



A “NEUROMUSCULAR LOOK” TO SARCOPENIA: IS IT A ‘MOVEMENT DISORDER’?

Murat KARA, MD¹, Levent ÖZÇAKAR, MD¹, Bayram KAYMAK, MD¹, Ayşe Merve ATA, MD² and Walter FRONTERA, MD, PhD, FRCP³

From the ¹Department of Physical and Rehabilitation Medicine, Hacettepe University Medical School, Ankara, Turkey, ²Department of Physical and Rehabilitation Medicine, Doctor Ayten Bozkaya Spastic Children Hospital and Rehabilitation Center, Bursa, Turkey,

³Department of Physical Medicine, Rehabilitation, and Sports Medicine, Department of Physiology and Biophysics, University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Objective: Impairment of physical function is the main determinant of morbidity/mortality in sarcopenia and frailty. Physical function tests are performed by the movement around the joints, and skeletal muscles are the main generators of the forces required to perform these functional tasks. However, the central nervous system, which initiates and coordinates muscle movements, controls the magnitude and temporal parameters of muscle forces.

Methods: Non-systematic literature review was performed about the effects of aging on neuromotor control.

Result: The ability of a muscle to produce force by aging is deteriorated not only by muscle structural changes, but also by neuromotor control dysfunction. With aging, changes in muscle structure and loss of volumes in brain structures related with movement and cognition have been shown. Age-related cognitive impairment can have considerable negative effects on the force generating capacity of skeletal muscles. In this sense, the relationship has been found between hand grip strength, gait speed, and cognition.

Conclusion: Treatments targeting muscle mass only would be insufficient unless we address the impairment of neurocognitive functions. It is essential that prescribing life-long exercise is important for healthy aging including the preservation of muscle mass/strength, physical and cognitive functioning, and independent living.

Key words: sarcopenia; physical function; cognitive impairment.

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Correspondence address: Ayse Merve Ata, Doctor Ayten Bozkaya Spastic Children Hospital and Rehabilitation Center, Bursa, Turkey. E-mail: amerveata@hotmail.com

Impairment of physical function is the main determinant of morbidity and mortality in sarcopenia and frailty (1). This impairment has been attributed mainly to age-related quantitative/qualitative changes in skeletal muscles, which has been accepted as a criterion for the diagnosis of sarcopenia (2). In elderly people, correlations of strength and performance tests with morbidity and mortality are higher than correlations

LAY ABSTRACT

Decline of physical function is the main cause of morbidity and mortality in sarcopenia and frailty. Physical function tests are performed to show the daily functional tasks. The central nervous system initiates, coordinates and controls muscle movements. Thus, the ability of a muscle to produce force by aging is determined not only by skeletal muscle, but also by neuromotor control systems. Therefore, treatments should contain targeting muscle mass and also neurocognitive functions. In this regard, an example of a rehabilitation program that influences both muscle and brain function is exercise. Accordingly, it is essential that prescribing life-long exercise is important for healthy and independent aging including the preservation of muscle, physical and cognitive functions.

with measurements of muscle mass (3). This is true for 2 very frequently used measurements, such as hand grip strength and gait speed.

Tests of physical function are performed with appropriate stabilization and movement of the body segments around the joints. Skeletal muscles are the main generators of forces needed to execute these functional tasks. However, the magnitude and temporal parameters of muscle contraction are controlled by the central nervous system. Thus, the force-generating capacity of a muscle is determined not only by its structural features (i.e. muscle mass/quality), but also by the neuromotor control systems mediated by the central nervous system (3). With ageing, not only changes in muscle structure (i.e. loss of muscle mass/quality), but also loss of volume in brain structures related to movement (as well as cognition) are thought to be responsible for the decline in muscle function (Table I) (4, 5).

Age-associated cognitive impairment, which is the loss of intellectual functions, such as thinking, remembering, reasoning, and planning, with age, can have considerable negative effects on the force-generating capacity of skeletal muscles (6). These effects may be mediated by the negative influence of impaired cognition on neuromotor control. There is now substantial evidence to suggest an association among hand grip strength, gait speed, and cognition (6–8). For example, a recent meta-analysis including 9

Table I. Effects of ageing on volumes of major brain structures related to movement and cognition

Division	Structure	Substructure	Main function	% variance in volume by age (4)	Main finding with ageing (5)
Cerebrum	Cerebral cortex	Cortical motor areas (Brodmann's area 4 and area 6)	Plan and execute voluntary movement Play important roles in executive (prefrontal), cognitive (dorsolateral prefrontal) and emotional (orbital-ventromedial prefrontal) control of motor behaviour	32 (WM)	Reduced GM volume, especially in prefrontal and parietal cortices
		Primary sensory areas	Receive and process sensory input		
		Multimodal association areas	Integrate sensory and motor information		
		Basal ganglia	Regulate motor performance	18	
	Limbic system	Caudate nucleus		46	Putamen is affected more (linearly) than caudate nuclei (non-linearly)
		Putamen		28	Affected linearly
		Globus pallidus		33	Affected nonlinearly
	Diencephalon	Hippocampus	A critical role in long-term episodic memory	29	Likely affected (linearly)
		Amygdaloid nuclei	Coordinate emotional responses	37	Affected linearly
	Thalamus		Processes most of the subcortical input projecting to cerebral cortex		
	Cerebellum		Plays role in cognitive functions, such as memory and attention		
			Modulates forces and range of movement	25 (cortex)	
			Stores memory for unconscious motor skills	14 (WM)	GM is affected linearly, while WM declines non-linearly
	Brainstem	Midbrain, pons, medulla oblongata, reticular formation	Coordinates movement Receive sensory information from the head and provide its motor control Convey information between the spinal cord and brain	5	Probably the best-preserved brain structure
	Spinal cord	Ascending tracts (somatic sensory) Descending tracts (somatic motor)	Regulate levels of arousal and awareness Receive and process sensory information from the trunk and limbs, and control movement of trunk and limbs	N/A	N/A

WM: white matter; GM: grey matter; N/A: not applicable.

longitudinal studies in older adults showed a positive correlation (overall $r=0.55$) between changes in hand grip strength and changes in cognitive function (6). Similarly, other longitudinal studies in older adults have shown that both low hand grip strength and slow gait speed at baseline predict future cognitive decline (9, 10). Furthermore, systematic reviews have shown that hand grip strength is positively associated with global cognition and some cognitive subdomains, including episodic memory, visuospatial ability and working memory (11). Finally, hand grip strength changes were more strongly related to mental state (which declines much later), whereas gait speed changes were more strongly related to changes in fluid cognition (which declines as early as midlife) (12).

All of the above strongly suggest that, during the ageing process, muscle structure and function as well as cognitive ability decrease, and that age-related declines in grip strength and gait speed occur simultaneously with both loss of muscle mass/quality and cognitive impairment. Evidence of this is the fact that the force produced during a maximum voluntary grip strength task is approximately half of what would be expected if the skeletal muscles were fully activated by the nervous system, probably due to impaired muscle activation by the central nervous system (13, 14). Furthermore, it was found that gait speed slows not only in musculoskeletal, but also in peripheral/

central nervous system diseases. Walking requires motor coordination, strength and balance, which are regulated by the cerebellum in connection with the cortical associative areas (supporting higher mental function), including the prefrontal cortex, which regulates several aspects of fluid cognition. Since grip strength and gait speed are associated with tasks that require higher neurocognitive processes, these measurements and impairments may also reflect the general health of higher brain functions and the decline in brain health associated with advanced adult age (15, 16).

The association in age-related decline in physical and cognitive functions may be mediated by 1 of 3 mechanisms (6, 11): (i) impaired physical function directly affects cognitive function; (ii) cognitive function directly results in impaired physical function; or (iii) a third factor simultaneously affects decline in both physical and cognitive performance. A “common cause” suggests the presence of an underlying mechanism that drives the association between physical and cognitive functions and the simultaneous presence of both impairments. The “common cause hypothesis” stems predominantly from the evidence for a strong correlation between age-related declines in both physical and cognitive functions reported in cross-sectional studies, and rarely from within-subject changes in longitudinal studies (6, 11, 17). In this regard, a common cause of the ageing process can operate at different physiological levels (12).

Biological changes within the central nervous system, such as white matter hyperintensity, brain ageing, shrinking of the hippocampus, smaller cortical surface area, more cortical thinning, and mitochondrial abnormalities within nerve cells, dopaminergic down-regulation, inadequate motor programming/coordination have been put forward as possible underlying mechanisms (8, 13, 18). It should be noted that these mechanisms are not mutually exclusive and may, in fact, work simultaneously. Authors of a recent review have argued that age-related mobility limitations are due to, in large part, to degradations in the central neural control of mobility. While relatively few studies have investigated the role of motor control of basal ganglia and its dopaminergic neurone function in age-related immobility, there is a strong theoretical basis to support such a role (19).

Based on the evidence, the investigation of sarcopenia and its associated functional decline should focus not only on skeletal muscle, but perhaps more importantly on the neuromuscular system including the central nervous system. Treatments targeting skeletal muscle mass only (e.g. nutritional supplementations, myostatin-inhibitors) would be insufficient unless we address the impairment of neurocognitive functions (e.g. with vitamin D, vitamin B12, antidepressants, and possibly dopamine agonists). Herein, a noteworthy example of a rehabilitation intervention that influences both muscle and brain functions would be exercise, i.e. physical activity, which is usually regular and performed to improve or maintain fitness and health (20, 21). Thus, it is reasonable to conclude that prescribing exercise is important for healthy ageing, i.e. preservation of muscle mass/strength, physical and cognitive functioning, and independent living (6, 22). Further longitudinal studies are necessary to better understand the role of central nervous system in age-related loss of muscle mass and function (12).

REFERENCES

- Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. *Front Aging Neurosci* 2014; 6: 192.
- Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederaholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; 48: 16–31.
- Clark BC. Neuromuscular changes with aging and sarcopenia. *J Frailty Aging* 2019; 8: 7–9.
- Fjell AM, Westlye LT, Amlie I, Espeseth T, Reinvang I, Raz N, et al. Minute effects of sex on the aging brain: a multi-sample magnetic resonance imaging study of healthy aging and Alzheimer's disease. *J Neurosci* 2009; 29: 774–783.
- Fjell AM, Walhovd KB. Structural brain changes in aging: courses, causes and cognitive consequences. *Rev Neurosci* 2010; 21: 187–221.
- Zammit AR, Piccinin AM, Duggan EC, Koval A, Clouston S, Robitaille A, et al. A coordinated multi-study analysis of the longitudinal association between hand grip strength and cognitive function in older adults. *J Gerontol B Psychol Sci Soc Sci* 2019 Jun II. pii: gbz072. [Epub ahead of print].
- Kobayashi-Cuya KE, Sakurai R, Suzuki H, Ogawa S, Takebayashi T, Fujiwara Y. Observational evidence of the association between hand grip strength, hand dexterity, and cognitive performance in community-dwelling older adults: a systematic review. *J Epidemiol* 2018; 28: 373–381.
- Rasmussen LJH, Caspi A, Ambler A, Broadbent JM, Cohen HJ, d'Arbeloff T, et al. Association of neurocognitive and physical function with gait speed in midlife. *JAMA Netw Open* 2019; 2: e1913123.
- Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline - a four-year prospective study in 2737 cognitively normal older adults. *J Nutr Health Aging* 2011; 15: 690–694.
- Chou MY, Nishita Y, Nakagawa T, Tange C, Tomida M, Shimokata H, et al. Role of gait speed and grip strength in predicting 10-year cognitive decline among community-dwelling older people. *BMC Geriatr* 2019; 19: 186.
- Zammit AR, Robitaille A, Piccinin AM, Muniz-Terrera G, Hofer SM. Associations between aging-related changes in grip strength and cognitive function in older adults: a systematic review. *J Gerontol A Biol Sci Med Sci* 2019; 74: 519–527.
- Clouston SA, Brewster P, Kuh D, Richards M, Cooper R, Hardy R, et al. The dynamic relationship between physical function and cognition in longitudinal aging cohorts. *Epidemiol Rev* 2013; 35: 33–50.
- Kwon YN, Yoon SS. Sarcopenia: neurological point of view. *J Bone Metab* 2017; 24: 83–89.
- McGrath R, Erlandson KM, Vincent BM, Hackney KJ, Hermann SD, Clark BC. Decreased hand grip strength is associated with impairments in each autonomous living task for aging adults in the United States. *J Frailty Aging* 2019; 8: 141–145.
- Carson RG. Get a grip: individual variations in grip strength are a marker of brain health. *Neurobiol Aging* 2018; 71: 189–222.
- Poole VN, Lo OY, Wooten T, Illoputaife I, Lipsitz LA, Esterman M. Motor-cognitive neural network communication underlies walking speed in community-dwelling older adults. *Front Aging Neurosci* 2019; 11: 159.
- Christensen H, Mackinnon A, Korten A, Jorm AF. The "common cause hypothesis" of cognitive aging: evidence for not only a common factor but also specific associations of age with vision and grip strength in a cross-sectional analysis. *Psychol Aging* 2001; 16: 588–599.
- Rygiel KA, Picard M, Turnbull DM. The ageing neuromuscular system and sarcopenia: a mitochondrial perspective. *J Physiol* 2016; 594: 4499–4512.
- Clark BC, Woods AJ, Clark LA, Criss CR, Shadmehr R, Grooms DR. The aging brain & the dorsal basal ganglia: implications for age-related limitations of mobility. *Adv Geriatr Med Res* 2019; 1. pii: e190008.
- Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. *Hum Brain Mapp* 2013; 34: 2972–2985.
- Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* 2015; 4: CD005381.
- Özçakar L, Ata AM, Quittan M, Michail X. A 'musculoskeletal look' to sarcopenia: Where do/should the physical and rehabilitation medicine physicians (physiatrists) stand? *Int J Rehabil Res* 2018; 41: 95–96.