

# Nutritional Recommendations for the Management of Sarcopenia

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The Society for Sarcopenia, Cachexia, and Wasting Disease convened an expert panel to develop nutritional recommendations for prevention and management of sarcopenia. Exercise (both resistance and aerobic) in combination with adequate protein and energy intake is the key component of the prevention and management of sarcopenia. Adequate protein

supplementation alone only slows loss of muscle mass. Adequate protein intake (leucine-enriched balanced amino acids and possibly creatine) may enhance muscle strength. Low 25(OH) vitamin D levels require vitamin D replacement. (*J Am Med Dir Assoc* 2010; 11: 391–396)

Conventionally, sarcopenia is the loss of muscle mass that occurs with aging.<sup>1,2</sup> Lean muscle mass is lost at the rate of approximately 1% per year after 30 years of age.<sup>3</sup> Although originally it was assumed that lean muscle mass was directly proportional to muscle strength, it is now recognized that

this is not always the case.<sup>4–6</sup> This has led to the suggestion that “dynopenia” should be used to signify loss of muscle power.<sup>7,8</sup> At present, the definition of sarcopenia is evolving, and the term sarcopenia is now often used to indicate the loss of muscle mass and function associated with chronic diseases.<sup>9–12</sup> Whereas sarcopenia was traditionally defined as loss of muscle mass, the inclusion of loss of muscle function in this definition should be considered. The rationale for such a wider definition of sarcopenia is that therapeutic approaches for both improvement of muscle mass and function are similar. This definition would, however, strongly overlap the definitions of “frailty.”<sup>13–16</sup>

The loss of muscle mass in sarcopenic persons has been divided into physiological and pathological. Pathological levels of sarcopenia have been defined as being below 2 standard deviations of mean lean body mass for healthy young persons.<sup>17,18</sup> Rigorous definitions tend to use appendicular lean mass and correct for height. Pathological sarcopenia is associated with an extremely high rate of disability.<sup>13</sup> In the United States, sarcopenia has been estimated to have an economic burden related to health care expenditures of \$18.5 billion per year. Sarcopenia is not necessarily associated with weight loss and therefore is distinct from cachexia.<sup>19</sup> Obese sarcopenic persons appear to have even worse outcomes.<sup>20,21</sup> Separate nutritional guidelines for cachexia have been developed.<sup>22</sup>

The second Cachexia Consensus Conference was convened by the Society for Sarcopenia, Cachexia, and Wasting Disorders in December 2008. The purpose of this conference was to develop consensus on the nutritional recommendations for persons with sarcopenia. This was done in parallel with the development of separate guidelines for cachexia.

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The literature for each of the nutrients was reviewed by 2 scientists and presented to the group together with draft recommendations. The reviewers gave precedent to meta-analyses over single studies. An open discussion and modified Delphi method were then used to create consensus on the recommendations. Following the meeting, the new recommendations were submitted to all panelists for further input. Finally, a systematic literature search on [www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed) was conducted using the term "sarcopenia" and various specific terms, eg, nutrition, amino acids, creatine, vitamin D, and so forth, with limits of "humans." The final search was done on January 16, 2010, and the results are given in **Table 1**. In addition, we also found articles based on references in review articles and on participants' knowledge of the literature. The final manuscript was then submitted to all panelists for alterations and approval.

All recommendations have been classified as follows (**Table 2**):

- A. A minimum of a single randomized placebo-controlled trial or a meta-analysis
- B. Small trials
- C. Expert opinion

## RECOMMENDATIONS

Aging is associated with physiological anorexia, decreased caloric intake, and weight loss,<sup>23–27</sup> which in turn is associated with a decline in muscle mass and increased mortality. These facts suggest that a balanced caloric supplement may be useful in preventing or reversing sarcopenia as part of a multimodal therapeutic approach. A number of studies and 2 meta-analyses in older persons with malnutrition and/or illness have shown positive effects of nutritional supplementation.<sup>28,29</sup> However, these persons had some degree of cachexia and, thus, no conclusion on the effect of supplements on physiological sarcopenia can be drawn. Persons with obesity and sarcopenia have very poor outcomes.<sup>20,21</sup> Although aggressive resistance exercise consistently mitigates sarcopenia, appropriate dietary approaches to this group are unknown.

### Protein

Older persons have a high risk of inadequate protein intake.<sup>30</sup> Kerstetter et al<sup>31</sup> reported that 32% to 41% of

women and 22% to 38% of men older than 50 years ingested less than the recommended dietary allowance for protein (0.8 g/kg/day). Virtually no older persons ingest the highest acceptable macronutrient distribution for protein of 35% of energy intake. In the Health, Aging, and Body Composition Study persons in the highest quintile of protein intake lost nearly 40% less appendicular lean mass than did those in the lowest quintile.<sup>32</sup> Other studies have also found a positive association between protein ingestion and muscle mass.<sup>33,34</sup>

Because of metabolic changes, older persons may produce less muscle protein than younger persons from the same amount of dietary protein.<sup>31</sup> However, larger amounts of protein (defined as protein or amino acid mixtures with more than 10 g of essential amino acids) produce responses equal to those in younger persons.<sup>35,36</sup> Many commentators have argued that the recommended daily allowance for protein, although sufficient for healthy individuals, fails to prevent muscle loss with aging.<sup>35–38</sup> In addition, it is recommended that the amount of protein ingested should be spread equally throughout the day, ie, equivalent amounts at breakfast, lunch, and dinner.<sup>39</sup> If additional protein supplementation is given it should be administered between meals.<sup>40</sup> Levels of protein intake as high as 1.6 g of protein/kg/d have been demonstrated to increase exercise-induced muscle hypertrophy in older persons.<sup>41</sup> Another study found that 1.0 g of protein/kg/d was the minimal amount required to maintain muscle mass.<sup>42</sup> For these reasons it is recommended that older persons ingest between 1.0 and 1.5 g of protein/kg/d.

Essential amino acids appear to be the primary stimulus of protein synthesis.<sup>43</sup> Leucine appears to be the most potent of these amino acids.<sup>44</sup> Leucine produces its anabolic effects in muscle by stimulating the mammalian target of rapamycin (mTOR) pathway.<sup>45</sup> mTOR is considered the nutrient sensor for leucine. Essential amino acids act synergistically with exercise to increase fractional protein synthesis.<sup>46</sup>

Supplementation with essential amino acids and carbohydrate prevents muscle protein loss in humans during bed rest.<sup>47</sup> A whey protein supplement has been shown to augment the muscle strengthening effects of resistance exercise.<sup>48,49</sup>

Solerte et al<sup>50</sup> studied 41 persons with sarcopenia with an age range of 66 to 84 years in a randomized trial. They provided 8 g of essential amino acids over 18 months. This treatment increased muscle mass, reduced tumor necrosis factor-alpha, and improved insulin sensitivity.

These findings led to our recommendation that a leucine-enriched balanced amino acid supplement should be used to slow muscle loss. This is particularly important when the older person is exercising.

Anabolic therapies such as growth hormone and testosterone have been shown to increase muscle mass and in some cases strength in older persons.<sup>51–56</sup> A calorie-protein supplement together with testosterone decreased hospitalizations in frail older men and women.<sup>57</sup> Thus, it would seem reasonable to consider protein supplementation in sarcopenic persons to enhance or maximize the effects of anabolic agents. There is a need for a reasonably powered clinical trial to test this hypothesis in sarcopenic patients.

**Table 1.** Results of Systematic Review of PubMed for Sarcopenia and Specific Nutrients

Sarcopenia and	Items	Review
Calories	3	2
Energy	147	51
Protein	282	149
Amino acids	49	28
Creatine	9	4
Vitamin D	19	10
n-3 fatty acids	0	0
Exercise	249	142
Nutrition	147	42

Search conducted on January 16, 2010.

**Table 2.** Sarcopenia Recommendations

- Aging is associated with a physiological anorexia, decreased protein and energy intake, and weight loss. This is associated with a decline in muscle mass and increased mortality.
- The metabolic efficiency in older persons is decreasing, requiring a higher protein intake for protein synthesis than in younger persons.
- This suggests that a balanced protein and energy supplement may be useful in preventing and reversing sarcopenia as part of a multimodal therapeutic approach. (A)
- Persons with obesity and sarcopenia have very poor outcomes. Appropriate dietary approaches for this group, other than aggressive resistance exercise, are unknown.
- As 15% to 38% of older men and 27% to 41% of older women ingest less than the recommended daily allowance for protein it is suggested that protein intake be increased. (B)
- It is recommended that the total protein intake should be 1 to 1.5 g/kg/day. (B)
- It is suggested that a leucine-enriched balanced essential amino acid mix may be added to the diet. (B)
- A trial of balanced amino acid supplementation alone and with exercise in sarcopenic patients is recommended.
- Creatine may enhance the effects of exercise in sarcopenic patients. (A)
- Long-term studies of the effect of creatine on sarcopenia need to be carried out.
- Based on treatment trials in patients with sarcopenia and on well-established human physiology, patients receiving anabolic therapies will have increased dietary energy needs to support increases in lean body mass. Whether the increase in dietary energy needs will require explicit nutritional support is an individualized decision. (B)
- Based on some treatment trials in patients with sarcopenia and on physiologic hypotheses, for optimal deposition of muscle mass, patients receiving anabolic therapies probably require adequate protein intake. Whether meeting dietary protein needs will require explicit nutritional support is an individualized decision. (B)
- There is a need for a reasonably powered clinical trial to test these hypotheses in sarcopenic patients.
- 25(OH) vitamin D levels should be measured in all sarcopenic patients. (A)
- Vitamin D supplementation in doses sufficient to raise levels above 100 nmol/L should be given as an adjunctive therapy. (A)
- Either vitamin D2 or D3 is an acceptable replacement. (A)
- Doses of 50,000 IU of vitamin D a week are safe. (A)
- Short-term resistance exercise improves strength and gait speed. (A)
- Aerobic exercise improves quality of life years (QALY) and is cost effective. (A)
- Epidemiology studies suggest positive effects of physical fitness on health.
- We recommend resistance and aerobic exercise for 20 to 30 minutes, 3 times a week. (A)

A = A minimum of a single randomized placebo-controlled trial or a meta-analysis; B = Small trials.

## Creatine

Supplementation with creatine monohydrate increases the available phosphocreatine.<sup>58</sup> Phosphocreatine is a form of energy storage that is necessary for high-power exercise. Numerous studies have shown that creatine improves exercise performance in young persons.<sup>59</sup> Creatine supplementation during upper arm immobilization slows the loss of muscle mass and strength in younger men.<sup>60</sup>

Studies in older people have provided some evidence of positive effects of creatine. Chrusch et al<sup>61</sup> studied 30 men older than 70 in a double-blind placebo-controlled trial. These older men received either creatine plus resistance exercise or placebo with resistance exercise. Creatine supplementation increased lean tissue mass as well as increased leg strength, power, and endurance. In a study of men and women 65 to 86 years, creatine supplementation for 14 days increased maximal isometric grip strength and physical working capacity at fatigue threshold.<sup>62</sup> Creatine alone or with conjugated linolenic acid increased lean body mass and improved strength.<sup>63,64</sup> Low-dose creatine together with a protein supplement increased lean mass and upper limb strength.<sup>65</sup>

Mixed results have been reported in studies of creatine supplementation in other chronic catabolic conditions. In persons with Parkinson's disease, creatine improved upper limb strength and chair rise performance.<sup>66</sup> Creatine supplementation increased body weight and muscle strength in patients with congestive heart failure.<sup>67</sup> Creatine did not improve strength in persons with chronic obstructive pulmonary disease<sup>68,69</sup> or HIV infection.<sup>70</sup>

Overall, although short-term studies suggest some benefit of use of creatine in addition to exercise in sarcopenic patients, there is a need for long-term studies on the effects of creatine on sarcopenia.

## Vitamin D

Levels of 25(OH) Vitamin D decline longitudinally with aging.<sup>71</sup> Numerous studies have reported extremely low vitamin D levels in older persons.<sup>72-75</sup> Low vitamin D levels are associated with low muscle strength.<sup>76,77</sup> Low vitamin D levels are associated with statin myopathy.<sup>78,79</sup> Replacement of vitamin D in persons with low levels increases strength and function and decreases falls.<sup>80</sup> Vitamin D replacement is associated with less mortality.<sup>81</sup>

Levels of 25(OH) vitamin D should be measured in all sarcopenic patients. Vitamin D should be supplemented in all persons with values less than 100 nmol/L. Holick et al<sup>82</sup> found both vitamin D2 and D3 are equally effective at maintaining 25(OH) vitamin D levels.

## Exercise

Bed rest results in rapid loss of muscle mass and strength in older persons.<sup>83,84</sup> Resistance exercise improved strength and decreased frailty in very old persons.<sup>85-89</sup> These effects can be maintained for at least 1 year.<sup>87,90,91</sup> Strength training improved distance walked in 6 minutes and gait speed.<sup>92</sup> Resistance exercise increases type II muscle fiber size and improves satellite muscle recruitment in older persons.<sup>93,94</sup>

Aerobic exercise remodels myofibers and increases muscle strength.<sup>95</sup> In older persons, aerobic exercise improves gait speed, quality of life years (QALY), and is cost effective.<sup>96–98</sup> Vibratory exercise also improves performance in sarcopenic individuals.<sup>99–101</sup>

Overall, a minimum of 20 to 30 minutes of resistance and aerobic exercise 3 times a week is recommended to slow muscle loss and prevent sarcopenia.

## CONCLUSION

**Table 2** provides the recommendations for nutritional management of sarcopenia. Exercise (aerobic and resistance) represents the key intervention. Adequate protein intake (leucine-enriched amino acids and possibly creatine) has good evidence. Low vitamin D levels should be corrected.

## REFERENCES

- Evans WJ. What is sarcopenia? *J Gerontol A Biol Sci Med Sci* 1995; 50(Spec):5–8.
- Roubenoff R, Hughes VA. Sarcopenia: Current concepts. *J Gerontol A Biol Sci Med Sci* 2000;55:M716–M724.
- Morley JE. Anorexia, sarcopenia, and aging. *Nutrition* 2001;17: 660–663.
- Rolland YM, Perry HM 3rd, Patrick P, et al. Loss of appendicular muscle mass and loss of muscle strength in young postmenopausal women. *J Gerontol A Biol Sci Med Sci* 2007;62:330–335.
- Raj IS, Bird SR, Shield AJ. Aging and the force-velocity relationship of muscles. *Exp Gerontol* 2010;45:81–90.
- Bauer JM, Kaiser MJ, Sieber CC. Sarcopenia in nursing home residents. *J Am Med Dir Assoc* 2008;9:545–551.
- Clark BC, Manini TM. Sarcopenia =/= dynapenia. *J Gerontol A Biol Sci Med Sci* 2008;63:829–834.
- Morley JE. Sarcopenia: Diagnosis and treatment. *J Nutr Health Aging* 2008;12:452–456.
- Rolland Y, Czerwinski S, Abellan van Kan G, et al. Sarcopenia: Its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging* 2008;12:433–450.
- Miller DK, Malmstrom TK, Andresen EM, et al. Development and validation of a short portable sarcopenia measure in the African American Health Project. *J Gerontol A Biol Sci Med Sci* 2009;64:388–394.
- Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. *J Appl Physiol* 2003;95:1851–1860.
- Muscaritoli M, Anker SD, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting disease” and “nutrition in geriatrics.” *Clin Nutr* 2010;29:154–159.
- Abellan van Kan G, Andre E, Bischoff Ferrari HA, et al. Carla Task Force on Sarcopenia: Propositions for clinical trials. *J Nutr Health Aging* 2009;13:700–707.
- Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: Toward a clinical definition. *J Am Med Dir Assoc* 2008;9:71–72.
- Morley JE. Developing novel therapeutic approaches to frailty. *Curr Pharm Des* 2009;15:3384–3395.
- Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–M156.
- Morley JE, Baumgartner RN, Roubenoff R, et al. Sarcopenia. *J Lab Clin Med* 2001;137:660–663.
- Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147: 755–763.
- Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004;52: 80–85.
- Rolland Y, Lauwers-Cances V, Cristini C, et al. Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (Epidemiologie de l'OSTeoporose). Study. *Am J Clin Nutr* 2009;89: 1895–1900.
- Baumgartner RN, Wayne SJ, Waters DL, et al. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004;12:1995–2004.
- Thomas DR, Ashmen W, Morley JE, Evans WJ. Nutritional management in long-term care: Development of a clinical guideline. Council for Nutritional Strategies in Long-Term Care. *J Gerontol A Biol Sci Med Sci* 2000;55:M725–M734.
- Morley JE. Weight loss in older persons: New therapeutic approaches. *Curr Pharm Des* 2007;13:3637–3647.
- Visvanathan R, Chapman IM. Undernutrition and anorexia in the older person. *Gastroenterol Clin North Am* 2009;38:393–409.
- Donini LM, Savina C, Cannella C. Eating habits and appetite control in the elderly: The anorexia of aging. *Int Psychogeriatr* 2003;15:73–87.
- McIntosh CG, Morley JE, Wishart J, et al. Effect of exogenous cholecystokinin (CCK)-8 on food intake and plasma CCK, leptin, and insulin concentrations in older and young adults: Evidence for increased CCK activity as a cause of the anorexia of aging. *J Clin Endocrinol Metab* 2001;86:5830–5837.
- Morley JE. Anorexia of aging: Physiologic and pathologic. *Am J Clin Nutr* 1997;66:760–773.
- Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009;(2): CD003288.
- Stratton RJ, Elia M. Are oral nutritional supplements of benefit to patients in the community? Findings from a systematic review. *Curr Opin Clin Nutr Metab Care* 2000;3:311–315.
- Fulgoni VL 3rd. Current protein intake in America: Analysis of the National Health and Nutrition Examination Survey, 2003–2004. *Am J Clin Nutr* 2008;87:1554S–1557S.
- Kerstetter JE, O'Brien KO, Insogna KL. Low protein intake: The impact on calcium and bone homeostasis in humans. *J Nutr* 2003;133: 8555–8615.
- Houston DK, Nicklas BJ, Ding J, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: The Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2008;87:150–155.
- Vellas BJ, Hung WC, Romero LJ, et al. Changes in nutritional status and patterns of morbidity among free-living elderly persons: A 10-year longitudinal study. *Nutrition* 1997;13:515–519.
- Lesourd B, Decarli B, Dirren H. Longitudinal changes in iron and protein status of elderly Europeans. SENECA Investigators. *Eur J Clin Nutr* 1996;50:S16–S24.
- Ferrando AA, Paddon-Jones D, Hays NP, et al. EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly. *Clin Nutr* 2010;29:18–23.
- Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. *Curr Opin Clin Nutr Metab Care* 2009; 12:86–90.
- Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. *Clin Nutr* 2008;27:675–684.
- Evans WJ. Protein nutrition, exercise and aging. *J Am Coll Nutr* 2004; 23:601S–609S.
- Sloane PD, Ivey J, Helton M, et al. Nutritional issues in long-term care. *J Am Med Dir Assoc* 2008;9:476–485.
- Wilson MM, Purushothaman R, Morley JE. Effect of liquid dietary supplements on energy intake in the elderly. *Am J Clin Nutr* 2002;75: 944–947.
- Campbell WW. Synergistic use of higher-protein diets or nutritional supplements with resistance training to counter sarcopenia. *Nutr Rev* 2007;65:416–422.
- Arnal MA, Mosoni L, Boirie Y, et al. Protein pulse feeding improves protein retention in elderly women. *Am J Clin Nutr* 1999;69: 1202–1208.

43. Laviano A, Muscaritoli M, Cascino A, et al. Branched-chain amino acids: The best compromise to achieve anabolism? *Curr Opin Clin Nutr Metab Care* 2005;8:408–414.
44. Rieu I, Balage M, Sornet C, et al. Leucine supplementation improves muscle protein synthesis in elderly men independently of hyperaminoacidemia. *J Physiol* 2006;575:305–315.
45. Drummond MJ, Rasmussen BB. Leucine-enriched nutrients and the regulation of mammalian target of rapamycin signaling and human skeletal muscle protein synthesis. *Curr Opin Clin Nutr Metab Care* 2008; 11:222–226.
46. Layman DK. Role of leucine in protein metabolism during exercise and recovery. *Can J Appl Physiol* 2002;27:646–663.
47. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab* 2004; 89:4351–4358.
48. Hays NP, Kim H, Wells AM, et al. Effects of whey and fortified collagen hydrolysate protein supplements on nitrogen balance and body composition in older women. *J Am Diet Assoc* 2009;109:1082–1087.
49. Paddon-Jones D, Sheffield-Moore M, Katsanos CS, et al. Differential stimulation of muscle protein synthesis in elderly humans following iso-caloric ingestion of amino acids or whey protein. *Exp Gerontol* 2006;41: 215–219.
50. Solerte SB, Gazzaruso C, Bonacasa R, et al. Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. *Am J Cardiol* 2008; 101:69E–77E.
51. Onder G, Della Vedova C, Landi F. Validated treatments and therapeutics prospectives regarding pharmacological products for sarcopenia. *J Nutr Health Aging* 2009;13:746–756.
52. Hoffman JR, Kraemer WJ, Bhasin S, et al. Position stand on androgen and human growth hormone use. *J Strength Cond Res* 2009;23:S1–S59.
53. Kaiser FE, Silver AJ, Morley JE. The effect of recombinant human growth hormone on malnourished older individuals. *J Am Geriatr Soc* 1991;39:235–240.
54. Wittert GA, Chapman IM, Haren MT, et al. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Gerontol A Biol Sci Med Sci* 2003;58:618–625.
55. Bhasin S, Storer TW. Anabolic applications of androgens for functional limitations associated with aging and chronic illness. *Front Horm Res* 2009;37:163–182.
56. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: A randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010; 95:639–650.
57. Chapman IM, Visvanathan R, Hammond AJ, et al. Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. *Am J Clin Nutr* 2009;89:880–889.
58. Candow DG, Chilibeck PD. Effect of creatine supplementation during resistance training on muscle accretion in the elderly. *J Nutr Health Aging* 2007;11:185–188.
59. Bemben MG, Lamont HS. Creatine supplementation and exercise performance: Recent findings. *Sports Med* 2005;35:107–125.
60. Johnston AP, Burke DG, MacNeil LG, Candow DG. Effect of creatine supplementation during cast-induced immobilization on the preservation of muscle mass, strength, and endurance. *J Strength Cond Res* 2009;23:116–120.
61. Chrusch MJ, Chilibeck PD, Chad KE, et al. Creatine supplementation combined with resistance training in older men. *Med Sci Sports Exerc* 2001;33:2111–2117.
62. Stout JR, Sue Graves B, Cramer JT, et al. Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64–86 years). *J Nutr Health Aging* 2007;11:459–464.
63. Tarnopolsky M, Zimmer A, Paikin J, et al. Creatine monohydrate and conjugated inoleic acid improve strength and body composition following resistance exercise in older adults. *PLoS One* 2007;2: e991.
64. Burke DG, Chilibeck PD, Parise G, et al. Effect of alpha-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. *Int J Sport Nutr Exerc Metab* 2003;13:294–302.
65. Candow DG, Little JP, Chilibeck PD, et al. Low-dose creatine combined with protein during resistance training in older men. *Med Sci Sports Exerc* 2008;40:1645–1652.
66. Hass CJ, Collins MA, Juncos JL. Resistance training with creatine monohydrate improves upper-body strength in patients with Parkinson disease: A randomized trial. *Neurorehabil Neural Repair* 2007;21: 107–115.
67. Kuethe F, Krack A, Richartz BM, Figulla HR. Creatine supplementation improves muscle strength in patients with congestive heart failure. *Pharmazie* 2006;61:218–222.
68. Deacon SJ, Vincent EE, Greenhaff PL, et al. Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;178:233–239.
69. Faager G, Soderlund K, Skold CM, et al. Creatine supplementation and physical training in patients with COPD: A double blind, placebo-controlled study. *Int J Chron Obstruct Pulmon Dis* 2006;1:445–453.
70. Sakkas GK, Mulligan K, DaSilva M, et al. Creatine fails to augment the benefits from resistance training in patients with HIV infection: A randomized, double-blind, placebo-controlled study. *PLoS One* 2009;4: e4605.
71. Perry HM 3rd, Horowitz M, Morley JE, et al. Longitudinal changes in serum 25-hydroxyvitamin D in older people. *Metabolism* 1999;48: 1028–1032.
72. Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: Mechanisms of action. *Mol Aspects Med* 2008;29: 361–368.
73. Hamid Z, Riggs A, Spencer T, et al. Vitamin D deficiency in residents of academic long-term care facilities despite having been prescribed vitamin D. *J Am Med Dir Assoc* 2007;8:71–75.
74. Morley JE. Vitamin D redux. *J Am Med Dir Assoc* 2009;10:591–592.
75. Braddy KK, Imam SN, Palla KR, Lee TA. Vitamin D deficiency/insufficiency practice patterns in a Veterans Health Administration long-term care population: A retrospective analysis. *J Am Med Dir Assoc* 2009;10:653–657.
76. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): The Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 2003;88:5766–5772.
77. Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: An authentic strength preserving hormone. *Mol Aspects Med* 2005;26:203–219.
78. Ahmed W, Khan N, Glueck CJ, et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. *Transl Res* 2009;153:11–16.
79. Lee P, Greenfield JR, Campbell LV. Vitamin D insufficiency—a novel mechanism of statin-induced myalgia? *Clin Endocrinol* 2009;71: 154–156.
80. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: A meta-analysis. *JAMA* 2004;291:1999–2006.
81. Autier P, Gandini S. Vitamin D supplementation and total mortality: A meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167:1730–1737.
82. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 2008;93:677–681.
83. Kortebéin P, Symons TB, Ferrando A, et al. Functional impact of 10 days of bed rest in healthy older adults. *J Gerontol A Biol Sci Med Sci* 2008;63:1076–1081.
84. Kortebéin P, Ferrando A, Lombeida J, et al. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 2007;297:1772–1774.

85. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med* 1994;330:1769–1775.
86. Fiatarone MA, Marks EC, Ryan ND, et al. High-intensity strength training in nonagenarians. Effects on skeletal muscle. *JAMA* 1990; 263:3029–3034.
87. Marini M, Sarchielli E, Brogi L, et al. Role of adapted physical activity to prevent the adverse effects of the sarcopenia. A pilot study. *Ital J Anat Embryol* 2008;113:217–225.
88. Morganti CM, Nelson ME, Fiatarone MA, et al. Strength improvements with 1 yr of progressive resistance training in older women. *Med Sci Sports Exerc* 1995;27:906–912.
89. Stasser B, Keinrad M, Haber P, Schobersberger W. Efficacy of systematic endurance and resistance training on muscle strength and endurance performance in elderly adults—a randomized controlled trial. *Wien Klin Wochenschr* 2009;121:757–764.
90. Capodaglio P, Capodaglio EM, Ferri A, et al. Muscle function and functional ability improves more in community-dwelling older women with a mixed-strength training programme. *Age Ageing* 2005;34:141–147.
91. Capodaglio P, Capodaglio Edda M, Facioli M, Saibene F. Long-term strength training for community-dwelling people over 75: Impact on muscle function, functional ability and life style. *Eur J Appl Physiol* 2007;100:535–542.
92. Morley JE. Anorexia, weight loss, and frailty. *J Am Med Dir Assoc* 2010; 11:225–228.
93. Harber MP, Konopka AR, Douglass MD, et al. Aerobic exercise training improves whole muscle and single myofiber size and function in older women. *Am J Physiol Regul Integr Comp Physiol* 2009;297: R1452–R1459.
94. Snijders T, Verdijk LB, van Loon LJ. The impact of sarcopenia and exercise training on skeletal muscle satellite cells. *Ageing Res Rev* 2009;8: 328–338.
95. van Swearingen JM, Perera S, Brach JS, et al. A randomized trial of two forms of therapeutic activity to improve walking: Effect on the energy cost of walking. *J Gerontol A Biol Sci Med Sci* 2009;64:1190–1198.
96. Bulthius Y, Mohammad S, Braakman-Jansen LM, et al. Cost-effectiveness of intensive exercise therapy directly following hospital discharge in patients with arthritis: Results of a randomized controlled clinical trial. *Arthritis Rheum* 2008;59:247–254.
97. Baker MK, Atlantis E, Fiatarone Singh MA. Multi-modal exercise programs for older adults. *Age Ageing* 2007;36:375–381.
98. Mian OS, Thom JM, Ardigo LP, et al. Effect of a 12-month physical conditioning programme on the metabolic cost of walking in healthy older adults. *Eur J Appl Physiol* 2007;100:499–505.
99. Cotev D, Hornby TG, Gordon KE, Schmit BD. Increases in muscle activity produced by vibration of the thigh muscles during locomotion in chronic human spinal cord injury. *Exp Brain Res* 2009;196:361–374.
100. Bogaerts AC, Delecluse C, Claessens AL, et al. Effects of whole body vibration training on cardiorespiratory fitness and muscle strength in older individuals (a 1-year randomized controlled trial). *Age Ageing* 2009;38:448–454.
101. Raimundo AM, Gusi N, Tomas-Carus P. Fitness efficacy of vibratory exercise compared to walking in postmenopausal women. *Eur J Appl Physiol* 2009;106:741–748.