Archives of Gerontology and Geriatrics 75 (2018) 20–27

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Full Length Article

Association of nutrition and immune-endocrine dysfunction with muscle mass and performance in cognitively impaired older adults

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ARTICLE INFO

Keywords:
Sarcopenia
Cognitive impairment
Inflammation
Endocrine

ABSTRACT

Background: With lean mass declining early in Alzheimer's disease, muscle quality beyond quantity is relevant to physical performance. We sought to identify potentially modifiable factors for the differential loss of muscle mass (pre-sarcopenia) and its performance (sarcopenia) in older adults with mild cognitive impairment (MCI) and mild-to-moderate Alzheimer's disease (AD).

Methods: This is a cross-sectional study of 108 community-dwelling older adults with MCI and mild-to-moderate AD. Participants were categorized as: (i) No sarcopenia (normal muscle mass), (ii) Pre-sarcopenia (low muscle mass without weakness or slowness), (iii) Sarcopenia (low muscle mass AND weak grip strength and/or slow gait speed) using Asian cut-offs. Muscle quality was defined as the ratio of grip and knee extension strength to average arm and leg lean mass respectively. We measured cognitive, functional and physical (Short Physical Performance Battery, SPPB) performance; physical activity level; nutritional status; and blood biomarkers of inflammation and endocrine dysfunction.

Results: SPPB ($p = 0.033$) and activity level ($p = 0.010$) were highest in the pre-sarcopenic group. Pre-sarcopenic group had highest arm muscle quality [10.6 (7.7–12.2) vs 13.9 (12.6–15.7) vs 11.3 (9.7–12.8), $p < 0.001$], despite significantly lower appendicular lean mass than non-sarcopenic group. In multi-nomial logistic regression reference to non-sarcopenic group, malnutrition independently increased risk for both pre-sarcopenia (Relative risk = 7.53, 95% C.I 1.20–47.51, $p = 0.032$) and sarcopenia (Relative risk = 11.91, 95% C.I 2.85–49.77, $p = 0.001$). A combined pro-inflammatory and endocrine deficient state significantly increased the risk of sarcopenia (Relative risk = 5.17, 95% C.I 1.31–20.37, $p = 0.019$).

Conclusion: Malnutrition is a precursor for progressive loss of muscle mass, but a pro-inflammatory and endocrine deficient state may potentially aggravate decline in muscle quality to culminate in frank sarcopenia.

1. Introduction

Body composition changes with progressive weight loss have been observed in the earliest clinical stages of Alzheimer's disease (AD) and may precede onset of dementia, being driven predominantly by the loss of lean mass (Burns, Johnson, Watts, Swerdlow, & Brooks, 2010; Johnson, Wilkin, & Morris, 2006). Weight loss, along with declines in muscle mass and performance, feature amongst the major components of the physical frailty syndrome (Fried, Ferruci, Darer, Williamson, & Anderson, 2004) which has been recognized as a distinct entity associated with aggravated risk for adverse outcomes amongst cognitively impaired older adults (Bilotta et al., 2012; Ni Mhaolain et al., 2012; Oosterveld et al., 2014).

There is substantial overlap between the physical frailty phenotype and sarcopenia, which is widely operationalized as decreased muscle function accompanying the decline in muscle mass with advancing age, and spans a continuum through pre-sarcopenia (low muscle mass), sarcopenia (low muscle mass with low muscle strength or poor performance), and severe sarcopenia (low muscle mass with low muscle strength and poor performance) (Cruz-Jentoft et al., 2010). Indeed, sarcopenia may be considered the biological substrate for the development of physical frailty. There is, however, dissociation between the loss of muscle mass and that of muscle strength, with higher rate of decline in muscle strength and its greater impact on future disability relative to muscle mass (Visser et al., 2005; von Haehling, Morley, & Anker, 2010). In addition, muscle strength but not muscle mass

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https://doi.org/10.1016/j.archger.2017.11.008
Received 12 July 2017; Received in revised form 8 October 2017; Accepted 14 November 2017
Available online 16 November 2017

independently predicted mortality in older adults (Newman et al., 2006). This observed discrepancy between muscle mass and muscle strength has shifted attention towards muscle quality as a more clinically relevant determinant of physical performance in older adults (Barbat-Artigas, Rolland, Zamboni, & Aubertin-Leheudre, 2012).

The consequences of muscle mass and strength declines extend beyond physical limitations, having been linked to cognitive impairment and dementia (Nourhaehemi et al., 2002; Shin, Kim, Kim, Shin, & Yoon, 2002). Further, low muscle quality as represented by strength per unit muscle mass has been associated with poorer cognitive performance (Canon & Crimmins, 2011). The significant association between sarcopenia and cognitive impairment raises the possibility of shared common pathways (Chang, Hsu, Wu, Huang, & Han, 2016). Endocrine systems involved in muscle anabolism such as insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone sulphate (DHEAS) have also been implicated in age-related cognitive decline (Cruz-Jentoft et al., 2014; Landi et al., 2012; Maggio et al., 2012; Watanabe et al., 2005), while a chronic inflammatory state has been linked to both muscle catabolism and AD (Holmes et al., 2009; Schaap et al., 2009). Beyond their individual detrimental effects, the potential for additive effects of inflammation and endocrine dysregulations has also been suggested (Cappola et al., 2008).

The observed association of sarcopenia but not pre-sarcopenia with dual impairments in cognitive and physical performance may be especially pertinent in cognitively impaired older adults (Tolea & Galvin, 2015), and suggests sarcopenia as a risk factor for accelerating disease progression and disability. Compared with sarcopenic individuals who are less likely to transition out, the pre-sarcopenic state with its greater potential for reversibility offers an intervention target to avoid progression (Murphy et al., 2014). Little is known about risk factors that differentiate pre-sarcopenia from non-sarcopenia and sarcopenia states, although the inconsistent translation of gains in muscle mass to improvements in muscle strength raises the hypothesis for differential pathways underlying muscle mass and function (Schroddder et al., 2012). Thus, this study sought to identify potentially modifiable factors associated with the differential loss of muscle mass (pre-sarcopenia) and its performance (sarcopenia) in cognitively impaired older adults.

2. Methods

2.1. Study population

This is a cross-sectional analysis of community-dwelling older adults with mild cognitive impairment (MCI) and mild-moderate Alzheimer's dementia (AD) attending a tertiary Memory Clinic, Tan Tock Seng Hospital, Singapore. Informed written consent was obtained from the patient or legally acceptable representative where appropriate, and the study was approved by the Domain Specific Review Board (DSRB) of the National Healthcare Group (NHG).

2.1.1. Diagnostic categories

MCI was defined as follows: (1) global Clinical Dementia Rating (CDR) (Morris, 1993) score of 0.5; (2) presence of subjective memory complaint which was corroborated by a reliable informant; (3) delayed recall > 1 SD below the age and education-adjusted means of healthy community-dwelling subjects derived from an earlier normative study (Sahadevan, Lim, Tan, & Chan, 2002); (4) relatively normal general cognitive function, defined as a score ≥ 21 for subjects with ≤ 6 years education and ≥ 24 for those with > 6 years of education on the locally validated modified Chinese version of Mini Mental State Examination (CMMSE) (Sahadevan, Lim, Tan, & Chan, 2000), (5) largely intact activities of daily living; and (6) no clinical dementia.

Mild-moderate AD subjects fulfilled National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for *probable AD* (McKhann et al., 1984), with global CDR of 0.5, 1 or 2, corresponding to very mild, mild or moderate dementia respectively. We excluded subjects with a diagnosis of *possible AD* in view of the confounding co-morbid diagnoses and differing clinical course in these individuals.

2.1.2. Eligibility criteria

Subjects were eligible if they were aged > 55 years, with a diagnosis of MCI or mild to moderate AD at baseline, community-dwelling, and accompanied by a reliable informant.

We excluded subjects with presence of other central nervous conditions (stroke disease, Parkinson's disease, subdural hematoma, normal pressure hydrocephalus, and brain tumor); presence of systemic conditions that can contribute to cognitive impairment (hypothyroidism, B12 deficiency, and hypercalcaemia); and presence of any active neuropsychiatric conditions producing disability. Subjects living in a sheltered or nursing home were also excluded.

The validity of the overall cognitive evaluation process and CDR scoring has been previously established (Chong and Sahadevan, 2003; Lim, Chin, Lam, Lim, & Sahadevan, 2005). Laboratory investigations to exclude potentially reversible causes of dementia via blood tests and neuroimaging were done. A multidisciplinary consensus meeting was conducted to review all relevant results for accurate clinical phenotyping of the cognitive disorder (*MCI* or *mild-moderate probable AD*). Patients meeting study eligibility criteria were then recruited.

2.2. Measures

2.2.1. Sarcopenia assessment and muscle quality

Grip strength was measured using the hydraulic hand dynamometer (North Coast@ Hydraulic Hand Dynamometer), with two trials of grip strength for each hand and all 4 trials averaged to yield strength. Knee extensor muscle strength of each leg was measured twice using an electronic dynamometer (BASELINE PUSHPULL Dynamometer), with the participant seated at the edge of a chair and maintaining the trunk in the upright position. The average of the 4 readings provided a measure of knee extension strength. Gait speed was based on the time to walk 3m.

Percentage body fat and lean mass measures were obtained via a dual-energy X-ray absorptiometry system (Discovery™ APEX 13.3; Hologic, Bedford, MA, USA). Appendicular skeletal mass was derived from the summation of muscle mass measurements in the four limbs.

We adopted the European Working Group on Sarcopenia in Older People (EWGSOP) consensus criteria (Cruz-Jentoft et al., 2010), but employing Asian gender-specific cut-off values for muscle mass, grip strength and gait speed (Chen et al., 2014), to delineate 3 groups: (i) No sarcopenia (normal muscle mass), (ii) Pre-sarcopenia (low muscle mass without impact on muscle strength or gait speed), (iii) Sarcopenia (low muscle mass AND weak grip strength and/or slow gait speed).

A measure of muscle quality was derived for each individual from the ratio of grip and knee extension strength to average arm and leg lean mass respectively.

2.2.2. Cognitive assessment

We used the CDR (Morris, 1993), a structured clinician rating, to determine dementia severity. The CDR is a global dementia rating scale and ratings in each of the six domains can be summed for a CDR sum-of-boxes (CDR-SB) score (range 0–18). The attending geriatrician, trained in administration of the CDR, rated each patient's CDR at baseline.

Cognitive performance was assessed using the locally-validated modified Chinese version of Mini-Mental State Examination (CMMSE), and MCI subjects also underwent a neuropsychological assessment (Sahadevan et al., 2000).

2.2.3. Other clinical co-variates

Demographic data and co-morbid vascular risk factors – hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, peripheral