Frailty and Sarcopenia in Older Adults

Potential for Nutrition and Exercise Strategies to Counteract Disabling Conditions

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Frailty is a common and important geriatric syndrome characterised by age-associated declines in physiologic reserve and function across multiorgan systems, leading to increased vulnerability for adverse health outcomes including falls, incident disability, hospitalisation and mortality.[1, 2] Frailty has been operationally defined by Fried *et al.* as meeting three out of five phenotypic criteria indicating compromised energetics: low handgrip strength, low energy, slowed walking speed, low physical activity, and/or unintentional weight loss.[1] Loss of muscle mass and function (sarcopenia) and malnutrition are key components of the frailty cycle.[1] Many alterations in metabolism and body composition occur as part of normal ageing but can become significant and pathological. It is known that total energy expenditure (TEE) reduces with ageing.[3, 4] Specific components of TEE such as basal metabolic rate (BMR), resting metabolic rate (RMR) and activity energy expenditure (AEE) reduce with ageing.[3, 4] Indeed, these reductions in energy expenditure (EE) are the hallmarks of physical frailty, and research has shown that individuals with frailty have reduced EE, reduced RMR, measured using indirect calorimetry and reduced TEE and AEE measured by doubly labelled water.[5, 6]

The reductions in BMR, RMR, AEE and overall TEE are largely due to alterations in body composition with ageing, i.e., there is a significant reduction in skeletal muscle mass (SMM) and fat free mass (FFM) compartments.[7, 8] SMM is critical for physical function and physical activity, and is a metabolically active tissue (increasing EE), with a dual functional role acting as labile source of amino acids that can be partitioned into different pathways during nutrient deprivation (e.g. gluconeogenesis) and immuno-inflammatory stress (e.g. acute phase protein production).[9] A key factor known to influence the loss of lean mass and is a risk factor for the development of malnutrition, sarcopenia and frailty is a loss of appetite (and reduction in food intake), or the 'anorexia of ageing'.[3, 10] This is thought to be due to physiological changes which occur with ageing such as alterations in taste and smell, appetite hormones (e.g. leptin and ghrelin), and a range of other factors such as effects of disease, medications, physical factors and social factors.[3, 10] Other factors known to influence the loss of lean mass include age-related changes in hormones (e.g. reduction in sex hormones and growth hormone - insulin-like growth factor (GH-IGF) axis activities), physical inactivity and inflammation (due to effects of illness, ageing, obesity, etc).[11]

Ultimately, the loss of SMM with ageing and chronic disease is intimately linked to poor clinical outcomes, which includes reduced functional performance, falls risk, physical disability, morbidity and mortality.[11, 12] This is termed 'sarcopenia' and is a major component of the physical frailty phenotype. Sarcopenia is now recognised as an independent condition with an International Classification of Diseases (ICD-10) code.[13] It has been currently defined as *"a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality"*.[12]

The importance of being able to easily screen for sarcopenia in all settings (hospital, care home, community, GP clinic) is a key and current issue. Suggested methods for screening include hand grip strength assessment, which is easy to perform, portable, cheap and non-invasive.[12] Another tool is the SARC-F screening questionnaire developed by Malmstrom and Morley.[14] The SARC-F has recently been used alongside the 'MUST' as a remote screening tool (R-MAPP) for sarcopenia and malnutrition in patients during the COVID-19 pandemic.[15] Other techniques for measuring lean mass and SMM include anthropometry (e.g. calf circumference), bioelectrical impedance assessment (BIA) and scanning techniques such dual-energy x-ray absorptiometry (DEXA), computed tomography (CT) and magnetic resonance imaging (MRI). Each technique has its pros and cons (e.g., accuracy, portability, cost, radiation exposure etc), and as the most important component of sarcopenia is physical function (as it closely relates to disability risk), having simple tools is key to practical screening.[12]

Nutrition

Nutrition is key to modulating risk of developing frailty and sarcopenia and may play an important role in treatment. As mentioned above one of the main issues with ageing and disease is a reduction in food, energy and protein intake. Higher energy intake has been shown to reduce odds risk of developing frailty in the recent Rotterdam study.[16] Overall diet quality has also been found to affect risk of frailty development.[17] Many recent studies have shown that adherence to a Mediterranean diet may reduce risk of frailty.[18-20] A Spanish study found that overall protein, animal protein and mono-unsaturated fat (MUFA) intake was associated with reduced frailty in older adults.[21] In particular, protein intake has been highlighted as an important factor in preserving skeletal muscle mass and function in older people. Recommendations have been developed and guided by expert consensus papers from the PROT-AGE study group and ESPEN.[22, 23] Both groups recommend 1.0-1.2 g/kg/body weight (BW)/day for healthy older people and for those with acute and chronic disease, 1.2-1.5 g/kg/BW/day. These updated recommendations were based upon a wealth of research indicating that ageing and disease has a detrimental effect on skeletal muscle. During ageing there is a reduced propensity to stimulate muscle protein synthesis with protein intake, termed 'anabolic resistance'.[24] Evidence shows that it may be possible to overcome this using higher doses of essential amino acids (EAAs).[22-24] These key papers cited also discuss the potential synergy between protein intake and effects of exercise (e.g., resistance training). One key aspect open to debate is the intake pattern of protein throughout the day. For example, protein spread feeding (evenly spreading protein intake throughout the day, e.g. 3-4 meals with ~20-30 g of protein per meal) has been suggested to be more anabolic, whereas protein pulse feeding (consuming ~70% of daily protein in one meal) may lead to greater whole-body anabolism.[25-27] Other recent studies have confirmed that consuming higher amounts of protein in one meal may be more anabolic.[28] More research needs to be performed to confirm which is the best approach. In terms of meal planning for older person it makes more sense to spread protein intake out throughout the day.

Other nutrients that may have a beneficial effect on SMM and function include vitamin D, the leucine metabolite β-hydroxy-β-methylbutyrate (HMB) and fish oils/omega-3 fatty acids. Older people are at risk of vitamin D deficiency due to reduced UV exposure and skin metabolism, and intake. A recent systematic review and meta-analysis of studies highlighted that low vitamin D (serum 25-hydroxyvitamin D levels) is associated with increased risk of frailty.[29] Papers have also discussed the relationship between vitamin D and risk of development of sarcopenia and treatment.[30] At present, research suggests that vitamin D has a positive effect on muscle, however, there is some controversy in study outcomes. HMB has been shown to have effective anabolic and anti-catabolic properties improving lean mass and function.[31] For example, in a 10-day bed rest study, HMB supplementation helped to preserve muscle mass in older participants.[32] Omega-3 fatty acids have also been shown to have some beneficial effects, e.g., on muscle mass and function. They have significant anti-inflammatory effects (e.g. reducing catabolic pro-inflammatory cytokines) and may have a positive effect on insulin sensitivity and muscle protein synthesis.[33] A recent systematic review and meta-analysis of studies showed that they have positive effects, although noted that larger trials are needed.[34] These specific nutrients should be considered alongside changes to overall diet, protein and energy intake, and physical activity, as they may have a synergistic effect with other nutrients.

Physical activity and exercise

It is known that frailty is associated with reduced AEE/physical activity (PA) and increased sedentary behaviour.[5, 35] A recent systematic review and meta-analysis of studies (112 studies; n = 43,796 individual participants) investigated the relationship between PA, sedentary behaviour and skeletal muscle strength and power in older adults.[36] It was found that higher PA and lower sedentary behaviour was associated with better muscle strength, in particular, with lower body strength, e.g., chair stand test. In particular, moderate-to-vigorous PA is highlighted to be of benefit. A recent Swedish study (n = 3,334 older adults of 70 years of age) noticed a significant relationship between the amount of moderate-to-vigorous PA completed and reduced risks of sarcopenia.[37] Landi *et al.* studied PA in the 'Longevity check-up 7+' (Lookup 7+) project in Italy, involving 6,242 participants, mean age 54.4 +/- 15.2 (range 18-98 years).[38] They showed a particular relationship between PA and chair stand performance (time taken to complete 5 repetitions), with sedentary individuals taking significantly longer to complete the test than those who were physically active. In particular, they showed that those who engaged in resistance training and combined resistance training + aerobic exercise, were faster than those who engaged in light PA walking. A recent systematic review and meta-analysis of studies was performed by Talar *et al.* investigating the effects of resistance training in frailty and sarcopenia (25 studies with 2,267 participants).[39] Resistance training was found to be highly effective in both early and late stages of frailty and sarcopenia.

Resistance training significantly improved hand grip strength, lower-limb strength, agility, gait speed, postural stability, functional performance and muscle mass in older adults. Resistance training can be practically undertaken in a safe and effective manner in older adults, for example, using some basic weight bearing and resistance band type activities. However, the inclusion of moderate-to-vigorous PA is noted with some caution as it may be more difficult to perform in individuals with reduced physical function and certain clinical conditions. One alternative being investigated in the field is sedentary behaviour fragmentation, whereby periods of sedentary behaviours (e.g., sitting and watching TV) are broken up with short periods of light PA. A recent study looked at using a sedentary behaviour fragmentation protocol (2 minutes of light PA per every 30 minutes of sedentary behaviour) and comparing it to 45-50 minutes of continuous daily light PA in 28 older women (age 73±5 years).[40] This was very interesting as both protocols had a significant beneficial effect on physical function, however, there was a greater effect using the sedentary behaviour fragmentation for handgrip strength. This paper was written in the context of the COVID-19 pandemic and associated lockdowns. Indeed, research has shown that pandemic had a particular negative impact upon PA levels, reducing overall PA and increasing sedentary behaviour time. This was recently summarised in a systematic review of studies (66 articles and 86,981 participants).[41] In the UK, Public Health England published a survey which showed that older adults performed less PA and muscle-strengthening activities in early-mid 2020.[42]

In addition to the beneficial effects of exercise alone, there is some suggestion of a potential synergy of exercise (e.g., resistance training) with nutrition.[43] Exercise has a number of beneficial effects on skeletal muscle such as improving blood flow, insulin sensitivity, mitochondrial function, growth factor release and satellite cell activation, stimulation of protein synthesis via mTOR activation and others.[43] This in turn may lead to muscle hypertrophy and enhanced strength and function. This may have potential synergy with protein and energy intake and be beneficial in frailty and sarcopenia. More controlled trials will need to be performed to fully establish this relationship.

Conclusions

Frailty and sarcopenia are leading causes of disability in older people. The ability to accurately screen for sarcopenia and physical frailty in routine clinical practice is of paramount importance. Use of simple, non-invasive, inexpensive and portable methods is recommended which can be used in all settings (e.g., hospital, care home, GP clinic, community and remote). Nutrition is of particular importance for prevention and treatment with focus on energy and protein intake, and diet quality (and Mediterranean type diets). Physical activity and exercise may also play an important role and may have synergistic effects with nutritional intake, although more research needs to be performed to confirm with certainty.

"Recent studies have shown a significant relationship between the amount of moderate-to-vigorous physical activity completed and reduced risks of sarcopenia."

References: **1.** Fried LP, et al (2001). Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci.; 56(3): M145-156. **2.** Chen X, et al. (2014). Frailty syndrome: an overview. Clin Interv Aging.; 9: 433-441. **3.** Roberts SB, & Rosenberg I. (2006). Nutrition and aging: changes in the regulation of energy metabolism with aging. Physiol Rev.; 86: 651-667. **4.** Manini, TM. (2010). Energy expenditure and aging. Ageing Res Rev.; 9(1): 1. **5.** Bastone A, et al. (2019). Energy Expenditure in Older Adults Who Are Frail: A Doubly Labeled Water Study. J Geriatr Phys Ther.; 42(3): 135-141. **6.** Abizanda P, et al. (2016). Energetics of Aging and Frailty: The FRADEA Study. J Gerontol A Biol Sci Med Sci.; 71(6): 787-796. **7.** Janssen I, et al. (2000). Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol.; 89(1): 81-88. **8.** Gallagher D, et al. (1997). Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. J Appl Physiol.; 83(1): 229-239. **9.** Wolfe, RR. (2006). The underappreciated role of muscle in health and disease. Am J Clin Nutr.; 84(3): 475-482. **10.** Landi F, et al. (2016). Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments. Nutrients.; 8: 69-72. **11.** Biolo G, et al. (2014). Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr.; 33(5): 737-748. **12.** Cruz-Jentoft AJ, et al. (2019). Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing.; 48(1): 16-31. **13.** Cao L, Morley JE. (2016). Sarcopenia Is Recognized as an Independent Condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code. J Am Med Dir Assoc.; 17(8): 675-677. **14.** Malmstrom TK, Morley JE. (2013). SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc.; 14(8): 531-532. **15.** Krznarić Ž, et al. (2020). A simple remote nutritional screening tool and practical guidance for nutritional care in primary practice during the COVID-19 pandemic. Clin Nutr.; 39: 1983-1987. **16.** Schoufour JD, et al. (2019). The association between dietary protein intake, energy intake and physical frailty: results from the Rotterdam Study. Br J Nutr.; 121(4): 393-401. **17.** Hengeveld LM, et al. (2019). Prospective Associations of Diet Quality With Incident Frailty in Older Adults: The Health, Aging, and Body Composition Study. J Am Geriatr Soc.; 67(9): 1835-1842. **18.** Ntanasi E, et al. (2018). Adherence to Mediterranean Diet and Frailty. J Am Med Dir Assoc.; 19(4): 315-322. **19.** Ghosh TS, et al. (2020). Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut.; 69(7): 1218-1228. **20.** Veronese N, et al. (2018). Adherence to a Mediterranean diet is associated with lower incidence of frailty: A longitudinal cohort study. Clin Nutr.; 37(5): 1492-1497. **21.** Sandoval-Insausti H, et al. (2016). Macronutrients Intake and Incident Frailty in Older Adults: A Prospective Cohort Study. J Gerontol A Biol Sci Med Sci.; 71(10): 1329-1334. **22.** Bauer J, et al. (2013). Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc.; 14(8): 542-559. **23.** Deutz NEP, et al. (2014). Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin. Nutr.; 33(6):929-936. **24.** Breen L, & Phillips SM. (2011). Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. Nutr Metab (Lond).; 9: 68. **25.** Paddon-Jones D, Rasmussen BB. (2009). Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care.; 12(1): 96-90. **26.** Bouillanne O, et al. (2013). Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: a randomized controlled trial. Clin Nutr.; 32(2): 186-192. **27.** Deutz NE, Wolfe, RR. (2013). Is there a maximal anabolic response to protein intake with a meal? Clin Nutr.; 32(2): 309-313. **28.** Park S, et al. (2020). The Anabolic Response to Dietary Protein Is Not Limited by the Maximal Stimulation of Protein Synthesis in Healthy Older Adults: A Randomized Crossover Trial. Nutrients.; 12(11): 3276. **29.** Ju SY, et al. (2018). Low 25-hydroxyvitamin D levels and the risk of frailty syndrome: a systematic review and dose-response meta-analysis. BMC Geriatr.; 18(1): 206.**30.** Remelli F, et al. (2019). Vitamin D Deficiency and Sarcopenia in Older Persons. Nutrients.; 11(12): 2861. **31.** Engelen M, Deutz N. (2018). Is β-hydroxy β-methylbutyrate an effective anabolic agent to improve outcome in older diseased populations? Curr. Opin. Clin Nutr Metab Care.; 21(3): 207-213. **32.** Deutz NEP, et al. (2013). Effect of β-hydroxy-β-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. Clin Nutr.; 32(5): 704-712. **33.** Dupont J, et al. (2019). The role of omega-3 in the prevention and treatment of sarcopenia. Aging Clin Exp Res.; 31(6): 825-836. **34.** Bird JK, et al. (2021). The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: A scoping systematic review and meta-analysis. Clin Nutr ESPEN.; 46: 73-86. **35.** dos Santos IS, et al. (2021). Association between frailty syndrome and sedentary behavior among community-dwelling older adults in the Amazon region: a cross-sectional study. Sao Paulo Med J.; 139(3): 226-233. **36.** Ramsey KA, et al. (2021). The association of objectively measured physical activity and sedentary behavior with skeletal muscle strength and muscle power in older adults: A systematic review and meta-analysis. Ageing Res Rev.; 67: 101266. **37.** Scott D, et al. (2021). Associations of accelerometer-determined physical activity and sedentary behavior with sarcopenia and incident falls over 12 months in community-dwelling Swedish older adults. J Sport Health Sci.; 10(5): 577-584. **38.** Landi F, et al. (2018). Impact of habitual physical activity and type of exercise on physical performance across ages in community-living people. PloS one.; 13(1): e0191820. **39.** Talar K, et al. (2021). Benefits of Resistance Training in Early and Late Stages of Frailty and Sarcopenia: A Systematic Review and Meta-Analysis of Randomized Controlled Studies. J Clin Med.; 10(8): 1630. **40.** Grant D, et al. (2020). The Effects of Displacing Sedentary Behavior With Two Distinct Patterns of Light Activity on Health Outcomes in Older Adults (Implications for COVID-19 Quarantine). Front physiol.; 11: 574595. **41.** Stockwell S, et al. (2021). Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review. BMJ Open SEM.; 7(1): e000960. **42.** Public Health England (2021). Wider impacts of COVID-19 on physical activity, deconditioning and falls in older adults. Accessed online: www.gov.uk/government/publications/covid-19-wider-impacts-on-people-aged-65-and-over (Mar 2022). **43.** Martone AM, et al. (2017). Exercise and Protein Intake: A Synergistic Approach against Sarcopenia. BioMed Res Int.; doi: 10.1155/2017/2672435.