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Editorial

"May the Force (and Size) Be with You": Muscle Mass and Function Are Important Risk Factors for Cognitive Decline and Dementia

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Dementia is a major public health priority. Global prevalence indicates that over 55 million people worldwide are living with dementia, with projections showing that this number will reach ~140 million by 2050 (1). According to the 2020 report of the Lancet Commission (1), up to 40% of dementia cases are attributable to modifiable risk factors. Bearing in mind the current lack of medications that can effectively prevent or reverse cognitive decline, it is critical to identify modifiable risk-factors for cognitive decline.

Sarcopenia is a condition characterized by a progressive and generalized loss of muscle mass and function (2). Epidemiological studies suggest that this condition may affect ~13% of adults 65 and older, and is substantially more prevalent in those aged >75 years and institutionalized older adults (3). Sarcopenia is associated with increased risk of morbidity, functional impairment, and mortality (3, 4). Of relevance, sarcopenia is associated with cognitive decline (5-9), whereby sarcopenia markers, such as weak grip strength and slow gait speed, are predictors of cognitive function and dementia (10, 11).

The putative biological mechanisms by which sarcopenia is associated with cognitive decline are not completely understood. The skeletal muscle is recognized as an important endocrine organ releases myokines (e.g., brain-derived neurotrophic factor and interleukins) when it contracts (12). Myokines have pleiotropic effects and play a significant role in multi-organ physiology and regulation, including brain tissue (12). Loss of muscle mass and function (e.g., muscle weakness, mobility impairment) are also associated with higher levels of inflammatory and oxidative stress, and vascular issues (e.g., microvascular dysfunction) (13-15)– each of which are associated with cognitive decline (16, 17). Briefly, reduced mobility due to sarcopenia can potentially contribute to reduced physical activity levels and social participation (18). Low physical activity and social isolation are each important risk factors for cognitive decline (18-20).

In this month's issue of the JNHA, we highlight two studies that show sarcopenia as a marker of cognitive decline and dementia. Firstly, Uchida and colleagues (21) examined the longitudinal associations of DXA-related body composition measures with cognitive performance among 515 community-dwelling older adults using data from the Japanese National Institute for Longevity Sciences – Longitudinal Study of Aging. They found sex differences in the relationship between changes in body composition and changes in cognitive function over a 4-year period. Specifically, males who exhibited higher declines in muscle mass over a 4-year period experienced significantly greater declines in global cognitive function compared with their male peers with maintained mass. This association was not observed among females.

The second paper by Li and colleagues (22) examined the associations of sarcopenia using SARC-F questionnaire – a established screening tool to identify people at risk for sarcopenia – or subjective memory complaints with the incidence of dementia during a 3-year follow-up using data from a population-based cohort of 2163 cognitively unimpaired older adults from Taiwan. In the adjusted analysis, compared with participants without sarcopenia or signs of subjective memory complaints, those with sarcopenia had a 2.4 times greater risk of incident dementia; participants with both sarcopenia and subjective memory complaints had a 2.49 times greater risk of incident dementia.

Several key gaps and questions remain about how muscle health impacts cognitive health. First, longer follow-up periods are needed to determine the time-course by which sarcopenia may impact cognitive health. Second, evidence seems to be leaning towards strength as being more critical than muscle mass in relation to cognitive health (23). In this sense, researchers should explore whether changes in muscle mass are related with cognitive declines, independently of muscle strength. Third, more studies are needed to advance our understanding of potential sex differences in the relationship between sarcopenia and cognitive outcomes. The prevalence of sarcopenia is higher among males compared with females (24) while females have a higher incidence of dementia compared with males (25). Biological (e.g., longevity, presence of hormonal and/or genetic variants such as APOE-e4), social (e.g., education attainment) and behavioral correlates (e.g., occupation and influence of multimorbidity and other health indicators) are potential factors that might help understand the link between sarcopenia and cognitive health among sexes (25). Future studies are needed to elucidate these potential relationships. Fourth, there are limitations to the current methods used to index muscle mass, particularly Dual-energy

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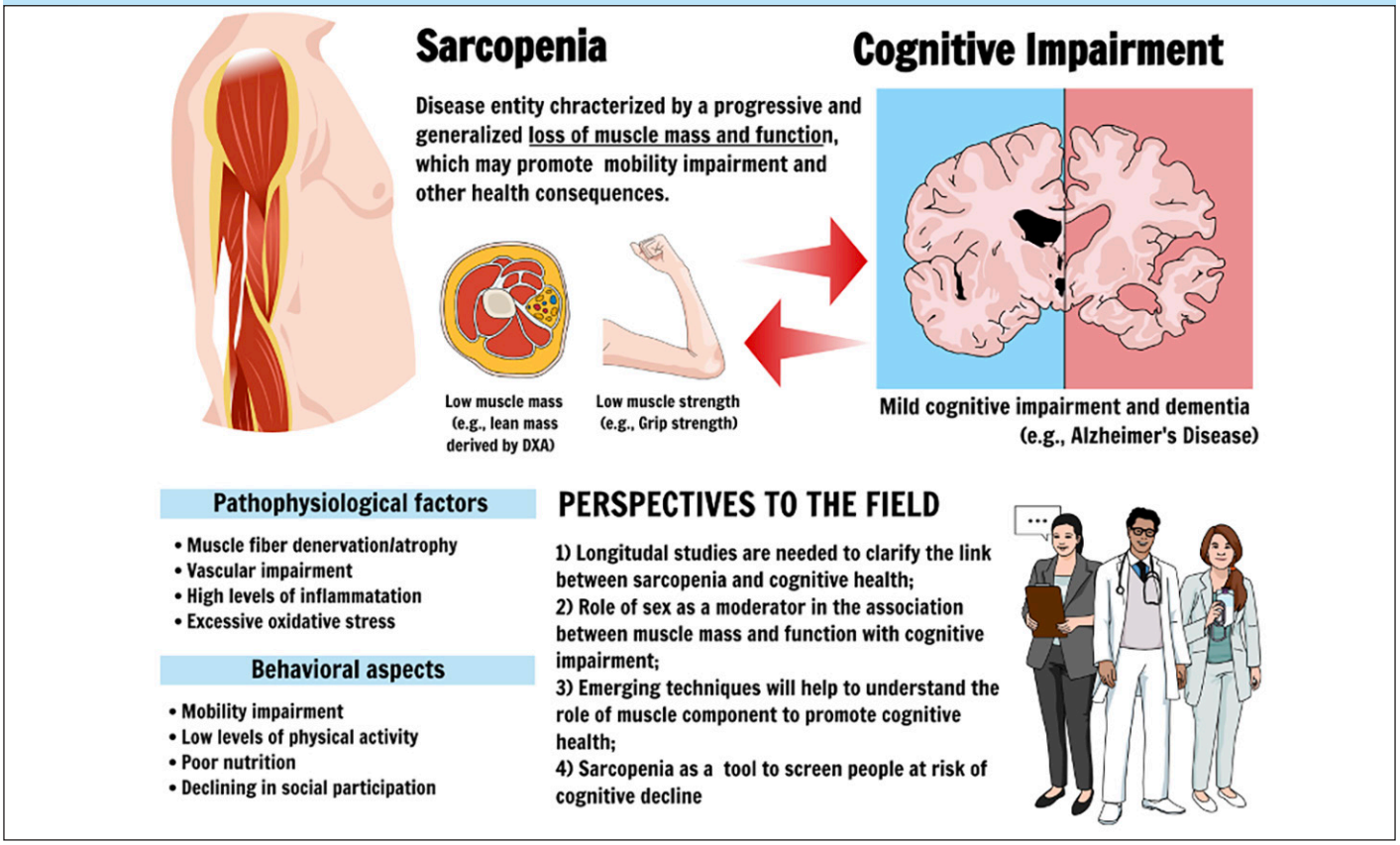
Figure 1. Shared mechanisms in the relationship between sarcopenia and cognitive impairment (Created with mindthegraph.com)



X-ray absorptiometry (DXA). DXA-derived measures allow to estimate appendicular lean soft tissue (ALST). ALST encompass components beyond muscle mass including water, fibrotic and connective tissues. As we age, the fraction of those components is higher, which may impair the "true" muscle mass estimation. There is some debate about the accuracy of DXA since it does not preclude other muscle composition elements which may play a significant role in the relationship between sarcopenia and other health outcomes. (26) Future studies should consider alternative techniques (e.g., Imaging derived measures such as CT- and MRI-scan; as well as D3-creatine dilution tests) to precisely comprehend the influence of muscle mass on cognitive health. Last, but not least, more studies should examine the role of sarcopenia as a screening tool for identify cognitive decline among older adults.

In summary, the findings from these studies provide new and important evidence about how sarcopenia is associated with cognitive decline. Clinicians and other health care specialists should consider adopting screening assessments that embrace sarcopenia phenotype (e.g., muscle mass and function) into their clinical routine. Further studies examining the effects of therapeutics (e.g., drugs and behavioral interventions including exercise and nutrition) to mitigate or reverse loss of muscle mass and function on cognitive and brain health are needed.

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