Review Article

Sarcopenia in Elderly Surgery

Emile CH Woo, [1,2] *BSc (Pharm), MD, FRCSC*, Belinda Rodis, [3] *BSc, MD, FRCPC*

Abstract

Sarcopenia is a condition in which patients have an abnormally low muscle mass with poor muscle function. It is prevalent in older patients and is often associated with frailty. It has gained increasing recognition as a significant indicator of poor surgical outcomes. In this review, we examine the concept of sarcopenia and its impact on surgical outcomes and current research on its management. We also discuss the diagnosis of sarcopenia in terms of muscle mass and muscle function and common definitions of both terms. An overview of the impact of sarcopenia on different surgical specialties is reviewed. Lastly, a survey of current treatments available for sarcopenia and their limited impact are discussed with a view to encouraging possible future studies.

Ann Acad Med Singapore 2019;48:363–9

Key words: Exercise, Frailty, Nutrition, Perioperative medicine, Prehabilitation

Background

Sarcopenia is prevalent in the ageing population and is associated with frailty. According to the Asian Working Group on Sarcopenia (AWGS), its prevalence in Asians ranges from between 4.1% to 11.5%.[1] The incidence of sarcopenia is also likely to be higher in populations with chronic disease. The onset of sarcopenia begins in early adulthood after the age of 35 and symptoms include decline in muscle mass, muscle strength and power.[2] Generally, there is greater decline in strength in the lower body than upper body[3] and reduced power generation is caused by decreased tendon stiffness.[4]

Definitions of sarcopenia vary, but they include some form of impairment in the amount and function of muscle mass.[1,5,6] Generally, cutoffs are set at 2 standard deviations below the norm in healthy adults and they differ in men and women. According to AWGS, sarcopenia refers to muscle mass ≤7.0 kg/m^2 in men and ≤5.4 kg/m^2 in women and handgrip strength ≤26 kg for men and ≤18 kg for women. A gait speed ≤0.8 m/s is also used as a cutoff for low physical performance.[1]

[1]Department of Surgery, University of British Columbia, Canada
[2]Providence Health Care, Canada
[3]Division of Geriatric Medicine, Fraser Health Authority, Canada
Address for Correspondence: A/Prof Emile Woo, 4610 Main Street, Vancouver, British Columbia V5V 3R7, Canada.
Email: wooe@mail.ubc.ca

The prevalence of sarcopenia increases with age and the risk factors include chronic disease, low body mass index and reduced activity and protein intake.[7–10] It is a multifactorial process that results from a combination of changes in endocrine function, chronic disease, inflammation, insulin resistance, muscle disuse and nutritional deficiencies.[11] In men, endocrine changes such as reduction in growth hormone (GH), insulin-like growth factor-1 (IGF-1) and testosterone levels lead to loss of lean body mass and increase in body fat. Additionally, insulin resistance, higher cortisol levels, inflammatory markers[7] and immune system changes[12] contribute to sarcopenia and alterations in protein metabolism. Low vitamin D level has also been linked to sarcopenia.[13] All these factors can combine with age to cause sarcopenia; however, sarcopenia tends to be more prevalent in disease processes.

Although sarcopenia is distinct from cachexia, studies often lump them together since it can be difficult to distinguish both conditions. Cachexia results from disease and underlying malignancy[14] and is characterised by wasting of muscles and loss of body fat due to illness. Often, surgical patients present with some form of cachexia or sarcopenia that is related to illnesses which require operative interventions.

Two components are assessed in the evaluation of sarcopenia: muscle mass and muscle function or strength.[1,5,6] Skeletal muscle mass is measured using dual-energy absorptiometry, bioimpedence assays and cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI). They can be performed manually or with the use of special software. Muscle strength is derived from grip or leg strength and muscle function is determined based on gait speed or performance in chair stand test. For easier reference, most studies have defined sarcopenia as low muscle mass.

Sarcopenia is a marker of physiologic reserve and frailty.[15] The definitions of frailty are varied, but generally it describes a syndrome that results from increased vulnerability to stressors. The 3 major definitions of frailty have included a physical frailty phenotype by Fried et al,[16] accumulation of deficits[17] and functional abilities.[18] Frailty is also shown to correlate with surgical outcomes, which is discussed later. Overall, sarcopenia is a marker of poor health.[19] While it may overlap with frailty, there is some evidence to suggest that both conditions do not necessarily represent the same entity even though they are often seen together.[15,20,21]

Sarcopenia also exists independently of weight loss. Sarcopenic obesity has, in fact, been associated with worse outcomes than sarcopenia.[22] Additionally, fatty infiltration into muscle mass can lead to poor muscle quality.[23] Empirical evidence has shown that sarcopenic obesity is associated with disability, falls, functional decline and mortality.[22]

Impact of Sarcopenia on Surgical Outcomes

There is growing recognition in the literature that the presence of sarcopenia is associated with poorer surgical outcomes. Most studies were performed in gastrointestinal surgeries since the simplest measure of sarcopenia is defined as low muscle mass at the L3 vertebral level commonly seen in preoperative CT images. Additionally, higher complication rates with more physiologically demanding surgery provide better comparisons of surgical patients.

In alimentary tract surgery, several studies in colorectal surgery have reported on the impact of sarcopenia on short- and long-term outcomes after surgical resection. In a retrospective Canadian study of 234 patients who underwent primary colorectal tumour resection, Lieffers et al[24] found that sarcopenia was associated with a higher incidence of postoperative infection in patients ≥65 years old than non-sarcopenic patients (23.1% vs 12.6%, respectively; $P = 0.036$). Multiple logistic regression analysis also showed sarcopenia was an independent predictor of infection (odds ratio [OR], 4.6; 95% confidence interval [CI], 1.5–13.9). Length of stay (LOS) in hospital was also higher in patients ≥65 years old than non-sarcopenic patients (15.7 ± 9.8 days vs 11.8 ± 6.4 days, respectively; $P = 0.018$).

In a recent retrospective study of 251 patients who underwent colorectal cancer surgery, Mosk et al[25] found a higher incidence—about 15%—of postoperative delirium in sarcopenic patients than patients with normal L3 muscle mass indices (25% vs 10%, respectively; $P < 0.0006$). Another recent retrospective study of 494 patients by Nakanishi et al[26] found that sarcopenia was an independent predictor for postoperative complications (OR, 1.82; 95% CI, 1.13–3.00; $P = 0.01$) on multivariate analysis, and it was especially true of patients who were graded ≥2 in the Clavien-Dindo classification of surgical complications. Patients also had significantly longer LOS. Their study did not find any effect of sarcopenia on overall survival at a median follow-up of 44 months.

Lastly, in their study of skeletal muscle index (SMI) and skeletal muscle density (SMD) in 650 patients who were followed up at 60 months after colorectal resection for cancer, Dolan et al[27] found that low SMI and low SMD were associated with lower overall survival on univariate analysis ($P < 0.02$); however, on multivariate analysis, only SMI was independently associated with overall survival (hazard ratio [HR], 1.50; 95% CI, 1.04–2.18; $P = 0.031$).

In patients who underwent upper gastrointestinal tract surgery, Zhang et al[28] reported that sarcopenia was an independent predictor of increased postoperative complications on multivariate analysis of 156 Chinese patients following curative gastric resection and graded ≥2 on Clavien-Dindo system (OR, 3.4; 95% CI, 1.3–8.8; $P = 0.013$). Low muscle density was also a risk factor for postoperative complications (OR, 12.7; 95% CI, 1.6–93.0; *P* = 0.017). Similarly, O'Brien et al[29] reported that sarcopenia was a predictor of serious in-hospital complications on multivariate analysis (OR, 3.508; *P* = 0.042) of 56 patients undergoing gastric cancer surgery at an Irish centre. They found that sarcopenia was associated with worse overall survival (HR, 10.915; *P* = 0.001). In their study of 102 consecutive patients who underwent radical esophagectomy, Soma et al[30] reported that sarcopenia was associated with a higher incidence of respiratory complications in patients ≥75 years old (OR, 18.37; 95% CI, 2.29–407.3) than non-sarcopenic elderly patients (OR, 5.86; 95% CI, 2.14–18.0).

In pancreatic surgery, 2 studies found poorer outcomes in sarcopenic patients. In their study, Pecorelli et al[31] found that a ratio ≥3.2 in total abdominal muscle area (TAMA) to visceral fat area (VFA) in obese sarcopenic patients was a strong predictor of mortality (OR, 6.76; *P* <0.001). They also found that patients who developed major complications had better survival if they had a low TAMA/VFA ratio. El Amrani et al[32] also reported that sarcopenic patients undergoing pancreatectomy had lower disease-free survival (11.1 months vs 22.5 months; *P* = 0.04) and heightened risk of death (HR, 2.04; *P* = 0.07) on multivariate analysis. In their study of 75 patients who underwent resection for biliary tract cancer, Limpawattana et al[33] reported that patients with the highest muscle masses (quartile 4) had longer survival than those with lower muscle mass (HR, 0.46; 95% CI, 0.22–0.95; *P* = 0.037). The patients in their study, however, had a median age of 57.

In emergency laparotomy, sarcopenic patients were reported to have higher surgical risk. A retrospective study[34] of 967 elderly patients (median age, 70.3 years) found that sarcopenic patients had a higher incidence of pulmonary complications (23.8% vs 38.2%, *P* <0.001) and cardiovascular complications such as myocardial infarction (0.6% vs 3.7%). Multivariate analysis also showed that sarcopenia was associated with higher mortality (OR, 2.54; *P* <0.0001), longer LOS (HR, 0.84; *P* = 0.04) and lower rate of favourable discharge destination (OR, 0.45; *P* <0.0001). An interesting finding from this study was the favourable effect that increasing abdominal wall fat had on discharge, postoperative complications (*P* <0.05) and mortality. Similar results were reported by Rangel et al[35] when they found that sarcopenia in their patients aged ≥70 years old was associated with higher in-hospital mortality (risk ratio [RR], 2.6; 95% CI, 1.6–3.7), 30-day mortality (HR, 3.7; 95% CI, 1.9–7.4), 90-day mortality (HR, 3.3; 95% CI, 1.8–6.0), 180-day mortality (HR, 2.5; 95% CI, 1.4–4.4) and at 1 year (HR, 2.4; 95% CI, 1.4–3.9).

Finally, a meta-analysis of 4 studies of emergency surgeries (734 patients) and 16 studies of elective abdominal surgeries (4590 patients) by Hajibandeh et al[36] had found that sarcopenia was associated with higher risk of 30-day mortality (RR, 2.15; *P* <0.0001), 1-year mortality (RR, 1.97; *P* <0.0001), total complications (RR, 2.07; *P* <0.0008), Intensive Care Unit (ICU) admission (RR, 1.38; *P* <0.003), longer LOS in ICU (mean difference [MD], 2.26; *P* <0.006) and overall LOS (MD, 2.46; *P* <0.00001). They also found that patients with sarcopenia who underwent elective abdominal surgery had higher mortality risk at 30 days (RR, 2.15; *P* <0.002).

Findings on the impact of sarcopenia on surgical outcomes are not confined to general surgery. In orthotopic lung transplantation, Hsu et al[37] reported that sarcopenia was associated with worse outcomes. Sarcopenic patients who had lower mean post-transplant forced expiratory volume 1 had a higher incidence of 17% of post-transplant graft failure (HR, 12.8; 95% CI, 3.3–48.8; *P* <0.01). Also, their mortality rate was 61.5% compared to 18.2% in non-sarcopenic patients (*P* <0.01). In their systemic review and meta-analysis of 6 cohort studies that comprised 1213 patients, Deng et al[38] found that sarcopenic patients had lower overall survival (RR, 1.63; 95% CI, 1.13–2.33; *P* <0.008) than their non-sarcopenic counterparts and it was more prevalent in those with early-stage non-small-cell lung carcinoma.

In orthopaedics, a recent case-controlled retrospective review of 99 prosthetic infections in patients who had undergone total hip or knee arthroplasty by Babu et al[39] reported that patients with high muscle mass—measured on the psoas-lumbar vertebral index—had lower infection risk (OR, 0.28; 95% CI, 0.109–0.715; *P* <0.008). Another recent study had examined whether sarcopenia predicted change in mobility after a hip fracture at 1-year follow-up. In their multicentre observational trial, Steihaug et al[40] reported that sarcopenia did not predict change in mobility, but was associated with lower mobility on the New Mobility Score at 1 year (5.8 ± 2.3 vs 6.8 ± 2.2; *P* = 0.003). They also reported that sarcopenia was associated with an elevated risk of admission to institutional care such as nursing homes or death (OR, 3.6; 95% CI, 1.2–12.2; *P* = 0.02).

Studies have also examined the negative cost implications of sarcopenia on health services. In their study on the relationship between cost and sarcopenia in the United States, Sheetz et al[41] found that there was an increase of US$6989.71 for every decrease of 1000 mm^2 in lean psoas area measured. According to Gani et al,[42] sarcopenic patients incurred an additional amount of US$14,322 in total hospitalisation cost compared to non-sarcopenic patients (US$38,804 vs US$24,482, respectively; *P* <0.001) in their study of 1169 patients who underwent colorectal or hepatobiliary surgery. Finally, van Vugt et al[43] reported an increase in cost of 4061 euros ($P = 0.015$) to the healthcare system for sarcopenic patients who underwent cancer surgery of the alimentary tract.

Treatment

Treatment of sarcopenia is limited and is commonly seen in the general population since there is a scarcity of perioperative data and findings. The different interventions are discussed in the next section. An active lifestyle and adequate nutrition are recommended to prevent sarcopenia onset.[10,44] Although physical exercise—a combination of endurance and resistance training—is shown to be an effective intervention,[45,46] the role of nutrition is less clear. This is attributed to lack of conclusive findings on the efficacy of either nutrition or its combination with physical exercise to prevent sarcopenia.[47] Other interventions are often poorly tolerated by patients or suffer from limited findings on their efficacy. Findings of a recent phase 2 trial of a novel treatment have shown promising results through improvement in muscle mass, strength and gait speed at 4 weeks.[48]

Physical Exercise and Nutrition

A combination of aerobic exercise and resistance training can improve sarcopenia. A recent systematic review[47] had found that resistance training can improve muscle mass, muscle strength and physical performance measures. When aerobics, balance, flexibility and resistance training are included in physical exercise, muscle strength and physical performance are improved; however, increase in muscle mass is variable.

Most studies on nutrition in sarcopenia had focused on healthy older adults and findings on frail older patients are scarce. The findings of several studies on the effect a high protein intake of 1–1.2 kg/day—together with physical exercise—can have on sarcopenia were inconclusive. One study did, however, find improvement in function in frail, obese older adults who were trying to lose weight after their enhanced protein intake in each meal was distributed throughout the day.[49] More studies are needed on optimal protein intake in the prevention of sarcopenia.

Other studies have investigated leucine-rich diets[50] and essential amino acids.[51] They have failed to demonstrate, conclusively, either the benefits of such diets and foods or in combination with physical exercise to prevent sarcopenia. Evidence that intake of creatine kinase supplementation with physical exercise can enhance muscle mass and muscle strength—but not muscle function—is also weak.[52] Although vitamin D is shown to correlate with sarcopenia, its intake does not improve the condition.[47]

Other Treatments

A recent systematic review[53] has shown that testosterone supplementation in men led to a moderate increase in muscle strength. However, it is associated with significant side effects such as cardiovascular events including heart failure,[54] worsening benign prostatic hypertrophy, liver toxicity and hyperviscosity[55] that are poorly tolerated in frail patients.

GH supplementation can improve muscle mass and muscle strength in individuals who are deficient in them, but this finding is not replicated in those who have adequate GH with or without physical exercise.[56] The side effects of GH supplementation include orthostatic hypotension, fluid retention, gynecomastia and carpal tunnel syndrome which limit its tolerability in sarcopenic patients.[57]

Ghrelin levels are correlated with sarcopenia in older adults. Ghrelin is an endogenous growth hormone secretagogue and its administration is known to stimulate appetite in patients. However, findings on its efficacy to prevent sarcopenia are limited and mixed,[58] and they were found primarily in young adults with cachexia. A possible side effect of ghrelin therapy includes worsening heart failure.[59]

Angiotensin-converting enzyme (ACE) inhibitors are a potential therapy after observational studies showed that they could improve physical performance. However, the mechanisms of action in these agents are not clear. ACE inhibition raises IGF-1 levels and has a trophic effect on myocardium. Additionally, it improves angiogenesis, endothelial function and suppresses inflammation,[60] all of which can theoretically improve muscle function. Previously, a randomised controlled trial had shown improvement in exercise capacity with perindopril administration;[61] however, a recent meta-analysis[62] and trial[63] had shown no benefit of ACE inhibition on physical function. At this point, it is unclear whether any real benefit can be had even as we await results of an ongoing trial[60] that compares ACE inhibitors with leucine supplementation.

A recent phase 2 trial of a type II activin receptor antagonist has shown encouraging results.[48] Bimagrumab administration was shown to prevent binding of ligands, myostatin and activin A that could inhibit muscle growth and protein anabolism. Sarcopenic patients were given 1–2 doses of bimagrumab and showed improvements in handgrip strength, lean body mass and muscle volume at 2 weeks. At 16 weeks, they showed a statistical and clinically significant improvement of 0.15 m/s with a baseline gait speed $\leq$0.8 m/s. Except for mild muscle spasms, bimagrumab therapy was otherwise well tolerated in patients. Though only a phase 2 study, these encouraging findings may augur well for treatment of sarcopenia.

Overall, there is a dearth of outcome data and findings on effective interventions in the management of sarcopenia. In the literature, 37 studies had shown that sarcopenia can be managed with exercise and nutritional supplementation.[47,64] They included 27 randomised controlled trials on patients ≥65 years old that demonstrated physical exercise improved muscle mass and muscle function—measured by gait speed and performance in the chair stand exercise—and 8 studies that showed the benefits of good nutrition. There is also evidence that seems to suggest physical exercise alone may not be as effective without proper nutritional support to ensure adequate protein intake.[65] In their meta-analysis of 22 studies comprising 721 subjects who were given either creatine or placebo during resistance training, Chilibeck et al[52] reported that the creatine group experienced more increase in lean tissue mass (MD, 1.37 kg; 95% CI, 0.97–1.76; P <0.00001), chest press strength (MD, 0.35 [range, 0.16–0.53]; P = 0.0002) and leg press strength (MD, 0.24 [range, 0.05–0.43]; P = 0.01). However, the data pertained to non-surgical patients who were followed up between 4 weeks and 18 months.

Perioperative Management of Sarcopenic Patients

Unfortunately, elderly patients who undergo surgery, especially oncology patients, do not have the luxury of a lengthy conditioning period. Only a handful of studies had investigated sarcopenia in preoperative elderly patients. In their small pilot study of 22 sarcopenic patients ≥65 years old undergoing gastric cancer surgery who were started on an exercise programme and given nutrition support prior to surgery, Yamamoto et al[66] reported that 4 patients became non-sarcopenic before surgery after an increase in their body weight and handgrip strength was seen. Unfortunately, their finding was limited by the lack of a control group and the fact that only 50% of patients completed the programme.

In another recent pilot study that looked at nutritional supplementation prior to radical cystectomy, Ritch et al[67] reported that 28 patients received oral supplementation and another 24 received only multivitamin supplementation 8 weeks prior to surgery. The oral supplementation group lost less weight before surgery (−5 kg vs −6.5 kg, P = 0.04) and the number of sarcopenic patients did not increase during the preoperative period. In the multivitamin group, there was an increase of 20% in the number of sarcopenic patients (P = 0.01). Postoperatively, no difference in LOS or 30-day hospital-free days was seen in both groups. There was a lower incidence of complications and readmissions in the oral supplementation group, but the result was not statistically significant.

Finally, the study by Pędziwiatr et al[68] of 124 patients (mean age, 65.9 years old) undergoing laparoscopic colon resection who were managed according to the principles of enhanced recovery after surgery found that 27.4% of patients had sarcopenia and 38.7% of them had myosteatosis. When compared to the non-sarcopenic group and non-myosteatotic group, there was a reduction in LOS and rates of postoperative complications and readmissions. They postulated that a laparoscopic approach may lower the risk associated with sarcopenia and myosteatotis.

A current focus in the literature is the use of preoperative geriatric assessment in elderly patients since sarcopenia is just one of the myriad conditions faced by this group of patients.[69,70] Frailty is also often present in elderly patients and is a major determinant of poor outcome, and it may well be a more powerful predictor of sarcopenia.[66] Prehabilitation also forms part of the discourse on geriatric assessment. Initially described as presurgical exercise training to improve the functional capacity of patients,[71] prehabilitation has been gaining recognition as a multimodal intervention that includes physical exercise, nutritional supplementation and mental conditioning to help patients manage surgical stressors.[66,72] However, a full review of prehabilitation is beyond the scope of this article.

Conclusion

In elderly patients undergoing surgery, sarcopenia poses a big health challenge and risk. In current literature, there are standard definitions and wide recognition that sarcopenia is associated with poor short- and long-term surgical outcomes, patient-specific outcomes and greater resource utilisation of health services. However, the evidence is mostly from small retrospective studies that included heterogenous definitions of sarcopenia based primarily on low muscle mass imaged on CT.

Research on treatment of sarcopenia is limited. Currently, exercise and nutritional intervention appear to be the most promising therapies, but their efficacy is only found in non-surgical patients. The biggest challenge in surgical patients is lack of conclusive findings that support improved outcomes in the perioperative period since the findings in the literature have been mixed.

Future challenges include identification of high-risk populations and intervention prior to surgical management; however, surgical management, especially for malignancy, is often expedited. The duration of therapy that is needed to improve treatment outcomes must also be determined. Additionally, the use of standard definitions of sarcopenia—rather than low muscle mass imaged on CT and MRI—would yield more robust evidence and findings. Larger, randomised controlled trials that identify patients who are at higher risk of complications and mortality would allow more accurate risk stratification of patients. The implications of these challenges include close monitoring of patients for complications, targeting aggressive interventions in patients who are more likely to have poor treatment outcomes and preoperative intervention to improve sarcopenia prior to surgery.

REFERENCES

1. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95–101.
2. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. J Appl Physiol 2000;88:1321–6.
3. Newman AB, Lee JS, Visser M, Goodpaster BH, Kritchevsky SB, Tylavsky FA, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. Am J Clin Nutr 2005;82:872–8.
4. Narici MV, Maganaris CN. Adaptability of elderly human muscles and tendons to increased loading. J Anat 2006;208:433–43.
5. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. International Working Group on Sarcopenia. J Am Med Dir Assoc 2011;12:249–56.
6. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Aging 2010;39:412–23.
7. Li CI, Li TC, Lin WY, Liu CS, Hsu CC, Hsiung CA, et al. Combined association of chronic disease and low skeletal muscle mass with physical performance in older adults in the Sarcopenia and Translational Aging Research in Taiwan (START) study. BMC Geriatr 2015;15:11.
8. Ebner N, Sliziuk V, Scherbakov N, Sandek A. Muscle wasting in ageing and chronic illness. ESC Heart Fail 2015;2:58–68.
9. Lardiés-Sánchez B, Sanz-París A. Sarcopenia and malnutrition in the elderly. In: Dionyssiotis Y, editor. Frailty and Sarcopenia: Onset, Development and Clinical Challenges. London: IntechOpen Limited; 2017. p. 71–80.
10. Steffl M, Bohannon RW, Sontakova L, Tufano JJ, Shiells K, Holmerova I, et al. Relationship between sarcopenia and physical activity in older people: a systematic review and meta-analysis. Clin Interv Aging 2017;12:835–45.
11. Kim TN, Choi KM. Sarcopenia: definition, epidemiology, and pathophysiology. J Bone Metab 2013;20:1–10.
12. Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: the potential role of an aged immune system. Ageing Res Rev 2017;36:1–10.
13. Arik G, Ulger Z. Vitamin D in sarcopenia: understanding its role in pathogenesis, prevention and treatment. Eur Geriatr Med 2016;7:207–13.
14. Rolland Y, Abellan van Kan G, Gillette-Guyonnet S, Vellas B. Cachexia versus sarcopenia. Curr Opin Clin Nutr Metab Care 2011;14:15–21.
15. Fougère B, Sourdet S, Lilamand M, Tabue-Teguod M, Teysseyre B, Dupuy C, et al. Untangling the overlap between frailty and low lean mass: data from Toulouse frailty day hospital. Arch Gerontol Geriatr 2018;75:209–13.
16. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.
17. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc 2004;52:1929–33.
18. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95.
19. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O. Health outcomes of sarcopenia: a systematic review and meta-analysis. PLoS One 2017;12:e0169548.
20. Mijnarends DM, Schols JM, Meijers JM, Tan FE, Verlaan S, Luiking YC, et al. Instruments to assess sarcopenia and physical frailty in older people living in a community (care) setting: similarities and discrepancies. J Am Med Dir Assoc 2015;16:301–8.
21. Reijnierse EM, Trappenburg MC, Blauw GJ, Verlaan S, de van der Schueren MA, Meskers CG, et al. Common ground? The concordance of sarcopenia and frailty definitions. J Am Med Dir Assoc 2016;17:371.
22. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, causes and consequences. Curr Opin Clin Nutr Metab Care 2008;11:693–700.
23. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 2005;60:324–33.
24. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer 2012;107:931–6.
25. Mosk CA, van Vugt JLA, de Jonge H, Witjes CD, Buettner S, Ijzermans JN, et al. Low skeletal muscle mass as a risk factor for postoperative delirium in elderly patients undergoing colorectal cancer surgery. Clin Interv Aging 2018;13:2097–106.
26. Nakanishi R, Oki E, Sasaki S, Hirose K, Jogo T, Edahiro K, et al. Sarcopenia is an independent predictor of complications after colorectal cancer surgery. Surg Today 2018;48:151–7.
27. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG,McSorley ST, McMillan DC. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. J Cachexia Sarcopenia Muscle 2019;10:111–22.
28. Zhang Y, Wang JP, Wang XL, Tian H, Gao TT, Tang LM, et al. Computed tomography-quantified body composition predicts short-term outcomes after gastrectomy in gastric cancer. Curr Oncol 2018;25:e411–22.
29. O'Brien S, Twomey M, Moloney F, Kavanagh RG, Carey BW, Power D, et al. Sarcopenia and post-operative morbidity and mortality in patients with gastric cancer. J Gastric Cancer 2018;18:242–52.
30. Soma D, Kawamura YI, Yamashita S, Wake H, Nohara K, Yamada K, et al. Sarcopenia, the depletion of muscle mass, an independent predictor of respiratory complications after oncological esophagectomy. Dis Esophagus 2019;32:doy092.
31. Pecorelli N, Carrara G, De Cobelli F, Cristel G, Damascelli A, Balzano G, et al. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. Br J Surg 2016;103:434–42.
32. El Amrani M, Vermersch M, Fulbert M, Prodeau M, Lecolle K, Hebbar M, et al. Impact of sarcopenia on outcomes of patients undergoing pancreatectomy: a retrospective analysis of 107 patients. Medicine (Baltimore) 2018;97:e12076.
33. Limpawattana P, Theerakulpisut D, Wirasorn K, Sookprasert A, Khuntikeo N, Chindaprasirt J. The impact of skeletal muscle mass on survival outcome in biliary tract cancer patients. PLoS One 2018;13:e0204985.
34. Francomacaro LM, Walker C, Jaap K, Dove J, Hunsinger M, Widom K, et al. Sarcopenia predicts poor outcomes in urgent exploratory laparotomy. Am J Surg 2018;216:1107–13.
35. Rangel EL, Rios-Diaz AJ, Uyeda JW, Castillo-Angeles M, Cooper Z, Olufajo OA, et al. Sarcopenia increases risk of long-term mortality in elderly patients undergoing emergency abdominal surgery. J Trauma Acute Care Surg 2017;83:1179–86.

36. Hajibandeh S, Jarvis R, Bhogal T, Dalmia S. Meta-analysis of the effect of sarcopenia in predicting postoperative mortality in emergency and elective abdominal surgery. Surgeon 2019;17:370–80.

37. Hsu J, Krishnan A, Lin CT, Shah PD, Broderick SR, Higgins RSD, et al. Sarcopenia of the psoas muscles is associated with poor outcomes following lung transplantation. Ann Thorac Surg 2019;107:1082–8.

38. Deng HY, Hou L, Zha P, Huang KL, Peng L. Sarcopenia is an independent unfavorable prognostic factor of non-small cell lung cancer after surgical resection: a comprehensive systematic review and meta-analysis. Eur J Surg Oncol 2019;45:728–35.

39. Babu JM, Kalagara S, Durand W, Antoci V, Deren ME, Cohen E. Sarcopenia as a risk factor for prosthetic infection after total hip or knee arthroplasty. J Arthroplasty 2019;34:116–22.

40. Steihaug OM, Gjesdal CG, Bogen B, Kristoffersen MH, Lien G, Hufthammer KO, et al. Does sarcopenia predict change in mobility after hip fracture? A multicenter observational study with one-year follow-up. BMC Geriatr 2018;18:65.

41. Sheetz KH, Waits SA, Terjimanian MN, Sullivan J, Campbell DA, Wang SC, et al. Cost of major surgery in the sarcopenic patient. J Am Coll Surg 2013;217:813–8.

42. Gani F, Buettner S, Margonis GA, Sasaki K, Wagner D, Kim Y, et al. Sarcopenia predicts costs among patients undergoing major abdominal operations. Surgery 2016;160:1162–71.

43. van Vugt JLA, Buettner S, Levolger S, Coebergh van den Braak RRJ, Suker M, Gaspersz MP, et al. Low skeletal muscle mass is associated with increased hospital expenditure in patients undergoing cancer surgery of the alimentary tract. PLoS One 2017;12:e0186547.

44. Makanae Y, Fujita S. Role of exercise and nutrition in the prevention of sarcopenia. J Nutr Sci Vitaminol (Tokyo) 2015;61:S125–7.

45. Phu S, Boersma D, Duque G. Exercise and sarcopenia. J Clin Densitom 2015;18:488–92.

46. Montero-Fernández N, Serra-Rexach JA. Role of exercise on sarcopenia in the elderly. Eur J Phys Rehabil Med 2013;49:131–43.

47. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int 2017;28:1817–33.

48. Rooks D, Praestgaard J, Hariry S, Laurent D, Petricoul O, Perry RG, et al. Treatment of sarcopenia with bimagrumab: results from a phase II, randomized, controlled, proof-of-concept study. J Am Geriatr Soc 2017;65:1988–95.

49. Porter Starr KN, Pieper CF, Orenduff MC, McDonald SR, McClure LB, Zhou R, et al. Improved function with enhanced protein intake per meal: a pilot study of weight reduction in frail, obese older adults. J Gerontol A Biol Sci Med Sci 2016;71:1369–75.

50. Tessier AJ, Chevalier S. An update on protein, leucine, omega-3 fatty acids, and vitamin D in the prevention and treatment of sarcopenia and functional decline. Nutrients 2018;10:E1099.

51. Gade J, Pedersen RJ, Beck AM. Effect of protein or essential amino acid supplementation during prolonged resistance exercise training in older adults on body composition, muscle strength, and physical performance parameters: a systematic review. Rehabil Process Outcome 2018;7:1–12.

52. Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access J Sports Med 2017;8:213–26.

53. Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ, Acha AA, Ostir GV. Androgen treatment and muscle strength in elderly men: a meta-analysis. J Am Geriatr Soc 2006;54:1666–73.

54. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–22.

55. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag 2009;5:427–48.

56. Borst SE. Interventions for sarcopenia and muscle weakness in older people. Age Ageing 2004;33:548–55.

57. Burton LA, Sumukadas D. Optimal management of sarcopenia. Clin Interv Aging 2010;5:217–28.

58. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options—a mini-review. Gerontology 2014;60:294–305.

59. Zhang G, Yin X, Qi Y, Pendyala L, Chen J, Hou D, et al. Ghrelin and cardiovascular diseases. Curr Cardiol Rev 2010;6:62–70.

60. Band MM, Sumukadas D, Struthers AD, Avenell A, Donnan PT, Kemp PR, et al. Leucine and ACE inhibitors as therapies for sarcopenia (LACE trial): study protocol for a randomised controlled trial. Trials 2018;19:6.

61. Witham MD, Sumukadas D, McMurdo ME. ACE inhibitors for sarcopenia—as good as exercise training? Age Ageing 2008;37:363–5.

62. Zhou LS, Xu LJ, Wang XQ, Huang YH, Xiao Q. Effect of angiotensin-converting enzyme inhibitors on physical function in elderly subjects: a systematic review and meta-analysis. Drugs Aging 2015;32:727–35.

63. Spira D, Walston J, Buchmann N, Nikolov J, Demuth I, Steinhagen-Thiessen E, et al. Angiotensin-converting enzyme inhibitors and parameters of sarcopenia: relation to muscle mass, strength and function: data from the Berlin Aging Study-II (BASE-II). Drugs Aging 2016;33:829–37.

64. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43:748–59.

65. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N, et al. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. Gastroenterology 2018;155:391–410.

66. Yamamoto K, Nagatsuma Y, Fukuda Y, Hirao M, Nishikawa K, Miyamoto A, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. Gastric Cancer 2017;20:913–8.

67. Ritch CR, Cookson MS, Clark PE, Chang SS, Fakhoury K, Ralls V, et al. Perioperative oral nutrition supplementation reduces prevalence of sarcopenia following radical cystectomy: results of a prospective randomized controlled trial. J Urol 2019;201:470–7.

68. Pędziwiatr M, Pisarska M, Major P, Grochowska A, Matłok M, Przęczek K, et al. Laparoscopic colorectal cancer surgery combined with enhanced recovery after surgery protocol (ERAS) reduces the negative impact of sarcopenia on short-term outcomes. Eur J Surg Oncol 2016;42:779–87.

69. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering tailored surgery to older cancer patients: preoperative geriatric assessment domains and screening tools—a systematic review of systematic reviews. Eur J Surg Oncol 2017;43:1–14.

70. Feng MA, McMillan DT, Crowell K, Muss H, Nielsen ME, Smith AB. Geriatric assessment in surgical oncology: a systematic review. J Surg Res 2015;193:265–72.

71. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care 2005;8:23–32.

72. Santa Mina D, Scheede-Bergdahl C, Gillis C, Carli F. Optimization of surgical outcomes with prehabilitation. Appl Physiol Nutr Metab 2015;40:966–9.