to neurodegeneration and cognitive dysfunction, as it is important in neuroprotection (25). Underlying mechanisms of insulin resistance leading to cognitive dysfunction are an increased tau protein concentration, altered hippocampal plasticity, altered amyloid precursor protein (APP) metabolism, and altered inflammatory response in the brain (25,27).

With regard to protein metabolism, mTOR is integral in nutrient sensing and protein synthesis, regulating cellular proliferation, growth, and senescence (18). Aging is linked to alterations in protein synthesis, degradation, folding, and trafficking. To maintain proteostasis, protein clearance (via autophagy or proteosomal degradation) and protein synthesis are important mechanisms influenced by mTOR. In addition, mTOR may underlie mitochondrial dysfunction as it regulates mitochondrial biogenesis, dynamics, and function (18). Therefore, disturbance of mTOR signaling as a result of aging affects mitochondrial function, glucose metabolism, energy production, and autophagy in the brain (28).

Finally, mitochondrial dysfunction occurs as a result of accumulation of mtDNA mutations due to an increase in ROS-mediated molecular damage. Both inflammation and mitochondrial dysfunction increase the production of ROS (29). As a result, impaired mitochondrial function in the brain may lead to a vicious cycle in which an increase of ROS may directly damage mitochondrial proteins and further impair cellular energy production (24,29).

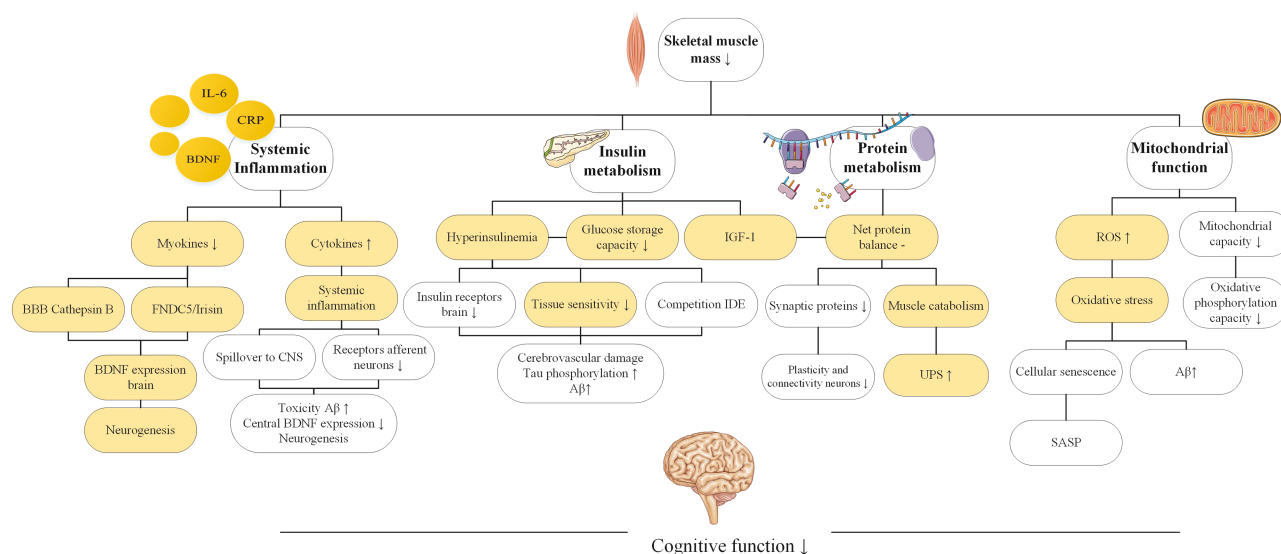
### Overview of Pathophysiological Mechanisms

Figure 1 gives an overview of the possible pathophysiological mechanisms explaining the association between sarcopenia and cognitive impairment.

#### Purported Mechanism 1: Systemic Inflammation

Low skeletal muscle mass in older adults is associated with low-grade, systemic inflammation (30), which in turn is associated with cognitive impairment and dementia (31). First, age-associated

physiological changes in the innate and adaptive immune function are called “immunosenescence” (32). Typically, these alterations lead to reduced immune competence to cope with infections, resulting in a compromised adaptive immune system. Second, nonresolving inflammation is also observed (32), which evolves into a low-grade, chronic inflammatory state and has been termed “inflamm-aging” (32). Moreover, systemic concentrations of proinflammatory cytokines originating from adipose tissue are higher in sedentary older individuals, who often have impaired muscle strength and muscle power (33) compared with physically active individuals (34). Similarly, the majority of circulating IL-6 diabetic people originate from adipose tissue (adipocytes and adipose tissue macrophages) (35). Comparatively, healthy nondiabetic individuals have significantly lower concentrations of circulating IL-6, compared with individuals with type 2 diabetes (36). Elevated concentrations of inflammatory markers in the systemic circulation, such as C-reactive protein (CRP) and IL-6, are associated with the risk of dementia (37), although local inflammation in the CNS and systemic inflammation are suggested to contribute to cognitive decline (38). Although the debate on the central or peripheral drivers of cognitive decline and dementia rages on, it is evident that the immune bidirectional crosstalk in the brain–periphery axis is a considerable contributor to this pathology. A purported mechanism is that peripheral proinflammatory cytokines interact via receptors on afferent neurons within the CNS (39). Systemic elevation of proinflammatory cytokines and chemokines can disrupt neurogenesis—plasma C-C motif chemokine ligand 11 (CCL11) demonstrated an age-associated increase in its concentration in plasma and cerebrospinal fluid (CSF) of healthy human volunteers between 20 and 90 years of age (40). In preclinical animal studies, intraperitoneal administration of CCL11 in young mice led to significant decreases in neurogenesis, but this deficit was rescued by systemic administration of CCL11 antibody (40). Furthermore, and more importantly, peripherally derived inflammatory cytokines can augment the CNS-localized inflammatory response, such as leading to the priming, and activation of resident



**Figure 1.** Overview of the purported pathophysiological mechanisms explaining the association between sarcopenia and cognitive function. Yellow marked fields could also be affected by the mediating role of exercise. Aβ = amyloid beta; BBB = blood–brain barrier; BDNF = brain-derived neurotrophic factor; CRP = C-reactive protein; CNS = central nervous system; CDLK-5 = cyclin-dependent-like kinase 5; FND5 = fibronectin type III domain containing 5; IDE = insulin-degrading enzyme; IGF-1 = insulin-like growth factor 1; IL-6 = interleukin 6; ROS = reactive oxygen species; SASP = senescence-associated secretory phenotype; UPS = ubiquitin–proteasome system. Full color version is available within the online issue.

microglial cells, that further drive the production of cytokines (eg, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) locally (41,42). The long-term activation of microglia and their chronic production of these cytokines can then disrupt normal neural processes, such as disrupting long-term potentiation (43), stimulate the production of, and increase the cytotoxicity of A $\beta$  (44), with the impaired clearance of such neurotoxins further driving the loss of other neuronal integrity.

### Role of proinflammatory cytokines

The prototypical cytokine, IL-6, behaves as an anti-inflammatory cytokine when secreted by type I and II skeletal muscle fibers during muscle contraction (45). IL-6 plays an important role in the homeostasis of the CNS as it acts with 2 types of signaling in nervous tissue: either via binding to a membrane receptor (classical signaling) or via the soluble form of its receptor (sIL-6R; trans-signaling), generated through alternative mRNA splicing, proteolysis of the membrane-bound IL-6R or through the release of extracellular vesicles (46). Because membrane-bound IL-6R are expressed on hepatocytes, most immune cells, myocytes, and hepatocytes, IL-6 signaling in these cells occurs *via* the classical route (46). Comparatively, trans-signaling occurs in other cell types lacking the membrane-bound IL-6R, such as neurons, where the ubiquitously expressed gp130 membrane protein permits the docking of the IL-6/sIL-6R, becomes a homodimer and leads to intracellular signaling pathways. IL-6 trans-signaling has also been discovered to be the main mechanism through which this cytokine's proinflammatory functions are mediated (47). In a number of murine models of human inflammatory diseases such as liver cancer, atherosclerosis, inflammatory bowel disease, the blockage of trans-signaling was sufficient to prevent disease progression (48), suggesting that IL-6 trans-signaling is responsible for the relevant pathology, and also during the inflammation seen in CNS aging (49).

Given that obese individuals present with higher plasma concentrations of IL-6R and A disintegrin and metalloprotease 17 (ADAM17), the latter a protease responsible for cleaving membrane-bound IL-6R into its soluble form (50), our working model posits that a combination of inactive muscle and excess adipose tissue (due to chronic sedentary behavior) drives IL-6 trans-signaling during "inflamm-aging" and neurodegeneration. IL-6 released from excess or inflamed adipose tissue bind to soluble IL-6R and mediate detrimental signaling in the CNS (51).

### Role of myokines

Contracting skeletal muscle behaves like an endocrine organ secreting cytokines and peptides, called "myokines" (52). Muscle atrophy and the loss of type II fibers, and subsequent switch to type I fibers may result in altered secretions of myokines. Myokines can be both pro- and anti-inflammatory and include IL-6, IL-8, IL-15 (53), and brain-derived neurotrophic factor (BDNF) (54), which is summarized elsewhere (52). According to the "Myokine Concept," physically inactive muscles suppress the endocrine function of muscle, favoring inflammation and thereby increasing the risk of dementia (55). In a 10-year longitudinal study, higher systemic concentrations of IL-6 effectively predicted cognitive decline in late midlife (56). Whether myokines cross the BBB remains speculative, although the fact that cytokines can cross the BBB via circumventricular organs that are in close proximity with the hypothalamus (57) suggest that this mechanism may also apply to myokines. In this respect, recent findings implicate a role for other novel, exercise-induced myokines, such as cathepsin B and FNDC5/irisin (58,59). Cathepsin B crosses the BBB

and upregulates local neurotrophin expression, the most well-known and studied being BDNF (58). Exercise increases the gene/protein expression of peroxisome proliferator-activated receptor-gamma coactivator-1-alpha (PGC1 $\alpha$ ) in skeletal muscle cells, a mediator of oxidative phosphorylation and mitochondrial biogenesis (58). As a result, PGC1 $\alpha$  induces the expression of a transmembrane precursor FNDC5, which is then cleaved and releases a peptide, irisin, into the systemic circulation (58). The purported mechanism is that the released myokine irisin crosses the BBB and upregulates the expression of BDNF, thereby influencing neurogenesis and positively affecting memory. However, whether the effect of irisin in the brain is due to exercise (and which type of exercise) is controversial and needs further investigation (58).

In community-dwelling older women, low plasma BDNF concentrations were associated with lower cognitive function (60) and with higher mortality risk during 5 years of follow-up (61). In patients with AD peripheral concentrations of BDNF were significantly lower compared with individuals with no AD (62). Peripheral concentrations of BDNF are of interest because muscular contraction leads to increased BDNF mRNA and protein expression in muscle tissue and an increase in BDNF protein concentrations in the systemic circulation (58). Central BDNF expression and function is reduced by elevated concentrations of proinflammatory cytokines, which affects neurogenesis (63). However, most BDNF found in systemic circulation after exercise was determined to have originated from the brain (52), and there is likely a BDNF threshold that needs to be achieved to modulate neurogenesis (64).

Another possible mechanism is that peripheral irisin concentrations might affect local concentrations of irisin in the brain (65). For instance, in AD models, the effects of exercise on memory and synaptic plasticity were attenuated by blockade of irisin (peripheral and brain) (65). In patients with AD, levels of FNDC5/irisin are lower in hippocampi and CSF compared with healthy individuals or patients with mild cognitive impairment (65). Moreover, a positive association was found between CSF concentrations of irisin and BDNF (66).

### Purported Mechanism 2: Insulin Metabolism

Skeletal muscle plays an important role in glucose homeostasis because it is the dominant tissue responsible for glucose storage and metabolism (67). Low skeletal muscle mass is associated with insulin resistance (68), and insulin resistance is an independent risk factor for cognitive decline (69). Impaired glucose tolerance often accompanies insulin resistance with aging (70). In older individuals without cognitive dysfunction, impaired glucose tolerance with aging was associated with longitudinal changes in brain function (regional cerebral blood flow) (71). Because energy metabolism in brain tissue is mainly dependent on glucose (72), elevated glucose concentrations in peripheral tissues impede normal glucose regulation and insulin sensitivity in the brain (73).

Insulin resistance increases with age (9). Both glucose and insulin pass the BBB and have intracerebral effects, such as synaptic remodeling, regulating the expression of neurotransmitters, and acting selectively in brain regions to increase glucose metabolism (74). Hyperinsulinemia downregulates the number of insulin receptors in the BBB and, thus, attenuates insulin transport in the brain (74). Eventually, chronic hyperinsulinemia dampens tissue sensitivity to insulin, leading to cerebrovascular damage (74).

Long-term exposure to elevated concentrations of glucose results in inappropriate secretion of insulin leading to hyperinsulinemia,

which negatively affects neurons (75). Both utilization and uptake of glucose are impaired in AD (75). Peripheral insulin resistance leading to hyperinsulinemia affects insulin signaling in the CNS, which stimulates tau phosphorylation, oxidative stress, and toxicity of A $\beta$ , contributing to cognitive decline (75).

The transport of insulin across the BBB occurs primarily via an energy-dependent saturable transport system (76). When insulin reaches the brain, it can bind to microvessels. Insulin binding to brain microvessels was higher in a mouse model of AD (aged mice compared with young mice). However, whether this is related to altered insulin levels at the transporter level is unclear (76). Thus, it has been described that chronic elevation of peripheral concentrations of insulin are associated with relatively lower insulin concentrations in the brain (74). Low insulin concentrations in the brain reduce A $\beta$  clearance due to decreased transport activity of A $\beta$  from intracellular to extracellular compartments, which is considered the primary site for A $\beta$  clearance (74). However, it is unclear whether this can be attributed to the high peripheral insulin concentrations that arise as a consequence of low skeletal muscle mass.

Another suggested mechanism in the link between peripheral hyperinsulinemia and AD is the accumulation of A $\beta$  due to direct competition of insulin-degrading enzyme (IDE) through which A $\beta$  degradation is attenuated, thereby increasing tau formation (75). However, neuronal uptake of glucose is not fully dependent on insulin and therefore, insulin signaling pathways are more ascribed to insulin resistance in the brain (75).

Insulin-growth factor 1 (IGF-1) is intimately involved in protein biosynthesis, and thus, the net balance of protein synthesis and breakdown determines the degree of muscle mass accrual (77). Recent studies found an association between lower serum IGF-1 levels and sarcopenia in older adults (78,79). The bioavailability of peripheral IGF-1 depends on its insulin-like growth factor-binding proteins (IGFBP), of which approximately 80% is bound to IGFBP-3 in the periphery (80). The associations between peripheral IGF-1 and IGFBP-3 have been evaluated, which showed that these measures were associated with cognition in older women, whereas the direction of this association remains to be elucidated (80).

### Purported Mechanism 3: Protein Metabolism

Skeletal muscle mass is negatively affected by decreased muscle protein synthesis (MPS) and increased muscle protein breakdown (MPB), which results in a negative net protein balance (81). Decreased skeletal MPS that accompanies aging is called “anabolic resistance” (82). The age-related decrease in protein synthesis comprises changes in protein folding, maintenance, and breakdown (83). Low muscle mass consequent to a negative net protein balance could also reflect lower protein concentrations in the brain, indirectly affecting cognition. Abnormal depositions of misfolded and aggregated proteins are common in several types of dementia (84,85). Due to oxidative damage, several proteins as markers of oxidative stress accumulate. As revealed by proteomic techniques in postmortem brains of older humans, oxidative damage by lipoxidation with aging occurs mostly in proteins involved in neurotransmission, proteostasis, and energy metabolism (86). These modifications and alterations in proteins are of interest because the degree of oxidative damage to specific proteins is more severe in AD brains (24).

Another probable mechanism linking low skeletal muscle mass with cognition is that low skeletal muscle mass is related to the upregulation of the ubiquitin-dependent proteolytic system (UPS), a major pathway that clears short-lived, damaged, and misfolded

nuclear and cytoplasmic proteins and is upregulated in AD (87). The UPS is related to the degradation of proteins and plays an essential role in neuronal signaling such as synaptic activity and neurotransmitter release (87). A key determinant in the AD pathophysiology is APP, an acute-phase protein that is described to be connected with the UPS (87). The suggested pathway is that dysfunction or overload of the UPS may cause accumulation of A $\beta$  in AD (87). In addition, an accumulation of ubiquitin is found in the A $\beta$  deposits and neurofibrillary tangles of AD (87). Although the upregulation of the UPS system has been described in regards to aging and cachexia, the relationship with sarcopenia requires further investigation (88).

### Purported Mechanism 4: Mitochondrial Function

The energetic needs for skeletal muscle contraction are provided by ATP, which is mainly driven by mitochondrial oxidative phosphorylation (89). Skeletal muscle mitochondria fulfill different roles with regard to metabolic regulation, that is, apoptosis, synthesis, and catabolism of metabolites, and production and quenching of ROS (89). Skeletal muscles use oxygen and in turn, produce large amounts of reactive oxygen and nitrogen species (RONS) (90). Under normal conditions, ROS are molecular signal transducers (17); however, overproduction of ROS in dysfunctional mitochondria can lead to increased oxidative stress and damage to organelles (90). One common pathogenic mechanism of both sarcopenia and dementia is the involvement of oxidative stress, which is described as the imbalance between the generation of, and detoxification of RONS in cells (90). One potential pathophysiological mechanism caused by impaired mitochondrial function is called “the oxidative stress theory,” according to which accumulation of RONS possibly leads to cellular senescence (90). Mitochondrial abnormalities (content, function, morphology) are common in individuals with low muscle mass (17). Mitochondrial dysfunction in the brain is also a potentially underlying mechanism in dementia (91,92). Whether peripheral mitochondrial dysfunction affects mitochondria in the brain needs to be clarified. With aging, skeletal muscles oxidative phosphorylation capacity decreases while deletions accumulate in mtDNA (19,93). These mutations can result in oxidative tissue damage (19). Skeletal myocytes are reliant on efficient production of ATP from functional mitochondria, and disruption of this machinery can drive cellular apoptosis—a precursor to loss in muscle tissue (94). Mitochondrial dysfunction drives cellular senescence (95), which blocks cell proliferation and leads to a senescence-associated secretory phenotype (95). This involves a constellation of proinflammatory cytokines and enzymes such as matrix metalloproteases (MMPs), which are a large family of cleavage proteins. MMPs might be a therapeutic target because it can degrade A $\beta$ , and MMP concentration is higher in AD brains (96). However, MMPs can also induce the transcription of inflammatory players (90,97). This may result in a feedback loop wherein oxidative stress and overproduction of ROS contribute to mitochondrial dysfunction (98). In particular, overproduction of ROS increases oxidative stress, which increases secretion and production of A $\beta$  (99,100).

The trafficking and accumulation of A $\beta$  in mitochondria of neurons is associated with impaired mitochondrial function (101). The “mitochondrial cascade hypothesis” suggests that age-associated mitochondrial decline occurs at a certain threshold and is concomitant with synaptic loss, A $\beta$  production, tau phosphorylation, and plaque deposition in the brain (102). With regard to A $\beta$  accumulation, it is suggested that in the first-place neurons will compensate bioenergetically for the decline in mitochondrial

mass (103). However, as A $\beta$  production increases, neurons can no longer compensate for the ongoing processes of A $\beta$  accumulation (103). Lastly, a decrease in mitochondrial mass that accompanies the hypometabolic state will decrease A $\beta$  production (103). Clinically, the “mitochondrial cascade” hypothesis suggests that amyloid accumulation already reaches a plateau before the manifestation of the actual symptoms of AD (104).

### **Interplay Between Inflammation, Insulin, Protein Metabolism, and Mitochondrial Function; Myokines: Muscle-Derived Peptides Orchestrating Interorgan Crosstalk**

Although the pathophysiological mechanisms were described as separate entities, there is an interplay between these mechanisms. We hypothesize that altered myokine release from skeletal muscle are the key modulators of the 4 physiological hallmarks that accompany cognitive decline. Myokines crosstalk with other molecular players in the brain to exert positive effects on neurogenesis, nervous system development, and neuroprotection in response to exercise (7). For instance, FNDC5 enhances neurogenesis by inducing BDNF locally in the hippocampus (105). In addition, the cleaved peptide product of FNDC5, irisin, enhances neuronal proliferation and differentiation. Irisin further stimulates neuroprotection via seronine/threonine kinase AKT/extracellular signal-regulated kinases 1 and 2 signaling pathways (7). In preclinical animal models, 2 weeks of voluntary wheel running resulted in an increase of IL-6 expression in murine hippocampus and a downregulation of the systemic concentrations of proinflammatory cytokines and inflammation (106).

BDNF exerts its beneficial effect on mitochondria by activating AMP-activated protein kinase and enhancing fatty acid oxidation (107). BDNF also upregulates the expression of PGC-1 $\alpha$ , a master transcription factor that regulates mitochondrial biogenesis, in cultured hippocampal neurons, thus, illustrating its important role for central energy metabolism (108). PGC-1 $\alpha$  is essential for energy metabolism including mitochondrial biogenesis and release of myokines such as FNDC5/Irisin and cathepsin B (107). PGC-1 $\alpha$  expression in response to exercise drives secretion of myokines (7). Therefore, physical inactivity or a sedentary lifestyle result in reduced release of myokines, but also contributes to production of proinflammatory cytokines as PGC-1 $\alpha$  decreases the activity of NF $\kappa$ B, which regulates proinflammatory gene expression (109).

Cathepsin B regulates the release of proapoptotic molecules and therefore influences mitochondrial cell death signaling (110). An important age-related alteration of the neuromuscular system is the decrease in the number of motor units, which includes the muscle fibers innervated from the peripheral axon (111). The quantity of myokines may be reduced due to low levels of physical activity that could contribute to the loss of motor units that accompanies aging, thereby influencing the aforementioned pathways of interest (inflammation, insulin metabolism, and mitochondria) in the brain microenvironment, via alterations to their paracrine and endocrine signaling (8). In this regard, neurturin, a glial cell line-derived neurotrophic factor, was recently shown to also function as a novel myokine. Neurturin is transcriptionally upregulated in skeletal muscle after voluntary wheel running in mice and after high-intensity sprint cycling in human subjects, and is involved in remodeling the postsynaptic properties of the neuromuscular junction (112). Note that the abovementioned examples do only refer to the interplay of myokines with the other mechanisms and do not comprehensively

reflect other possible complex interplays between all the described pathophysiological mechanisms.

### **Bidirectional Relationship: Brain and Muscle?**

Most of the studies in this review are cross-sectional studies. Longitudinal studies evaluating the pathophysiological mechanisms between muscle mass, and cognition as an outcome are scarce. The described pathophysiological mechanisms are not necessarily unidirectional and could be bidirectional, as cognition could influence skeletal muscle mass in a retrograde manner because similar associations were found between low muscle mass, muscle strength, and cognitive impairment and vice versa (113–115). The key take away from this review is that the described mechanisms may lead to a negative spiral, in which cognitive impairment may further exacerbate the loss in muscle mass and vice versa, and therefore, reverse causation cannot be excluded.

### **Future Perspectives**

Physical inactivity is a major risk factor for both sarcopenia and cognitive impairment, and most studies highlight the positive effects of physical activity on dementia and cognitive impairment (116,117). In general, physical exercise has a positive influence on cognitive function by increasing synaptic plasticity and the underlying systems that support neurogenesis (104). Various types of exercise affect different pathophysiological pathways; however, this is beyond the scope of this review. As shown by numerous observational studies, there is an inverse association between exposure to nonsteroidal anti-inflammatory drugs and risk of AD, whose effects may vary with the degree of cognitive decline (118,119). Clinical implications regarding myokines are that they cross the BBB and therefore may be a target for therapy as they influence the brain microenvironment. For instance, skeletal muscle produces irisin through cleavage of FNDC5 and then bound to its receptors on neurons, which stimulates expression of BDNF, enhancing cognition (65,120). In addition, the production of FNDC5 in the brain will be stimulated by exercise through PGC-1 $\alpha$  (in skeletal muscle), which also stimulates BDNF expression (105). Thus, exercise stimulates BDNF expression in the brain and preserves cognition via irisin-induced signaling mechanisms (120). Recognizing the underlying pathophysiological mechanisms of muscle mass with cognition is important to gain insight into dementia as well as into the development of targeted interventions. Therefore, future research should focus on longitudinal and interventional studies to evaluate the causality of the relationship between muscle mass and cognitive impairment and the interplay of the underlying mechanisms.

### **Conclusion**

There is substantial evidence supporting 4 pathophysiological mechanisms that may underlie the association between low muscle mass and cognitive impairment, that is, systemic inflammation, insulin, protein metabolism, and mitochondrial function. Low skeletal muscle mass and alterations in myokine secretion leading to inflammation and lower peripheral glucose storage due to low muscle mass are the mechanisms with the most evidence in the association with impaired cognition. However, it remains unclear if these mechanisms are directly or indirectly caused by skeletal muscle mass loss or if a bidirectional relationship exists. The underlying mechanisms of protein metabolism and mitochondrial function because of

low skeletal muscle mass needs further exploration in relation to cognition.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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## Conflict of Interest

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