Sarcopenia and Cognitive Function

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Sarcopenia is a geriatric syndrome characterized by the progressive degeneration of muscle mass and function. It is associated with cognitive impairment, defined as a decline in cognitive domains such as language, memory, reasoning, social cognition, planning, making decisions, and solving problems. Several studies have shown that skeletal muscle can regulate brain functions, including mood, learning, locomotor activity, and neuronal injury protection, showing the existence of muscle-brain crosstalk.

1. Sarcopenia

Sarcopenia is a common condition in older individuals, characterized by progressive muscle mass and function degeneration. It is associated with severe complications, including falls, functional decline, frailty, and mortality [1][2]. The prevalence of sarcopenia varies from 9.9% to 40.4%, depending on its definition [1]. Nowadays, there is no consensus on defining the cut-off points, making sarcopenia diagnosis challenging.

The pathogenesis of sarcopenia remains poor clear and involves an interplay between sedentary lifestyle, aging, obesity, inflammation, and oxidative stress that affect muscle mass and function [2].

A sedentary lifestyle, defined as activities that do not increase energy expenditure, impacts muscle mass and metabolism. Indeed, only seven days of decubitus resulted in a loss of muscle mass, and a prolonged period, 90–120 days, reduced 30% of the muscle volume [3][4]. Studies conducted on old immobilized animals have examined the effects of bed rest on skeletal muscle metabolism, demonstrating a disruption in the balance between protein synthesis and degradation in favor of catabolism [3][4].

Interestingly, aging alters both the homeostasis of skeletal muscle, compromising the equilibrium between cell regeneration and differentiation [5] and the rate of protein synthesis and degradation [6]. It is associated with reducing skeletal muscle stem cells (satellite cells) in type II fiber. Major pathways associated with changes in satellite cells during aging include Notch and Wnt signaling; the first is associated with proliferation while the second is differentiation of muscle cells [7]. Studies demonstrated that the expression of Notch signaling decreased with age during aging [8]. Wnt canonical pathway switched to the not canonical pathway resulting in the inability of satellite cells to self-renewal [9]. However, the hypothesis that loss of satellite cell activity is the cause of sarcopenia has been confuted. In male sedentary mice, the depletion of satellite cells, resulting in impaired muscle regeneration, did not contribute to muscle size or fiber type composition, despite low regenerative capacity, but contributed to age-related muscle fibrosis [10].

With advancing age, the intake of amino acids is inadequate, resulting in a decreased protein synthesis rate and the proteolysis system's inability (ubiquitination and lysosomal degradation) to remove oxidized proteins, inducing a progressive decline in skeletal muscle mass function [6][11].

Pathogenic inter-relationship between adipose tissue and muscle is also crucial in sarcopenia and contributes to functional and physiological impairment. Obesity is characterized by increased production of fatty acids (FAs) that are not only stored in adipose tissue (AT) but can outflow and accumulate ectopically in skeletal muscle [12]. FAs, in the form of triglycerides (TG), diacylglycerols (DAG), and ceramides, accumulate both in intermuscular adipose tissue (IMAT) as in intramyocellular lipids (IMCLs), inducing impaired single-fiber contractility via mitochondrial dysfunction, impaired β-oxidation of FAs, and increased reactive oxygen species (ROS) production, leading to lipotoxicity and insulin resistance (IR) [13][14].

These events' primary outcome is muscle fiber insufficiency with a decline in muscle mass and function [15]. Indeed, IMCLs attract immune cells, such as M1-type macrophages, mast cells, Th1, Th17, and other cells, that produce an array of pro-inflammatory cytokines [16][17][18][19]. Activated adipocytes produce pro-inflammatory adipokines, like leptin,

osteopontin, chemerin, and a lower expression of SIRT1 in the subcutaneous abdominal fat [20], creating a pro-inflammatory vicious circle providing local and systemic, chronic low-grade inflammation [21][22], which is also related to glucose metabolism derangement [23]. Furthermore, this unfavorable adipokines/cytokine profile increases IR and contributes to ectopic fat distribution [24].

2. Sarcopenia as a Risk Factor for Cognitive Decline

In the literature, it is well documented that sarcopenia increases the risk of cognitive decline [25]. Despite the contradictory results that could be due to different criteria and cut-off points to assess used sarcopenia components [26], a recent systemic review and meta-analysis demonstrated that the association between sarcopenia and cognitive impairment was independent of the study population, sarcopenia definition, and cognitive impairment degree (odds ratio 2.2, 95% CI 1.2–4.2) [27].

In particular, a cross-sectional study based on 3025 women aged 75 years and older demonstrated an association between muscle strength, a central component of sarcopenia, and cognitive function. Lower handgrip (HGS), used to measure muscle strength, was associated with cognitive impairment, measured by a short portable mental status questionnaire (SPMSQ) (OR 1.81 and 95% confidence interval: 1.33–2.46) [28][29]. Which cognitive domains are affected by muscle strength are poorly described. A cross-sectional study, conducted on 1799 participants aged more than 60 years old, demonstrated a higher digit symbol substitution test (DSST) score, used to measure visuospatial and motor speed was more significant in higher quadriceps strength groups indicating that muscle strength was associated with frontal lobe executive functions [29]. Another study of 555 participants, aged 85 years at baseline, suggested that HGS was associated with processing speed and memory function [30].

Even muscle mass is considered a predictor of cognitive decline, the link between muscle mass and cognitive impairment is not consistently documented [26].

Although the exact mechanisms involved have not yet been defined, risk factors may partially explain the association between cognitive decline and sarcopenia. Direct cross-talk between muscle and brain, mediated by exercise-induced myokines release, has been demonstrated [31][32]. Physical activity restores and maintains cognitive functions and metabolism [33][34] and ameliorates the process of neurological diseases [35], inducing muscle cells, metabolically active, to produce and release myokines. It was proposed that all factors released in response to exercise should be termed "exerkines" [36].

3. Role of Physical Exercise in Muscle and Brain Cross-Talk

Physical activity is a non-pharmacological intervention that ameliorates brain function [37]. It has been reported that exercise increases the volume and intensifies the prefrontal cortex's function, hippocampus, which are neuronal regions related to memory and cognition [38][39][40][41]. Studies conducted on people with AD, the most common form of dementia, have demonstrated that exercise can improve cognitive and physical function [42]. Moreover, activity was associated with a 30–40% reduction in the risk of developing AD than physically inactive individuals [43].

A longitudinal observational study demonstrated an association between physical activity and a lower likelihood of cognitive decline (RR 0.65, 95% CI 0.55–0.76) [44]. Similar results were obtained from another study that demonstrated that the group with cognitive impairment had more deficient performance gait speed test than the control group [45]. The exercise-induced improvement in cognitive function was also demonstrated in older adults. A meta-analytic study examined aerobic fitness effects on cognitive vitality of healthy but sedentary older adults. The study has indicated that physical activity impacts positively on cognition [46].

Physical exercise mediates the beneficial effects promoting cerebral angiogenesis, increasing neurogenesis and plasticity of the hippocampus, increasing cerebral blood flow, diminishing blood-brain barrier (BBB) permeability and function [47], and enhancing oxygen-rich blood delivery to the brain [48][49][50][51].

In skeletal muscle, physical exercise activates compensatory and adaptive mechanisms to obtain energy that can be reached via metabolic regulation or changes in gene expression [52]. Exercise regulates myokines' expression, contributing to autocrine regulation of metabolism in the muscle and paracrine/endocrine regulation of other adjacent/remote organs [37]. Studies conducted on exercise showed that physical activity, increasing circulating levels of myokines in the bloodstream, exert beneficial effects on the brain. The myokines regulate brain functions, including mood, learning, locomotor activity, and protecting neuronal injury in animal or in vitro models [36][37][50].

So, altered synthesis and production of myokines due to physical inactivity may be associated with adverse implications in the brain, such as cognitive impairment and neurogenerative events [53], showing that muscle may influence the brain's health (Figure 1).
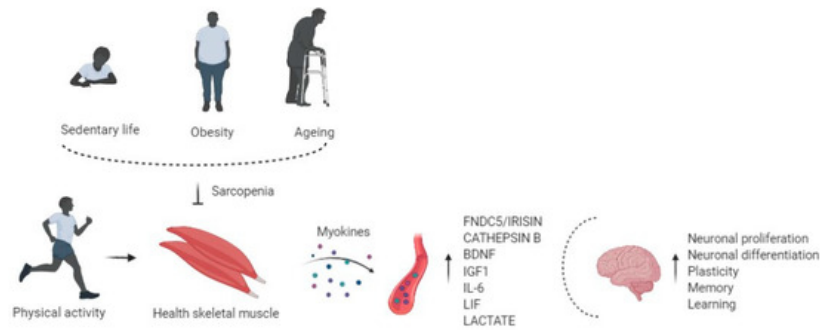

Figure 1. Physical activity enhances circulating levels of myokines in the bloodstream, affects the brain regulating neuronal proliferation and differentiation, plasticity, memory, and learning. Risk factors of sarcopenia, such as physical inactivity, obesity, and aging, alter the myokines' production and release, impairing cognitive function.

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