appendicular skeletal muscle with a value lower than 2 standard deviations from that measured in the healthy population, and a fat mass greater than the 60th percentile of an age-matched population [10, 11]. Another study classified sarcopenic obesity as cases with a percentage body fat in the upper two quintiles and a relative muscle mass in the lower two quintiles [12]. Muscle mass and fat mass are assessed by several methods including BMI, mid-upper arm circumference, bioelectrical impedance analysis, dual energy X-ray absorptiometry, and computer tomography [2]. However, there is no standardized definition and diagnostic criteria for sarcopenic obesity.

Sarcopenic obesity is associated with adverse health effects such as physical disability, cardiovascular disease risk, and death [10, 11, 13, 14]. The relative risk (RR) for incident disability in obese sarcopenic subjects was reported to be 2.63 (95% confidence interval (CI), 1.19 to 5.85) after adjustment for age, sex, physical activity level, length of follow-up, and prevalent morbidity in the elderly [10]. Significantly higher odds ratios (ORs) for difficulty climbing stairs (OR, 2.45; 95% CI 0.99 to 6.04), going down stairs (OR, 3.41; 95% CI, 1.35 to 8.57), or rising from a chair or bed (OR, 2.89; 95% CI, 1.01 to 8.30) were observed more frequently in women with sarcopenic obesity than in women with sarcopenia alone [11]. Cardiovascular disease risk was also reported to be increased by 23% (95% CI, 0.99 to 1.54) in a sarcopenic-obese group in community-dwelling elderly subjects [12]. In addition, sarcopenic obesity was found to be an independent predictor of survival (hazard ratio (HR), 4.2; 95% CI, 2.4 to 7.2) in patients with solid tumors of the respiratory and gastrointestinal tracts [13]. In contrast, other studies found no association between sarcopenic obesity and functional limitations [12, 15]. Despite these inconsistent findings between studies, sarcopenic obesity is regarded as an important current and future public health issue.

Numerous interventional studies for sarcopenia and obesity treatment have been performed. However, a literature search we conducted showed there are no intervention studies for sarcopenic obesity in humans. Therefore, it is necessary to make inferences from separate intervention studies on sarcopenia and obesity. In this review, we first review nutrition, exercise and pharmaceutical therapies used to treat sarcopenia and obesity in humans, and then summarize a comprehensive approach for inhibiting sarcopenic obesity.

2. NUTRITION THERAPIES

2.1. Nutrition Therapies for Sarcopenia

Protein and amino acid supplementation can counteract sarcopenia, as low protein intake is known to be associated with declining muscle mass in older adults [16]. A Cochrane Database of Systematic Review found that protein and energy supplementation produced a small but consistent weight gain of 2.2% in older people (95% CI, 1.8 to 2.5), while mortality may be reduced in older people who are undernourished (RR, 0.79; 95% CI, 0.64 to 0.97) [11]. However, that review found no evidence of a reduction in the length of hospital stay with supplementation (-0.8 days; 95% CI, -2.8 to 1.3) [17]. A recent systematic review on the effectiveness of nutritional supplementation on muscle mass in the treatment of sarcopenia in old age also confirmed an improvement in muscle mass and muscle strength [18]. Many essential acids including large amounts of leucine are needed to effectively counteract sarcopenia [6].

Consuming sufficient energy is important, as loss of muscle mass can be a result of calorie restriction or starvation. Biolo *et al.* [19] investigated the effects of the interaction of inactivity and calorie restriction on whole-body composition and protein kinetic regulation in nine healthy volunteers. Lean body mass was measured using dual-energy X-ray absorptionometry before and at the end of 14-day periods of bed rest and controlled ambulation in subjects receiving either a hypocaloric (approximately 80% of total energy expenditure) or normal diet. During the eucaloric period, lean body mass decreased −0.1 ± 0.1 kg during ambulatory conditions and −0.3 ± 0.2 kg with bed rest. During the hypocaloric periods, lean body mass decreased −0.3 ± 0.3 kg during ambulatory conditions and −1.1 ± 0.1 kg with bed rest ($p < 0.01$ for activity effect; $p = 0.04$ for diet effect; $p = 0.03$ for interaction). These results indicate that physical inactivity under conditions of negative energy balance may lead to a rapid loss of lean body mass, and that such a catabolic effect can be prevented, at least in the short term, by a moderate level of physical activity. Evidence from other studies also suggests that maintaining protein intake during a period of disuse attenuates disuse atrophy [20], with 91% of patients with the disuse syndrome being classified as malnourished [21]. Maintaining energy and protein intake and physical activity is therefore important for preventing sarcopenia.

Because both resistance training and protein supplementation are effective treatments for sarcopenia, resistance training combined with supplements containing amino acids would be expected to be the most effective option for preventing and treating age-related muscle wasting and weakness [5-7]. Kim *et al.* [22] found that the combination of exercise and amino acid supplementation were effective for enhancing muscle strength, muscle mass, and walking speed in sarcopenic women. In a meta-analysis of protein supplementation during prolonged resistance-type exercise training, protein supplementation showed a positive effect on fat-free mass and one-repetition maximum leg press strength compared with placebo in both younger and older subjects [23]. Therefore, treatment of sarcopenia should include resistance training and protein and amino acid supplementation.

2.2. Nutrition Therapies for Obesity

Low-calorie diets can counteract obesity, as reducing caloric intake below expenditure results in weight loss. For example, a balanced diet providing an energy deficit of 500 to 750 kcal per day from daily energy requirements with approximately 1 g of high-quality protein per kilogram of body weight per day was prescribed in a 1-year, randomized, controlled trial on combined weight loss and exercise [24]. An initial weight loss goal of more than 5% was realistic and appeared to be associated with improvements in cardiovascular risk factors mainly in people with several concomitant factors [25].

There are many types of diets that produce weight loss. Balanced low-calorie diets are a standard strategy for losing body weight. Meta-analyses also showed low-carbohydrate diets were associated with significant decreases in body weight (-7.04 kg; 95% CI, -7.20 to -6.88) [26], whereas lower total fat intake was associated with a lower relative body weight (-1.6 kg; 95% CI, -2.0 to -1.2) [27]. A meta-analysis comparing low-carbohydrate and low-fat diets demonstrated that individuals assigned to low-carbohydrate diets lost more weight than individuals randomized to low-fat diets (weighted mean difference (WMD), -3.3 kg; 95% CI, -5.3 to -1.4) after 6 months [28]. However, this difference was no longer obvious after 12 months (WMD, -1.0 kg; 95% CI, -3.5 to 1.5) [28]. Another meta-analysis showed that reduction in body weight was not significantly different between low-carbohydrate and low-fat diets [29].

Meta-analysis also showed high-protein diets produced more weight loss than low-protein diets (standardized mean difference (SMD) -0.36; 95% CI, -0.56 to -0.17) [30]. Another meta-analysis showed that energy-restricted, isocaloric, high-protein and low-fat diets were better for reducing body weight (0.79 kg; 95% CI, -1.50 to -0.08) and fat mass (-0.87 kg; 95% CI, -1.26 to -0.48 kg), compared with a standard-protein, low-fat diet [31]. The Mediterranean diet was also reported to have a significant effect on weight (mean difference (MD) between -1.75 kg; 95% CI, -2.86 to -0.64) [32]. In a Cochrane Database of Systematic Review, diets with a low glycemic index or low glycemic load were shown to result in a greater decrease in body weight (WMD -1.1 kg; 95% CI -2.0 to -0.2) [33]. Very-low-calorie diets that provided less than 800 kcal/day have been used to induce rapid weight loss. Very-low-calorie diets induced significantly greater short-term weight losses (16.1 ± 1.6% vs. 9.7 ± 2.4% of initial weight, respectively; $p = 0.0001$) compared with conventional low-calorie diets that provided between 800 and 1800 kcal/day [34]. However, there were no significant long-term weight losses with the two diets (6.3 ± 3.2% vs. 5.0 ± 4.0%, respectively; $p > 0.2$) [34].

Although intervention with a low-calorie diet only was effective for reducing body weight, meta-analysis showed a pooled weight loss of 1.14 kg (95% CI, 0.21 to 2.07) was greater in the diet-plus-exercise group than the diet-only group [35]. In a 1-year, randomized, controlled trial, combination of a low-calorie diet and exercise were shown to maintain more lean body mass than either intervention alone [24]. On the basis of these results, a combination of a low-calorie diet and exercise would be recommended for obese elderly subjects.

3. EXERCISE THERAPIES

3.1. Exercise Therapies for Sarcopenia

Resistance training has been shown to be the most promising intervention for decreasing the effects of sarcopenia, as it induces skeletal muscle hypertrophy, and enhances muscle strength. A systematic review of the effects of exercise intervention for increasing muscle mass in elderly subjects identified 5 of 6 articles that concluded high-intensity resistance training resulted in significant increases in soft lean tissue and muscle mass [36]. On the other hand, the remaining three articles indicated that moderate-intensity resistance training did not affect soft lean tissue or muscle mass [36]. High-intensity resistance training of sufficient duration, frequency, repetitions, and sets is therefore effective for counteracting the loss of muscle mass associated with advancing age.

A meta-analysis of resistance exercise for muscular strength in older adults revealed that higher intensity training was associated with greater improvement in strength [37]. The increases in strength ranged from 9.8 to 31.6 kg, while the percent changes were 29 ± 2, 24 ± 2, 33 ± 3, and 25 ± 2 for leg presses, chest presses, knee extensions, and lateral pulls, respectively [37]. A Cochrane Database of Systematic Review reported progressive resistance strength training was also an effective intervention for improving physical functioning in older people as it increased muscle strength (SMD, 0.84; 95% CI, 0.67 to 1.00) and gait speed (MD, 0.08 m/s; 95% CI, 0.04 to 0.12) in older adults [38]. Careful attention should be paid when determining the amount and frequency of resistance training in the elderly, as excess intensive strength training in these people may impair effective gains in muscle strength and mass.

During disuse, skeletal muscle loss occurs at a rate of approximately 0.5% of total muscle mass per day [20]. The substantial loss of skeletal muscle mass during disuse is accompanied by a decline in strength ranging between 0.3% and 4.2% per day [20]. Physical activity and aerobic exercise are therefore important not only for increasing muscle mass, but also for maintaining muscle mass and preventing sarcopenia. Daily ambulatory activity with moderate intensity estimated by accelerometer has been shown to correlate positively with lower body muscle size and function in older adults [39]. Although there is conflicting data on the effects of short-term ambulation training, it is possible that relatively long periods of walking, jogging, or intermittent running for over half a year can increase leg muscle size in elderly adults [39].

3.2. Exercise Therapies for Obesity

Exercise and physical activity has beneficial effects, not only in causing a loss of weight but also reducing cardiovascular risk [40]. A Cochrane Database of Systematic Review reported that exercise combined with diet resulted in a greater weight reduction than diet alone (WMD -1.1 kg; 95% CI, -1.5 to -0.6), while raising exercise intensity increased the magnitude of weight loss (WMD -1.5 kg; 95% CI, -2.3 to -0.7) [41]. A meta-analysis of isolated aerobic exercise and weight loss showed that 6-month exercise programs were associated with a modest reduction in weight (WMD -1.6 kg; 95% CI, -1.64 to -1.56), while a 12-month program was also associated with a modest reduction in weight (WMD -1.7 kg; 95% CI, -2.29 to -1.11) [42]. Another meta-analysis showed that pedometer-based walking interventions were associated with weight loss (-1.27 kg; 95% CI, -1.85 to -0.70), with participants losing an average 0.05 kg per week during the intervention [43]. These results indicate that aerobic exercise alone can induce weight loss. However, a low-calorie diet should be combined with exercise as the effect of aerobic exercise on weight reduction is minimal.

Resistance training is another exercise therapy for obesity. A meta-analysis showed resistance training reduced fat mass by 2.33 kg (95% CI, -4.71 to 0.04) in patients with abnormal glucose metabolism [44]. A systematic review on the effect of exclusive resistance training on body composition and cardiovascular risk factors in overweight or obese children, showed that 4 of 6 studies reported significant changes in body composition, with an increase in fat-free mass and BMI associated with a decrease in fat mass [45].

A meta-analysis of aerobic versus resistance exercise training on reduction of visceral fat showed that there was a significant pooled effect size for the comparison between aerobic exercise and controls (-0.33; 95% CI, -0.52 to -0.14), but not for the comparison between progressive resistance training and controls (0.09; 95% CI, -0.17 to 0.36) [46]. This result suggests that aerobic exercise is a central point for exercise programs aimed at reducing visceral fat. However, recent randomized, controlled trials on the effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in overweight and obese subjects demonstrated there were significant improvements in body weight (-1.6%, $p = 0.044$) in the combination exercise group compared with the control and resistance groups [47]. Significant improvements in body fat percentage (-2.6%, $p = 0.008$) and abdominal fat percentage (-2.8%, $p = 0.034$) were also observed in the combination exercise group compared with controls [47]. A combination of aerobic exercise and resistance training is therefore recommended for overweight and obese adults.

4. PHARMACEUTICAL THERAPIES

4.1. Pharmaceutical Therapies for Sarcopenia

4.1.1. Testosterone

Although the mechanisms by which testosterone increases skeletal muscle are poorly understood, it has been shown to positively regulate insulin-like growth factor-1 and myostatin [5]. A meta-analysis indicated

that testosterone supplementation increased fat-free mass and muscle strength in men aged older than 45 years with low or low-normal testosterone levels [48]. Testosterone replacement was associated with a significantly greater increase in lean body mass (2.7 kg; 95% CI, 1.6 to 3.7), grip strength (3.3 kg; 95% CI, 0.7 to 5.8), and a greater reduction in fat mass (-2.0 kg; 95% CI, -3.1 to -0.8) compared with placebo [48]. Another meta-analysis of testosterone or dihydrotestosterone replacement therapy in men with a mean age of 65 years or greater revealed that the mean g-index adjusted for sample size was 0.53 (95% CI, 0.21 to 0.86) [49]. A mean g-index of 0.53 indicated that androgen treatment produced an approximately 19.3% increase in muscle strength [49].

Although testosterone treatment resulted in significant increases in fat-free mass and muscle strength, a meta-analysis of adverse effects of testosterone therapy in adult men showed it was also associated with a significant increase in hemoglobin (WMD, 0.80 g/dl; 95% CI, 0.45 to 1.14) and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13) [50]. No significant effects on mortality, prostate disease, or cardiovascular outcomes were observed in that study [50]. On the other hand, a testosterone gel was shown to be associated with an increased risk of cardiovascular adverse events (total risk OR, 10.6; 95% CI, 1.3 to 84.5) in older men with limited mobility and a high prevalence of chronic disease [51]. Testosterone increases fat-free mass and muscle strength, and if no contraindications for its use are apparent it could be used as a first-line pharmaceutical therapy in sarcopenic elderly men for several months whilst monitoring side effects.

4.1.2. Growth Hormone

Growth hormone (GH) is a single-chain peptide of 191 amino acids, produced and secreted mainly by the somatotrophs of the anterior pituitary gland. GH coordinates the postnatal growth of multiple target tissues, including skeletal muscle. A systematic review of randomized, controlled trials of GH therapy in healthy, elderly subjects showed that those treated with GH therapy had a decreased overall fat mass (-2.1 kg; 95% CI, -2.8 to -1.35) and increased overall lean body mass (2.1 kg; 95% CI, 1.3 to 2.9), compared with those not receiving treatment [52]. However, subjects treated with GH were shown to be significantly more likely to experience soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia, and were somewhat more likely to develop diabetes mellitus and impaired fasting glucose. Therefore, GH therapy cannot be recommended as sarcopenia treatment in healthy, elderly subjects due to its adverse effects [52].

Subsequent to this systematic review, another study in healthy, elderly adults showed administration of the oral GH secretagogue, capromorelin, improved body composition and physical function (lean body mass increased with capromorelin 1.4 kg vs. placebo 0.3 kg, $p = 0.001$) [53]. Adverse events included fatigue, insomnia, and small increases in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance [53]. Several randomized, controlled trials on growth hormone and/or testosterone in healthy, elderly subjects also revealed that body composition and muscle performance were improved and enhanced by GH supplementation [54-57]. For example, lean body mass increased by 2.0 ± 0.5 kg in the GH group ($p = 0.004$) and by 1.8 ± 0.5 kg in the GH and testosterone group ($p = 0.007$) compared with placebo [54]. However, GH therapy is still not recommended as a treatment for sarcopenia due to its adverse effects.

4.1.3. Ghrelin

Ghrelin is a 28-amino-acid peptide produced mainly by cells in the stomach, and is a natural ligand for the GH-secretagogue receptor [58]. Ghrelin plays a critical role in a variety of physiological processes, by stimulating GH secretion and regulating energy homeostasis by stimulating food intake and promoting adiposity *via* a GH-independent mechanism. Because of their combined anabolic effects on skeletal muscle and appetite, ghrelin and low-molecular-weight agonists of the ghrelin receptor are considered attractive candidates for treating sarcopenia.

Oral administration of the ghrelin mimetic MK-677 at a dose of 25 mg once daily for 1 year in healthy elderly adults older than 60 years was shown to cause significant increases in fat-free mass (placebo -0.5 kg; 95% CI, -1.1 to 0.2, vs. ghrelin mimetic 1.1 kg; 95% CI, 0.7 to 1.5, $p < 0.001$) [59]. However, that study did not show a significant increase in strength or function in the ghrelin-mimetic treatment group, compared with the placebo group. Patients with osteoarthritis undergoing elective total hip replacement who received intravenous injections of 2 mg/kg of ghrelin twice-daily for 3 weeks beginning 1 week before surgery, had significant increases in lean body mass ($p = 0.012$) and decreases in fat mass ($p = 0.017$) [60]. In contrast, muscle strength and walking ability did not differ significantly [60]. Although ghrelin appears to increase

lean body mass in the elderly, increased fat-free mass may not result in changes in muscle strength or physical function. Long-term, large-scale clinical trials are therefore required to recommend ghrelin as a treatment for sarcopenia.

4.1.4. Vitamin D

Vitamin D deficiency is one cause of proximal myopathy and sarcopenia which improves with vitamin D supplementation [61, 62]. Vitamin D appears to down-regulate myostatin expression and up-regulate follistatin expression, an inhibitor of myostatin. As a low vitamin D level has been shown to be associated with an increased risk of mobility limitation and disability in community-dwelling subjects [63], vitamin D supplementation appears a reasonable treatment option in sarcopenia, especially in elderly subjects with vitamin D deficiency. An association between low vitamin D and low muscle mass has been reported in several studies [64-67]. On the other hand, Marantes *et al.* [68] found the association between low vitamin D and low muscle mass occurred only in subjects younger than 65 years.

A systematic review that examined mainly community-dwelling, older women showed the association between vitamin D supplementation and physical performance remained controversial [69]. Four of the 5 studies and 2 of the 3 studies which tested the effect of vitamin D supplementation on balance and gait, respectively, showed no significant effect [69]. Four studies showed a significant effect on muscle strength, although this effect was not observed in three other studies [69]. In a recent systematic review and meta-analysis of 17 randomized, controlled trials, vitamin D supplementation was reported to have no significant effect on grip strength (SMD, -0.02; 95% CI, -0.15 to 0.11) or proximal lower limb strength (SMD, 0.1; 95% CI, -0.01 to 0.22) in adults with a baseline 25(OH)D > 25 nmol/L [70]. However, pooled data from two studies on vitamin D-deficient participants (25(OH)D < 25 nmol/L) demonstrated a large effect of vitamin D supplementation on hip muscle strength (SMD, 3.52; 95% CI, 2.18 to 4.85) [70]. Vitamin D supplementation is therefore recommended for increasing muscle strength only in elderly subjects with vitamin D deficiency.

4.2. Pharmaceutical Therapies for Obesity

4.2.1. Orlistat

Orlistat alters fat digestion by inhibiting pancreatic lipase and induces weight loss by increasing fecal fat excretion, due to the fat not being completely hydrolyzed. A Cochrane Database of Systematic Review showed obese and overweight patients treated with orlistat lost 2.7 kg of weight (95% CI, 2.3 to 3.1) compared with placebo [71]. The number of patients achieving 10% or greater weight loss was 12% higher (95% CI, 8 to 16) with orlistat therapy [71]. An updated meta-analysis of long-term pharmacotherapy for obesity and overweight revealed that orlistat reduced weight by 2.9 kg (95% CI, 2.5 to 3.2) compared with placebo [72]. A recent meta-analysis on the effects of anti-obesity drugs on cardiovascular risk factors showed that orlistat treatment was associated with a reduction of 2.39 kg in weight (95% CI, -3.34 to -1.45) , a reduction of 0.27 mmol/L in total cholesterol (95% CI, -0.36 to -0.17), a reduction of 0.21 mmol/L in low-density lipoprotein (95% CI, -0.30 to -0.12), a reduction of 0.12 mmol/L in fasting glucose (95% CI, -0.20 to -0.04), a reduction of 1.85 mmHg in systolic blood pressure (95% CI, -3.30 to -0.40), and a reduction of 1.49 mmHg in diastolic blood pressure (95% CI, -2.39 to -0.58) [73]. Orlistat is suggested as first-line pharmaceutical therapy for obesity as there is no evidence it is associated with an increased risk of cardiovascular events.

4.2.2. Lorcaserin

Lorcaserin is a selective agonist of the serotonin 2c receptor, and selectively activates central receptors and decreases food intake through the proopiomelanocortin system of neurons. In 2012, the United States Food and Drug Administration approved lorcaserin as an addition to a reduced-calorie diet and exercise regimen for obese or overweight (BMI ≥ 27 kg/m^2) patients with at least one medical comorbidity, such as type 2 diabetes, hypertension, high cholesterol, or sleep apnea. A meta-analysis of randomized, controlled trials of 1 year duration reported weight loss of 3.23 kg (95% CI, 2.70 to 3.75) and a reduction in BMI of 1.16 kg/m^2 (95% CI, 0.98 to 1.34) compared with placebo [74]. The use of lorcaserin for 8 and 12 weeks reduced weight by 1.60 kg (95% CI, 0.34 to 2.86) and 2.9 kg (95% CI, 2.2 to 3.5), respectively [74]. Headache, nausea, and dizziness were found to be significantly higher in patients receiving lorcaserin than those receiving placebo [74]. Data on long-term weight loss and safety with lorcaserin treatment are still required.

4.2.3. Phentermine-Topiramate

Phentermine is a noradrenergic sympathomimetic drug that stimulates the release of norepinephrine or

inhibits its reuptake into nerve terminals. Topiramate is an antiepileptic drug used to treat certain types of seizures in people who have epilepsy. In 2012, the United States Food and Drug Administration approved the combination of phentermine and topiramate for weight loss in obese or overweight (BMI ≥ 27 kg/m^2) patients with at least one medical comorbidity.

In the CONQUER randomized, controlled trial, changes in bodyweight after 56 weeks were -1.4 kg (least-squares mean -1.2%; 95% CI, -1.8 to -0.7), -8.1 kg (-7.8%; 95% CI, -8.5 to -7.1; p < 0.0001), and -10·2 kg (-9·8%; 95% CI, -10·4 to -9·3; p < 0.0001) in patients assigned to placebo, phentermine 7.5 mg plus topiramate 46.0 mg, or phentermine 15.0 mg plus topiramate 92.0 mg, respectively [75]. In the EQUIP randomized, controlled trial, patients in the placebo, phentermine 3.75 mg plus topiramate 23 mg, and phentermine 15 mg plus topiramate 92 mg groups lost 1.6%, 5.1%, and 10.9% of baseline body weight after 56 weeks, respectively (p < 0.0001) [76]. The SEQUEL randomized, controlled trial showed weight loss was maintained for over 2 years with 9.3% and 10.5% weight loss from baseline for phentermine 7.5 mg plus topiramate 46 mg and phentermine 15 mg plus topiramate 92 mg, respectively (p < 0.0001) [77]. Adverse reactions occurred in 5% or more of the study subjects and included parasthesia, dizziness, dysgeusia, insomnia, constipation, and a dry mouth [78]. Long-term weight loss and safety data of phentermine-topiramate treatment is necessary before its use as a first-line treatment can be recommended.

4.2.4. Vitamin D

An association between low vitamin D and obesity has been reported [79-80]. A meta-analysis indicated that there was a significant inverse weak correlation between serum 25(OH)D levels and BMI in adult population (Fisher's Z = -0.15; 95% CI, -0.19 to -0.11), except for women living in developing countries [79]. Another meta-analysis revealed that each 1 kg/m^2 higher BMI was associated with 1.15% lower 25(OH)D [80]. Low vitamin D level has been also shown to be associated with sarcopenic obesity in adult population [67, 81-83]. On the other hand, Kim *et al.* [66] found the association between low vitamin D and sarcopenia, regardless of obesity in the older population.

The effect of vitamin D supplementation on obesity remains controversial. A randomized, double blind clinical trial with 20,000 IU cholecalciferol twice a week, or 20,000 IU once a week plus placebo, or placebo twice a week for 12 months reported that there was no significant change in weight, waist-to-hip ratio or percentage body fat in any of the groups [84]. Another randomized, controlled trial showed that weight loss was not affected significantly by vitamin D supplementation (83 μg per day) or placebo (-5.7 ± 5.8 kg vs. -6.4 ± 5.6 kg; p = 0.248) [85]. Supplementation with vitamin D (25 μg per day as cholecalciferol) for 12 weeks caused a statistically significant decrease in body fat mass in the vitamin D group compared to the placebo group (-2.7 ± 2.1 kg vs. -0.47 ± 2.1 kg; p < 0.001) [86]. However, body weight and waist circumference did not change significantly in both groups. Rosenblum *et al.* [87] found that calcium and vitamin D supplemented orange juice (1050 mg calcium and 300 IU vitamin D per day) was not effective for weight change in overweight and obese adults (−2.1 ± 2.7 kg vs. −2.8 ± 3.7 kg, p = 0.3748). In contrast, the reduction of visceral adipose tissue was significantly greater in the calcium and vitamin D group than in the control group. Further clinical trials are therefore required to recommend vitamin D as a treatment for obesity.

5. COMPREHENSIVE APPROACH

Sarcopenia treatment should include resistance training and protein and amino acid supplementation. Physical activity and aerobic exercise are important for maintaining muscle mass and preventing sarcopenia. Obesity treatment should include low-calorie, high-protein diets, aerobic exercise, and resistance training. A combination of nutrition therapies (low-calorie, high-protein diets, protein and amino acid supplementation) and exercise therapies (resistance training and aerobic exercise) would therefore be expected to be the most effective option for preventing and treating sarcopenic obesity.

A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults revealed that 81% of the energy restriction groups and 39% of the energy restriction plus exercise groups lost ≥ 15% of their body weight as fat-free mass [88]. The exercise groups had modest changes in body weight and fat-free mass [88]. Another review of 18 randomized, controlled trials of exercise with or without diet components indicated that 3-18 month programs that included aerobic and strengthening exercise (2-3 days per week) with calorie restriction (typically 750 kcal deficit/day), induced the greatest change in functional performance measures compared with exercise or diet

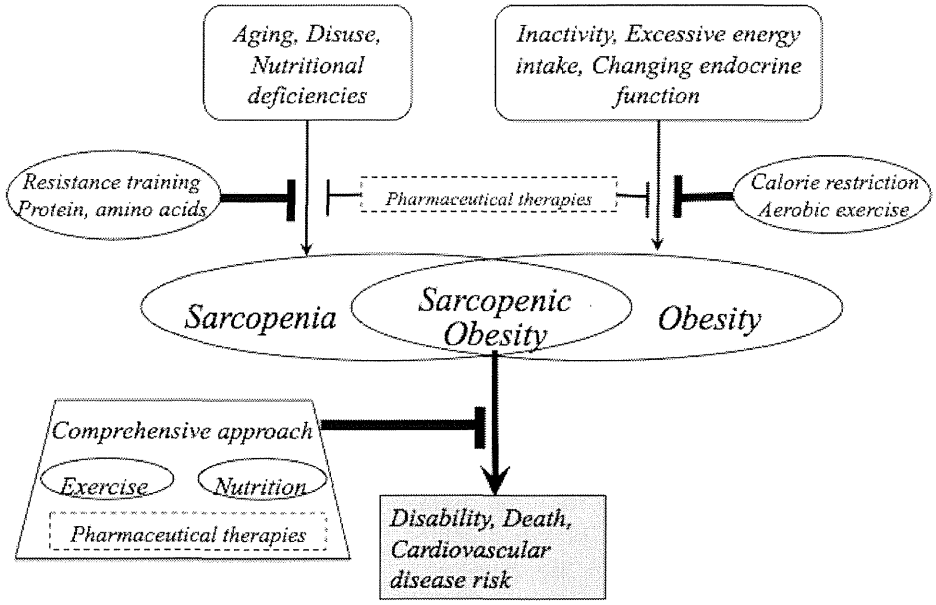


Figure 1: Comprehensive approach to sarcopenic obesity including nutrition, exercise, and pharmaceutical therapies.

alone [89]. Sakuma *et al.* [90] recommended multiple exercises including flexibility training, aerobic exercise, and resistance training, combined with nutrition therapy including caloric restriction (range of 200-750 kcal) and higher intake of protein (up to 1.5 g/kg) of high biological quality to attenuate the symptoms of sarcopenic obesity. However, there have been no intervention studies for sarcopenic obesity, with only observational studies having been reported for the condition. This is due partly to the fact that there is no standardized definition or diagnostic criteria for sarcopenic obesity. Therefore, future research for counteracting sarcopenic obesity should consider determining a standardized definition and diagnostic criteria for the condition and also undertake a multimodal intervention study for sarcopenic obesity.

In case of severe sarcopenic obesity or failure to achieve muscle gain and weight loss through nutrition and exercise therapies, pharmaceutical therapies can be added to treat the condition. In a systematic review of adding drug therapy, exercise, behavior therapy, or combinations of these interventions for obesity indicated that adding orlistat, exercise, or behavior modification to dietary advice improved long-term weight loss [91]. Weight loss program using a very-low-energy diet and orlistat induced both fat loss and fat-free mass loss (fat-free mass to fat mass loss ratio: 1 to 5.9) [92]. In contrast, testosterone replacement was associated with increasing lean body mass and reducing fat mass [48]. In the comprehensive approach for sarcopenic obesity, testosterone or orlistat can be suggested as first-line pharmaceutical therapies, depending on the severity of sarcopenia and obesity. Vitamin D supplementation is recommended in elderly subjects with vitamin D deficiency. However, careful attention should be paid to the adverse effects of testosterone, orlistat, and vitamin D supplementation.

6. CONCLUSION

Sarcopenic obesity is an important current and future public health issue. The impact of sarcopenic obesity on physical disability, cardiovascular disease risk, and death is becoming a primary concern amongst nutritionists, geriatricians, and public health officers. Although there are no intervention studies for sarcopenic obesity, nutrition therapies should include caloric restriction (range of 200-750 kcal), high protein diets (up to 1.5 g/kg), and protein and amino acid supplementation. Exercise therapies for sarcopenic obesity should include both aerobic exercise and resistance training. A combination of nutrition and exercise therapies would be expected to be the most effective option for preventing and treating sarcopenic obesity. In cases of severe sarcopenic obesity or failure to achieve muscle gain and weight loss through nutrition and exercise therapies, pharmaceutical therapies such as testosterone, orlistat, and vitamin D supplementation can be added to the treatment regimen. As shown in Figure **1**, the comprehensive approach to sarcopenic obesity includes nutrition, exercise, and pharmaceutical therapies.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

This study was supported by a Grant-in-Aid for the Comprehensive Research on Aging and Health from the Ministry of Health, Labor, and Welfare of Japan.

REFERENCES

[1] Rosenberg IH. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. Am J Clin Nutr 1989; 50: 1231-3. Reference: Available from: URL http://ajcn.nutrition.org/content/50/5/1231.full.pdf

[2] Rosenberg IH. Sarcopenia: Origins and clinical relevance. J Nutr 1997; 127: 990S-1S. Reference: Available from: URL http://jn.nutrition.org/content/127/5/990S.long

[3] 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 Ageing 2010; 39: 412-23. http://dx.doi.org/10.1093/ageing/afq034

[4] 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. J Am Med Dir Assoc 2011; 12: 249-56. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377163/

[5] Sakuma K, Yamaguchi A. Molecular mechanisms in aging and current strategies to counteract sarcopenia. Curr Aging Sci 2010; 3: 90-101. http://dx.doi.org/10.2174/1874609811003020090

[6] Sakuma K, Yamaguchi A. Sarcopenia: molecular mechanisms and current therapeutic strategy. In Cell Aging, Nova Science Publishers, Huntington, NY, USA, 2011, pp 93-152.

[7] Sakuma K, Yamaguchi A. Novel intriguing strategies attenuating to sarcopenia. J Aging Res 2012; 251217. http://dx.doi.org/10.1155/2012/251217

[8] Heber D, Ingles S, Ashley JM, Maxwell MH, Lyons RF, Elashoff RM. Clinical detection of sarcopenic obesity by bioelectrical impedance analysis. Am J Clin Nutr 1996; 64(3 Suppl): 472S-7S. Reference: Available from: URL http://ajcn.nutrition.org/content/64/3/472S.long

[9] Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: A critical appraisal of the current evidence. Clin Nutr 2012; 31: 583-601. http://dx.doi.org/10.1016/j.clnu.2012.06.010

[10] Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res 2004; 12: 1995-2004. http://dx.doi.org/10.1038/oby.2004.250

[11] Rolland Y, Lauwers-Cances V, Cristini C, Abellan van Kan G, Janssen I, Morley JE, *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: 1895-900. http://dx.doi.org/10.3945/ajcn.2008.26950

[12] Davison KK, Ford ES, Cogswell ME, Dietz WH. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. J Am Geriatr Soc 2002; 50: 1802-9. http://dx.doi.org/10.1046/j.1532-5415.2002.50508.x

[13] Stephen WC, Janssen I. Sarcopenic-obesity and cardiovascular disease risk in the elderly. J Nutr Health Aging 2009; 13: 460-6. http://dx.doi.org/10.1007/s12603-009-0084-z

[14] Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, *et al.* Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008; 9: 629-35. http://dx.doi.org/10.1016/S1470-2045(08)70153-0

[15] Bouchard DR, Dionne IJ, Brochu M. Sarcopenic/obesity and physical capacity in older men and women: data from the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec longitudinal Study. Obesity (Silver Spring) 2009; 17: 2082-8. http://dx.doi.org/10.1038/oby.2009.109

[16] Houston DK, Nicklas BJ, Ding J, Harris TB, Tylavsky FA, Newman AB, *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: 150-5. Reference: Available from: URL http://ajcn.nutrition.org/content/87/1/150.long

[17] 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.

[18] Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. J Am Med Dir Assoc 2013; 14: 10-7. http://dx.doi.org/10.1016/j.jamda.2012.08.001

[19] Biolo G, Ciocchi B, Stulle M, Bosutti A, Barazzoni R, Zanetti M, *et al.* Calorie restriction accelerates the catabolism of lean body mass during 2 wk of bed rest. Am J Clin Nutr 2007; 86: 366-72. Reference: Available from: URL http://ajcn.nutrition.org/content/86/2/366.long

[20] Wall BT, van Loon LJ. Nutritional strategies to attenuate muscle disuse atrophy. Nutr Rev 2013; 71: 195-208. http://dx.doi.org/10.1111/nure.12019

[21] Wakabayashi H, Sashika H. Association of nutrition status and rehabilitation outcome in the disuse syndrome: A retrospective cohort study. General Med 2011; 12: 69-74. Reference: Available from: URL http://www.jstage.jst.go.jp/article/general/12/2/12_2_69/_pdf

[22] Kim HK, Suzuki T, Saito K, Yoshida H, Kobayashi H, Kato H, *et al.* Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. J Am Geriatr Soc 2012; 60: 16-23. http://dx.doi.org/10.1111/j.1532-5415.2011.03776.x

[23] Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr 2012; 96: 1454-64. http://dx.doi.org/10.3945/ajcn.112.037556

[24] Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, *et al.* Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011; 364: 1218-29. http://dx.doi.org/10.1056/NEJMoa1008234

[25] Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes (Lond) 2005; 29: 1153-67. http://dx.doi.org/10.1038/sj.ijo.0802982

[26] Santos FL, Esteves SS, da Costa Pereira A, Yancy WS Jr, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev 2012; 13: 1048-66. http://dx.doi.org/10.1111/j.1467-789X.2012.01021.x

[27] Hooper L, Abdelhamid A, Moore HJ, Douthwaite W, Skeaff CM, Summerbell CD. Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. BMJ 2012; 345: e7666. http://dx.doi.org/10.1136/bmj.e7666

[28] Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr, Brehm BJ, *et al.* Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006; 166: 285-93. http://dx.doi.org/10.1001/archinte.166.3.285

[29] Hu T, Mills KT, Yao L, Demanelis K, Eloustaz M, Yancy WS Jr, *et al.* Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol 2012; 176: S44-54. http://dx.doi.org/10.1093/aje/kws264

[30] Santesso N, Akl EA, Bianchi M, Mente A, Mustafa R, Heels-Ansdell D, *et al.* Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. Eur J Clin Nutr 2012; 66: 780-8. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3392894/

[31] Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012; 96: 1281-98. http://dx.doi.org/10.3945/ajcn.112.044321

[32] Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. Metab Syndr Relat Disord 2011; 9: 1-12. http://dx.doi.org/10.1089/met.2010.0031

[33] Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. Cochrane Database Syst Rev 2007; 3: CD005105.

[34] Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring) 2006; 14: 1283-93. http://dx.doi.org/10.1038/oby.2006.146

[35] Wu T, Gao X, Chen M, van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. Obes Rev 2009; 10: 313-23. http://dx.doi.org/10.1111/j.1467-789X.2008.00547.x

[36] Miyachi M, Ando D, Oida Y, Oguma Y, Ono R, Kitabatake Y, *et al.* Treatment indications for sarcopenia: a systematic review of exercise intervention effect. Nihon Ronen Igakkai Zasshi 2011; 48: 51-4. [Article in Japanese] Reference: Available from: URL http://www.jstage.jst.go.jp/article/geriatrics/48/1/48_1_51/_pdf

[37] Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. Ageing Res Rev 2010; 9: 226-37. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892859/

[38] Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst Rev 2009; 3: CD002759.

[39] Ozaki H, Loenneke JP, Thiebaud RS, Stager JM, Abe T. Possibility of leg muscle hypertrophy by ambulation in older adults: a brief review. Clin Interv Aging 2013; 8: 369-75. http://dx.doi.org/10.2147/CIA.S43837

[40] Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, *et al.* Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009; 301: 2024-35. http://dx.doi.org/10.1001/jama.2009.681

[41] Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. Cochrane Database Syst Rev 2006; 4: CD003817.

[42] Thorogood A, Mottillo S, Shimony A, Filion KB, Joseph L, Genest J, *et al.* Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. Am J Med 2011; 124: 747-55. http://dx.doi.org/10.1016/j.amjmed.2011.02.037

[43] Richardson CR, Newton TL, Abraham JJ, Sen A, Jimbo M, Swartz AM. A meta-analysis of pedometer-based walking interventions and weight loss. Ann Fam Med 2008; 6: 69-77. http://dx.doi.org/10.1370/afm.761

[44] Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports Med 2010; 40: 397-415. http://dx.doi.org/10.2165/11531380-000000000-00000

[45] Dietz P, Hoffmann S, Lachtermann E, Simon P. Influence of exclusive resistance training on body composition and cardiovascular risk factors in overweight or obese children: a systematic review. Obes Facts 2012; 5: 546-60. http://dx.doi.org/10.1159/000341560

[46] Ismail I, Keating SE, Baker MK, Johnson NA. A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. Obes Rev 2012; 13: 68-91. http://dx.doi.org/10.1111/j.1467-789X.2011.00931.x

[47] Ho SS, Dhaliwal SS, Hills AP, Pal S. The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. BMC Public Health 2012; 12: 704. http://dx.doi.org/10.1186/1471-2458-12-704

[48] Bhasin S, Calof OM, Storer TW, Lee ML, Mazer NA, Jasuja R, *et al.* Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab 2006; 2: 146-59. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2072878/

[49] 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. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1752197/

[50] Fernández-Balsells MM, Murad MH, Lane MA, Lampropulos JF, Albuquerque F, Mullan RJ, *et al.* Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010; 95: 2560-75. http://dx.doi.org/10.1210/jc.2009-2575

[51] 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. http://dx.doi.org/10.1056/NEJMoa1000485

[52] Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, *et al.* Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 2007; 146: 104-15. http://dx.doi.org/10.7326/0003-4819-146-2-200701160-00005

[53] White HK, Petrie CD, Landschulz W, *et al.* Effects of an oral growth hormone secretagogue in older adults. J Clin Endocrinol Metab 2009; 94: 1198-206. http://dx.doi.org/10.1210/jc.2008-0632

[54] Giannoulis MG, Sonksen PH, Umpleby M, MacLean D, Taylor A, Lyles K, *et al.* The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. J Clin Endocrinol Metab 2006; 91: 477-84. http://dx.doi.org/10.1210/jc.2008-0632

[55] Giannoulis MG, Jackson N, Shojaee-Moradie F, Nair KS, Sonksen PH, Martin FC, *et al.* The effects of growth hormone and/or testosterone on whole body protein kinetics and skeletal muscle gene expression in healthy elderly men: a randomized controlled trial. J Clin Endocrinol Metab 2008; 93: 3066-74. http://dx.doi.org/10.1210/jc.2007-2695

[56] Sattler FR, Castaneda-Sceppa C, Binder EF, Schroeder ET, Wang Y, Bhasin S, *et al.* Testosterone and growth hormone improve body composition and muscle performance in older men. J Clin Endocrinol Metab 2009; 94: 1991-2001. http://dx.doi.org/10.1210/jc.2008-2338

[57] Schroeder ET, He J, Yarasheski KE, Binder EF, Castaneda-Sceppa C, Bhasin S, *et al.* Value of measuring muscle performance to assess changes in lean mass with testosterone and growth hormone supplementation. Eur J Appl Physiol 2012; 112: 1123-31. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448487/

[58] Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999; 402: 656-60. http://dx.doi.org/10.1038/45230

[59] Nass R, Pezzoli SS, Oliveri MC, Patrie JT, Harrell FE Jr, Clasey JL, *et al.* Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann Intern Med 2008; 149: 601-11. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757071/

[60] Akamizu T, Iwakura H, Ariyasu H, Murayama T, Sumi E, Teramukai S, *et al.* Effects of ghrelin treatment on patients undergoing total hip replacement for osteoarthritis: different outcomes from studies in patients with cardiac and pulmonary cachexia. J Am Geriatr Soc 2008; 56: 2363-5. http://dx.doi.org/10.1111/j.1532-5415.2008.02031.x

[61] Al-Said YA, Al-Rached HS, Al-Qahtani HA, Jan MM. Severe proximal myopathy with remarkable recovery after vitamin D treatment. Can J Neurol Sci 2009; 36: 336-9.

[62] Fabbriciani G, Pirro M, Leli C, Cecchetti A, Callarelli L, Rinonapoli G, *et al.* Diffuse muscoskeletal pain and proximal myopathy: do not forget hypovitaminosis D. J Clin Rheumatol 2010; 16: 34-7. http://dx.doi.org/10.1097/RHU.0b013e3181c3b2c0

[63] Houston DK, Neiberg RH, Tooze JA, Hausman DB, Johnson MA, Cauley JA, *et al.* Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: The Health ABC Study. J Gerontol A Biol Sci Med Sci 2013; 68: 181-7. http://dx.doi.org/10.1093/gerona/gls136

[64] Visser M, Deeg DJ, Lips P, Longitudinal Aging Study Amsterdam. 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: 5766-72. http://dx.doi.org/10.1210/jc.2003-030604

[65] Scott D, Blizzard L, Fell J, Ding C, Winzenberg T, Jones G. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. Clin Endocrinol (Oxf) 2010; 73: 581-7. http://dx.doi.org/10.1111/j.1365-2265.2010.03858.x

[66] Kim MK, Baek KH, Song KH, Il Kang M, Park CY, Lee WY, *et al.* Vitamin D deficiency is associated with sarcopenia in older Koreans, regardless of obesity: the Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) 2009. J Clin Endocrinol Metab 2011; 96: 3250-6. http://dx.doi.org/10.1210/jc.2011-1602

[67] Seo JA, Cho H, Eun CR, Yoo HJ, Kim SG, Choi KM, *et al.* Association between visceral obesity and sarcopenia and vitamin D deficiency in older Koreans: the Ansan Geriatric Study. J Am Geriatr Soc 2012; 60: 700-6. http://dx.doi.org/10.1111/j.1532-5415.2012.03887.x

[68] Marantes I, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd, Amin S. Is vitamin D a determinant of muscle mass and strength? J Bone Miner Res 2011; 26: 2860-71. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248226/

[69] Annweiler C, Schott AM, Berrut G, Fantino B, Beauchet O. Vitamin D-related changes in physical performance: a systematic review. J Nutr Health Aging 2009; 13: 893-8. http://dx.doi.org/10.1007/s12603-009-0248-x

[70] Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: A systematic review and meta-analysis. Osteoporos Int 2011; 22: 859-71. http://dx.doi.org/10.1007/s00198-010-1407-y

[71] Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2004; 3: CD004094.

[72] Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 2007; 335: 1194-9. http://dx.doi.org/10.1136/bmj.39385.413113.25

[73] Zhou YH, Ma XQ, Wu C, , Lu J, Zhang SS, Guo J, *et al.* Effect of anti-obesity drug on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2012; 7: e39062. http://dx.doi.org/10.1371/journal.pone.0039062

[74] Chan EW, He Y, Chui CS, Wong AY, Lau WC, Wong IC. Efficacy and safety of lorcaserin in obese adults: a meta-analysis of 1-year randomized controlled trials (RCTs) and narrative review on short-term RCTs. Obes Rev 2013. http://dx.doi.org/10.1111/obr.12015

[75] Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, *et al.* Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011; 377: 1341-52. http://dx.doi.org/10.1016/S0140-6736(11)60205-5

[76] Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, *et al.* Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012; 20: 330-42. Reference: Available from: URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3270297/

[77] Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, *et al.* Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012; 95: 297-308. http://dx.doi.org/10.3945/ajcn.111.024927

[78] Smith SM, Meyer M, Trinkley KE. Phentermine/Topiramate for the treatment of obesity (March). Ann Pharmacother 2013; 47: 340-9. http://dx.doi.org/10.1345/aph.1R501

[79] Saneei P, Salehi-Abargouei A, Esmaillzadeh A. Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis. Obes Rev 2013; 14: 393-404. http://dx.doi.org/10.1111/obr.12016

[80] Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, *et al.* Causal relationship between obesity and vitamin D status: bi-directional mendelian randomization analysis of multiple cohorts. PLoS Med 2013; 10: e1001383. http://dx.doi.org/10.1371/journal.pmed.1001383

[81] Hwang B, Lim JY, Lee J, Choi NK, Ahn YO, Park BJ. Prevalence rate and associated factors of sarcopenic obesity in korean elderly population. J Korean Med Sci 2012; 27: 748-55. http://dx.doi.org/10.3346/jkms.2012.27.7.748

[82] Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ. Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. Arch Gerontol Geriatr 2013; 56: 270-8. http://dx.doi.org/10.1016/j.archger.2012.09.007

[83] Kim TN, Park MS, Lim KI, Choi HY, Yang SJ, Yoo HJ, *et al.* Relationships between sarcopenic obesity and insulin resistance, inflammation, and vitamin D status: the Korean Sarcopenic Obesity Study. Clin Endocrinol (Oxf) 2013; 78: 525-32. http://dx.doi.org/10.1111/j.1365-2265.2012.04433.x

[84] Sneve M, Figenschau Y, Jorde R. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. Eur J Endocrinol 2008; 159: 675-84. http://dx.doi.org/10.1530/EJE-08-0339

[85] Zittermann A, Frisch S, Berthold HK, Götting C, Kuhn J, Kleesiek K, *et al.* Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr 2009; 89: 1321-7. http://dx.doi.org/10.3945/ajcn.2008.27004

[86] Salehpour A, Hosseinpanah F, Shidfar F, Vafa M, Razaghi M, Dehghani S, *et al.* A 12-week double-blind randomized clinical trial of vitamin D_3 supplementation on body fat mass in healthy overweight and obese women. Nutr J 2012; 11: 78. http://dx.doi.org/10.1186/1475-2891-11-78

[87] Rosenblum JL, Castro VM, Moore CE, Kaplan LM. Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. Am J Clin Nutr 2012; 95: 101-8. http://dx.doi.org/10.3945/ajcn.111.019489

[88] Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutr Rev 2010; 68: 375-88. http://dx.doi.org/10.1111/j.1753-4887.2010.00298.x

[89] Vincent HK, Raiser SN, Vincent KR. The aging musculoskeletal system and obesity-related considerations with exercise. Ageing Res Rev 2012; 11: 361-73. http://dx.doi.org/10.1016/j.arr.2012.03.002

[90] Sakuma K, Yamaguchi A. Sarcopenic obesity and endocrinal adaptation with age. Int J Endocrinol 2013; 204164. http://dx.doi.org/10.1155/2013/204164

[91] Avenell A, Brown TJ, McGee MA, Campbell MK, Grant AM, Broom J, *et al.* What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. J Hum Nutr Diet 2004; 17: 293-316. http://dx.doi.org/10.1111/j.1365-277X.2004.00530.x

[92] Dixon JB, Strauss BJ, Laurie C, O'Brien PE. Changes in body composition with weight loss: obese subjects randomized to surgical and medical programs. Obesity (Silver Spring) 2007; 15: 1187-98. http://dx.doi.org/10.1038/oby.2007.639

Received on 24-05-2013 Accepted on 20-06-2013 Published on 30-06-2013

DOI: http://dx.doi.org/10.6000/1929-5634.2013.02.02.5

The Journal of Frailty & Aging©

PRESBYPHAGIA AND SARCOPENIC DYSPHAGIA: ASSOCIATION BETWEEN AGING, SARCOPENIA, AND DEGLUTITION DISORDERS

H. WAKABAYASHI

Corresponding author: Hidetaka Wakabayashi, Department of Rehabilitation Medicine, Yokohama City University Medical Center, 4-57 Urafune-chou, Minami ward, Yokohama city, Japan 232-0024, Phone: +81-45-261-5656, Fax: +81-45-253-9955, E-mail: noventurenoglory@gmail.com

Abstract: Presbyphagia refers to age-related changes in the swallowing mechanism in the elderly associated with a frailty in swallowing. Presbyphagia is different from dysphagia. Sarcopenic dysphagia is difficulty swallowing due to sarcopenia of generalized skeletal muscles and swallowing muscles. Age-related loss of swallowing muscle mass becomes evident in the geniohyoid muscle and tongue. Elderly subjects with both sarcopenia and dysphagia may have not only disease-related dysphagia but also sarcopenic dysphagia. In cases of aspiration pneumonia, deterioration in activity-, disease-, and nutrition-related sarcopenia of generalized skeletal muscles and swallowing muscles may develop into sarcopenic dysphagia. Assessment of sarcopenic dysphagia includes evaluation of both dysphagia and sarcopenia. The 10-item Eating Assessment Tool (EAT-10) and a water test combined with pulse oximetry are useful for dysphagia screening. Assessment of the multi-factorial causes of sarcopenia including nutritional review is important, because rehabilitation of sarcopenic dysphagia differs depending on its etiology. Consensus diagnostic criteria for sarcopenic dysphagia were proposed at the 19th Annual Meeting of the Japanese Society of Dysphagia Rehabilitation. Rehabilitation for sarcopenic dysphagia includes treatment of both dysphagia and sarcopenia. The core components of dysphagia rehabilitation are oral health care, rehabilitative techniques, and food modification. The causes of adult malnutrition may also contribute to the etiology of secondary sarcopenia and sarcopenic dysphagia. Therefore, nutrition management is indispensable for sarcopenic dysphagia rehabilitation. In cases of sarcopenia with numerous complicating causes, treatment should include pharmaceutical therapies for age-related sarcopenia and comorbid chronic diseases, resistance training, early ambulation, nutrition management, protein and amino acid supplementation, and non-smoking.

Key words: Rehabilitation, malnutrition, frailty, swallowing muscle, EAT-10.

Background

The term presbyphagia refers to age-related changes in the swallowing mechanism in the elderly (1). Presbyphagia is characterized by frailty of swallowing. Modification of swallowing related solely to aging is called primary presbyphagia, while swallowing changes due to diseases in the elderly is called secondary presbyphagia (2). Presbyphagia represents healthy swallowing in elderly subjects (3), and not dysphagia. Although the exact prevalence of presbyphagia is unknown, the number of healthy older adults who have penetration and aspiration during assessment of normal swallowing by simultaneous manometry and flexible endoscopic evaluation was 75% and 30%, respectively (4). Another study that investigated the relationship of aspiration status with tongue and handgrip strength in healthy older adults using flexible endoscopic evaluation of swallowing showed that 37% of healthy elderly were aspirators (5). These results indicate that presbyphagia is common in healthy older adults.

The term sarcopenic dysphagia refers to difficulty swallowing due to sarcopenia of generalized skeletal muscles and swallowing muscles (6, 7). In frail elderly patients with oropharyngeal dysphagia, impaired safety of deglutition and aspirations are caused mainly by delayed closure of the laryngeal vestibule (8). Impaired efficacy and residue are related mainly to weak tongue bolus propulsion forces and slow hyoid motion (8). These impairments in frail elderly patients with oropharyngeal dysphagia may be associated with sarcopenia of the tongue and suprahyoid muscles, indicating the presence of sarcopenic dysphagia. The exact prevalence of sarcopenic dysphagia is unknown. The prevalence of sarcopenia assessed by appendicular skeletal muscle mass (in kgs) divided by squared height (in meters) has been estimated to range between 13% to 24% in adults over 60 years of age, and to more than 50% in people aged 80 or older (9). The prevalence of dysphagia has been reported to range between 11.4%–38% in community-dwelling elderly individuals (10-14), and 40%–68% in nursing home residents (15-17). These findings suggest that sarcopenia and dysphagia are common in elderly subjects. Frail elderly subjects with both sarcopenia and dysphagia may have not only disease-related dysphagia caused by conditions such as stroke, brain injury, neuromuscular diseases, head and neck cancer, and connective tissue diseases, but also sarcopenic dysphagia due to sarcopenia of generalized skeletal muscles and swallowing muscles.

Dysphagia management is regarded as an important current and future public health issue in geriatric medicine and rehabilitation medicine, because presbyphagia and dysphagia are common in the elderly, and increases the risk of related complications such as aspiration pneumonia, choking, dehydration, malnutrition, and a lower quality of life following loss of the joy of eating. The first part of this review focuses on

Received September 30, 2013
Accepted for publication October 12, 2013

presbyphagia and sarcopenic dysphagia, followed by a summary of sarcopenic dysphagia assessment and rehabilitation for sarcopenic dysphagia.

Presbyphagia

Presbyphagia refers to age-related changes in the swallowing mechanism. Presbyphagia may present in several ways: as a lack of muscle strength complicating bolus propulsion; diminished lingual pressure, obstructing bolus driving; halting of the bolus whilst swallowing, leading to a more difficult cleansing of residues; a decline in taste and smell that makes it more difficult to initiate swallowing; difficulty in controlling the bolus from the anticipatory phase; entry of the bolus into the lower airway; and finally, lack of teeth and wearing, or not wearing complete dentures which influences chewing (17).

Age-related changes in the generation of lingual pressure is a contributing factor to presbyphagia. Healthy older individuals have significantly reduced isometric tongue pressures compared with their younger counterparts (18). A longer duration of swallowing occurs largely before the more automatic pharyngeal phase of the swallow is initiated. Co-morbidities such as xerostomia, esophageal motility, sensory changes, sarcopenia, and medications can affect swallowing function (18). Although elderly subjects with presbyphagia do not have dysphagia, they may easily develop the condition because of diminished functional reserve.

Sarcopenia

The term sarcopenia was used by Rosenberg to describe an age-related decrease in muscle mass, and originated from the Greek words sarx (flesh) and penia (loss) (19, 20). This term was applied initially to denote loss of muscle mass. In 2010, the European Working Group on Sarcopenia in Older People described sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, associated with a risk of adverse outcomes such as physical disability, poor quality of life, and death (21). In 2011, the International Working Group on Sarcopenia defined the disease as an "age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multi-factorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same (22)." Decreased muscle strength and physical function are now also included in the definition of sarcopenia.

The European Wording Group on Sarcopenia in Older People categorized sarcopenia into two types for use in clinical practice (21). Primary sarcopenia is considered to be age-related when no other cause is evident, other than ageing itself. Secondary sarcopenia should be considered when one or more other causes are evident, such as activity-, disease-, or nutrition-related sarcopenia. The etiology of sarcopenia in the elderly is multi-factorial and therefore it may not be possible to characterize each individual as having either primary or secondary sarcopenia (21). For example, 88%-91% of elderly inpatients with hospital-associated deconditioning and the disuse syndrome are malnourished and may experience not only activity-related sarcopenia, but also age-, nutrition-, and disease-related sarcopenia (23, 24).

Sarcopenia of swallowing muscles

Sarcopenia of swallowing muscles is characterized by their loss of mass and strength associated with generalized loss of skeletal muscle mass and strength. Swallowing muscles include the intrinsic muscle of the tongue and the mimic, masticatory, suprahyoid, infrahyoid, palatal, pharyngeal, and esophageal muscles. Age-related loss of muscle mass of intrinsic muscle of the tongue and geniohyoid muscle has been studied in the elderly.

Tamura et al. (25) evaluated thickness of the central part of the tongue in the elderly using ultrasonography and showed mid-arm muscle area and age were associated independently with tongue thickness. These results indicate that tongue muscle mass is associated with generalized skeletal muscle mass and aging. In elderly subjects with sarcopenia, age-related loss of both the intrinsic muscle mass of the tongue and generalized skeletal muscle mass can occur simultaneously.

Feng et al. (26) assessed the geniohyoid muscle in healthy older adults using computed tomography. This muscle helps elevate and stabilize the hyoid bone, thus protecting the airway. A decrease in the cross-sectional area of the geniohyoid muscle has been shown to occur with increasing age, with this area being significantly smaller in aspirators compared with non-aspirators, but only in older men. Increasing fatty infiltration in the middle and posterior portions of the geniohyoid muscle was also shown to be associated with aging. These findings suggest that geniohyoid muscle atrophy may be a component of decreased swallowing safety and aspiration in older adults with presbyphagia and sarcopenic dysphagia.

Butler et al. (5) demonstrated that lower anterior and posterior isometric and swallowing tongue strength were dependent on aspiration status in healthy, older adults. Although there was no difference in handgrip strength between aspirators and non-aspirators, there was a correlation between handgrip and posterior tongue strength (5). These results indicate that tongue strength may decrease with the advent of generalized loss of skeletal muscle strength, and may be related

with aspiration in healthy, older adults.

Sarcopenic dysphagia

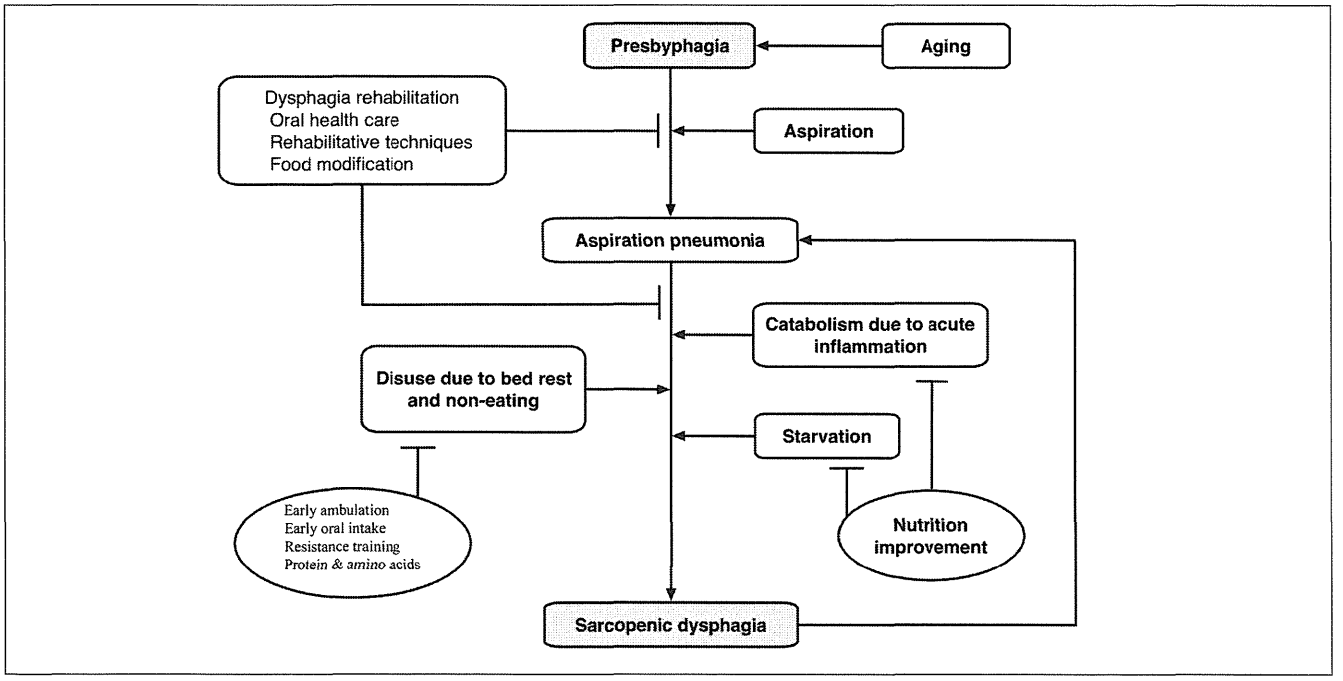
Sarcopenic dysphagia is the condition where a subject has difficulty swallowing due to sarcopenia of the swallowing muscles and generalized skeletal muscles. The most common cause of dysphagia is stroke. In contrast, sarcopenic dysphagia is rarely diagnosed, because the concept and diagnostic criteria for the condition have not been defined. However, sarcopenic dysphagia may be common in elderly subjects with sarcopenia and dysphagia.

Kuroda et al. (6) explored the possible presence of sarcopenic dysphagia by examining the relationship between thinness and swallowing function in older Japanese adults with suspected swallowing disorders. The circumference of the mid-upper arm of the patients ranged from 11.2 to 26.2 cm (mean 19.4 ± 3.5 cm), and correlated significantly with swallowing function measured using a graded water-swallowing test. This finding suggested that swallowing impairment was related to thinness. The most likely explanation for these results is that the general reduction in lean body mass, including the swallowing muscles, is responsible for the association between mid-upper arm circumference and swallowing function, and indicates the presence of sarcopenic dysphagia (6).

One mechanism of sarcopenic dysphagia in frail, elderly subjects is an overlap between all the serious acute diseases that cause sarcopenia. Frail, elderly subjects with either age-related sarcopenia, presbyphagia, malnutrition, periodontal diseases, or chronic diseases (e.g. chronic obstructive pulmonary disease, chronic heart failure, chronic kidney disease) can eat regular or soft diets. However, the functional reserve of swallowing is limited in these frail individuals. For example, if they develop aspiration pneumonia, sarcopenia of generalized skeletal muscles and swallowing muscles rapidly deteriorate, because of activity-, nutrition-, and disease-related sarcopenia (Figure 1). Patients with aspiration pneumonia tend to be prescribed non-eating and bed rest during pneumonia treatment. Activity-related sarcopenia and disuse muscle atrophy develop during non-eating and bedridden periods, with peripheral parenteral nutrition being a common feeding route during pneumonia treatment. Nutrition-related sarcopenia may worsen during non-eating periods and peripheral parenteral nutrition, because it is difficult to satisfy energy expenditure under these conditions without oral intake and enteral nutrition. Disease-related sarcopenia may also be exacerbated by aspiration pneumonia as it is the cause of invasion and acute inflammation and results in catabolism of generalized skeletal muscles and swallowing muscles. Therefore, frail elderly subjects with presbyphagia can simultaneously experience activity-, disease-, and nutrition-related sarcopenia of generalized skeletal muscles and swallowing muscles, resulting in the development of sarcopenic dysphagia (7).

Figure 1

Aspiration pneumonia, etiology of sarcopenia, and sarcopenic dysphagia. Sarcopenic dysphagia is not only the result of aspiration pneumonia, but also an important cause of recurrent aspiration pneumonia



Assessment of sarcopenic dysphagia

Sarcopenic dysphagia assessment includes evaluation of both dysphagia and sarcopenia.

Dysphagia assessment

Screening for dysphagia is important, because presbyphagia and dysphagia are common in elderly subjects, with early detection preventing complications such as aspiration pneumonia, choking, dehydration, and malnutrition.

Belafsky et al. (27) developed the 10-item Eating Assessment Tool (EAT-10, Table 1), a 10-item questionnaire for dysphagia screening, with each item scored from 0 to 4. The EAT-10 was designed specifically to address the clinical need for a rapidly self-administered and easily-scored questionnaire to assess the severity of dysphagia symptoms. An EAT-10 score ≥ 3 is abnormal and indicates the presence of swallowing difficulties. The EAT-10 has been confirmed to have excellent internal consistency, test-retest reproducibility, and criterion-based validity (27).

Table 1

10-item Eating Assessment Tool. The subject is asked: "To what extent are the following scenarios problematic for you?". Each item is scored from 0 (No problem) to 4 (Severe problem) according to the severity of the problem

1. My swallowing problem has caused me to lose weight.
2. My swallowing problem interferes with my ability to go out for meals.
3. Swallowing liquids takes extra effort.
4. Swallowing solids takes extra effort.
5. Swallowing pills takes extra effort.
6. Swallowing is painful.
7. The pleasure of eating is affected by my swallowing.
8. When I swallow food, it sticks in my throat.
9. I cough when I eat.
10. Swallowing is stressful.
If the total score of the EAT-10 items is 3 or higher, the subject may have problems at efficiently and safely swallowing.

In a previous study, we translated the EAT-10 into Japanese, and determined the reliability and validity of the Japanese version of the questionnaire (28). A cross-sectional study was performed in 393 frail, elderly subjects aged 65 years or older with dysphagia or suspected dysphagia. The severity of dysphagia was assessed using the Dysphagia Severity Scale, a 7-point ordinal scale consisting of 1, saliva aspiration; 2, food aspiration; 3, water aspiration; 4, occasional aspiration; 5, oral problems; 6, minimal problems; and 7, within normal limits (29). Points 1–6 indicate the presence of dysphagia, while points 1–4 represents dysphagia with aspiration. A total of 237 patients (60%) responded to the EAT-10. The Cronbach's alpha coefficient was 0.946. The elderly subjects who could not respond to the EAT-10 were likely to have dysphagia. The sensitivity and specificity of not responding EAT-10 for dysphagia were 0.489 and 0.951, and for dysphagia with aspiration were 0.640 and 0.792, respectively. The median EAT-10 score of the 237 respondents was 1 (interquartile range: 0-9), with 101 respondents having a score ≥ 3. Our study showed there was a significant correlation between the EAT-10 score and the Dysphagia Severity Scale ($r=-0.530$, $p<0.001$). The sensitivity and specificity of the EAT-10 with a score ≥3 for dysphagia were 0.522 and 0.897, and for dysphagia with aspiration 0.758 and 0.749, respectively. EAT-10 is therefore a useful questionnaire to detect presbyphagia and dysphagia in frail elderly subjects.

Another screening method for dysphagia is bedside dysphagia tests, such as water or food swallowing tests, pulse oximetry, or cervical auscultation. A systematic review of bedside screening tests to detect dysphagia in patients with neurological disorders, showed the water test combined with pulse oximetry using coughing, choking, and voice alteration as endpoints was currently the best method (30). If the EAT-10 and bedside dysphagia screening tests are abnormal, further dysphagia assessment including observation of eating, videofluoroscopy, or videoendoscopic evaluation of swallowing is recommended. Although there are no characteristic swallowing changes in sarcopenic dysphagia, videofluoroscopy and videoendoscopic evaluation of swallowing can detect reduced laryngeal elevation, insufficient opening of the upper esophageal sphincter, pharyngeal residues in the valleculae and piriform sinus, and aspiration.

Sarcopenia assessment

Sarcopenia assessment should include muscle mass and strength and physical performance. Muscle mass is assessed using either computed tomography, magnetic resonance imaging, dual energy X-ray absorptiometry, bioimpedance analysis, ultrasonography, or anthropometry. Muscle strength is evaluated by handgrip strength or knee flexion/extension strength, while physical performance is assessed by the Short Physical Performance Battery, usual gait speed, or timed get-up-and-go test. Sarcopenia of swallowing muscles can be evaluated by measuring the muscle mass of the geniohyoid muscle or tongue thickness, and muscle strength of lingual pressure and head lift strength. However, further research is necessary to develop methods for measuring the mass and strength of the swallowing muscles.

Assessment of the multi-factorial causes of sarcopenia is also important, because sarcopenic dysphagia rehabilitation may differ depending on the causes of the disorder. Activity-related sarcopenia is suspected in elderly subjects with either

hospital-associated deconditioning, the disuse syndrome (23, 24), history of no oral intake, bed rest, or a sedentary lifestyle for some period of time. Disease-related sarcopenia should be considered in elderly patients with a past or present history of advanced organ failure (heart, lung, liver, kidney, and brain), inflammatory disease, malignancy, or endocrine disease (21). Nutrition-related sarcopenia is suspected in elderly subjects with inadequate dietary intake of energy and/or protein which may occur with malabsorption, gastrointestinal disorders, or use of medications that cause anorexia (21). In fact, nutritional assessment is necessary when evaluating sarcopenic dysphagia, because a systematic review of nursing home patients showed difficulties swallowing or chewing and poor oral intake were associated with weight loss, low BMI, and malnutrition (31). Another systematic review of the relationship between dysphagia and malnutrition following stroke, reported the overall odds of being malnourished were higher in dysphagic subjects compared with subjects with intact swallowing (odds ratio, 2.425; 95% confidence interval, 1.264-4.649, $p < 0.008$) (32). These results indicate that elderly patients with dysphagia often have malnutrition as a complication. Causes of adult malnutrition are classified as being associated with either acute illness or injury, chronic illness, or social and environmental circumstances (33). The causes of adult malnutrition may also be involved in the etiology of nutrition- and disease-related sarcopenia, and may contribute to the development of sarcopenic dysphagia. Therefore, nutritional assessment is indispensable for evaluating sarcopenic dysphagia.

Consensus diagnostic criteria for sarcopenic dysphagia

A symposium of "sarcopenia and dysphagia rehabilitation" was held during the 19th Annual Meeting of the Japanese Society of Dysphagia Rehabilitation (symposium chair: Ichiro Fujishima and Hidetaka Wakabayashi). Consensus diagnostic criteria for sarcopenic dysphagia were proposed at the symposium (Table 2). Sarcopenic dysphagia is diagnosed only in patients with dysphagia and generalized sarcopenia (generalized loss of skeletal muscle mass and strength). Although some imaging test studies of swallowing muscles have been reported (25, 26), there is no cut-off point for judging loss of swallowing muscle mass. Therefore, evaluating the loss of swallowing muscle mass using imaging tests and a definitive diagnosis for sarcopenic dysphagia remains relatively difficult at present. Further research is necessary to determine the cut-off points for loss of swallowing muscle mass. However, if there are no other causes of dysphagia except sarcopenia in the patient's clinical history, dysphagia is likely to be caused by sarcopenia, with sarcopenic dysphagia being considered as the most probable diagnosis. In cases in whom the existence of dysphagia may be caused by other conditions such as stroke, brain injury, neuromuscular diseases, head and neck cancer, and connective tissue diseases, it is possible to diagnose sarcopenic dysphagia if the main cause of dysphagia is considered to be sarcopenia.

Table 2
Consensus diagnostic criteria for sarcopenic dysphagia

1) Presence of dysphagia.
2) Presence of generalized sarcopenia (generalized loss of skeletal muscle mass and strength).
3) The results of imaging tests (computed tomography, magnetic resonance imaging, ultrasonography) are consistent with a loss of swallowing muscle mass.
4) The causes of dysphagia are excluded except for sarcopenia.
5) The main cause of dysphagia is considered to be sarcopenia (if other causes of dysphagia such as stroke, brain injury, neuromuscular diseases, head and neck cancer, and connective tissue diseases exist).
Definite diagnosis: 1, 2, 3, 4
Probable diagnosis: 1, 2, 4
Possible diagnosis: 1, 2, 5

Sarcopenic dysphagia rehabilitation

Therapy for sarcopenic dysphagia includes dysphagia rehabilitation and treatment of sarcopenia.

Dysphagia rehabilitation

The core components of dysphagia rehabilitation are oral health care, rehabilitative techniques, and food modification. In a systematic literature review of oral health care in frail older people, two studies showed that improvement of oral health care diminished the risk of developing aspiration pneumonia and also the risk of dying directly from aspiration pneumonia (34). Oral health care, consisting of tooth brushing after each meal, cleaning dentures once a day, and professional oral health care once a week, appeared to be the best intervention to reduce the incidence of aspiration pneumonia (34).

Rehabilitative technique, especially swallow muscle strength training, is an important component of dysphagia rehabilitation and presbyphagia treatment, although high quality evidence on its effectiveness is limited. A systematic review of the head lift exercise on the swallow function, reported positive effects including an increase in the anterior excursion of the larynx and anteroposterior diameter of the upper esophageal sphincter opening, associated with elimination of dysphagic symptoms (35). Lingual resistance exercise is another rehabilitative technique for patients with lingual weakness, swallowing disability due to frailty, other age-related conditions, or stroke (36, 37).

Compensatory procedures such as modification of food texture and liquid thickness are important strategies for dysphagia rehabilitation. Foods may be chopped, mashed, or puréed to compensate for chewing and swallowing difficulties,

while liquids can be thickened to slow their transit through the oral and pharyngeal phases of swallowing to avoid aspiration. Because the number of levels of modification and characteristics vary within and across countries, the need for international standardized terminology and definitions for texture-modified foods and liquids for individuals with dysphagia have been emphasized (38). In Japan, texture-modified foods are now very advanced, and incorporate energy content (kcal), protein (g) and measures of hardness, adhesiveness, and cohesiveness for each food level (38). Instructions are also provided on whether the food should be served cold (15°C) or warm (45°C). Japanese clinicians also determine whether purée or jelly textures of extremely texture-modified foods are safer or easier to swallow (38).

Sarcopenia treatment

Treatment of sarcopenia should include resistance training combined with supplements containing amino acids, because these are considered to be the most effective option (39, 40). Treatment of activity-related sarcopenia is to avoid non-eating, bed rest, and a sedentary lifestyle, and to promote early oral intake, early mobilization, and physical activity. Treatment for disease-related sarcopenia requires therapies for advanced organ failure, inflammatory disease, malignancy or endocrine disease, while therapy for nutrition-related sarcopenia involves appropriate nutrition management to increase muscle mass. The causes of adult malnutrition may also contribute to the etiology of secondary sarcopenia and sarcopenic dysphagia. Therefore, nutrition management is indispensable for sarcopenic dysphagia rehabilitation. In cases of sarcopenia complicated by age-, activity-, nutrition-, and disease-related factors, treatment should include pharmaceutical therapies for age-related symptoms and comorbid chronic diseases, resistance training, early ambulation, nutrition management, protein and amino acid supplementation, and encouragement to stop smoking cigarettes (39, 40).

Conclusions

Presbyphagia and sarcopenic dysphagia are important current and future public health issues, because they are common in the elderly population and can lead to aspiration pneumonia, the prevalence of which is increasing in the aged society. Although there are no intervention studies for presbyphagia and sarcopenic dysphagia, therapies for sarcopenic dysphagia including dysphagia rehabilitation, sarcopenia treatment, and nutrition management appear to be important for treating these conditions. Developing diagnostic criteria for presbyphagia and sarcopenic dysphagia is necessary for epidemiological and intervention studies. Consensus diagnostic criteria for sarcopenic dysphagia were therefore proposed at the 19th Annual Meeting of the Japanese Society of Dysphagia Rehabilitation. Further research is also required on presbyphagia and sarcopenic dysphagia, especially evaluating swallowing muscle mass and strength in elderly subjects.

This manuscript was presented at the 20th International Association of Gerontology and Geriatrics World Congress of Gerontology and Geriatrics, Seoul, June 25, 2013, and the 19th Annual Meeting of the Japanese Society of Dysphagia Rehabilitation, Okayama, September 23, 2013.

Conflict of Interest: H. Wakabayashi has received reimbursement for travel expenses from Nestlé Health Sciences.

Acknowledgements: This study was supported by a Grant-in-Aid for the Comprehensive Research on Aging and Health from the Ministry of Health, Labor, and Welfare of Japan.

References

1. Jahnke V. Dysphagia in the elderly. HNO 1991; 39: 442-444. [German]
2. Ginocchio D, Borghi E, Schindler A. Dysphagia assessment in the elderly. Nutritional Therapy Metabolism 2009; 27: 9-15.
3. Humbert IA, Robbins J. Dysphagia in the elderly. Phys Med Rehabil Clin N Am 2008; 19: 853-866.
4. Butler SG, Stuart A, Markley L, Rees C. Penetration and aspiration in healthy older adults as assessed during endoscopic evaluation of swallowing. Ann Otol Rhinol Laryngol 2009; 118: 190-198.
5. Butler SG, Stuart A, Leng X, et al. The relationship of aspiration status with tongue and handgrip strength in healthy older adults. J Gerontol A Biol Sci Med Sci 2011; 66: 452-458.
6. Kuroda Y, Kuroda R. Relationship between thinness and swallowing function in Japanese older adults: implications for sarcopenic dysphagia. J Am Geriatr Soc 2012; 60: 1785-1786.
7. Wakabayashi H, Fujimoto A. Dysphagia due to sarcopenia: potential and practice of rehabilitation nutrition. 2012. Ishiyaku, Tokyo [Japanese]
8. Rofes L, Arreola V, Romea M, et al. Pathophysiology of oropharyngeal dysphagia in the frail elderly. Neurogastroenterol Motil 2010; 22: 851-858.
9. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998; 147: 755-763.
10. Bloem BR, Lagaay AM, van Beek W, Haan J, Roos RA, Wintzen AR. Prevalence of subjective dysphagia in community residents aged over 87. BMJ 1990; 300: 721-722.
11. Kawashima K, Motohashi Y, Fujishima I. Prevalence of dysphagia among community-dwelling elderly individuals as estimated using a questionnaire for dysphagia screening. Dysphagia 2004; 19: 266-271.
12. Roy N, Stemple J, Merrill RM, Thomas L. Dysphagia in the elderly: preliminary evidence of prevalence, risk factors, and socioemotional effects. Ann Otol Rhinol Laryngol 2007; 116: 858-865.
13. Serra-Prat M, Hinojosa G, López D, et al. Prevalence of oropharyngeal dysphagia and impaired safety and efficacy of swallow in independently living older persons. J Am Geriatr Soc 2011; 59: 186-187.
14. Holland G, Jayasekeran V, Pendleton N, Horan M, Jones M, Hamdy S. Prevalence and symptom profiling of oropharyngeal dysphagia in a community dwelling of an elderly population: a self-reporting questionnaire survey. Dis Esophagus 2011; 24: 476-480.
15. Steele CM, Greenwood C, Ens I, Robertson C, Seidman-Carlson R. Mealtime difficulties in a home for the aged: not just dysphagia. Dysphagia 1997; 12: 43-50, discussion 51.
16. Park YH, Han HR, Oh BM, et al. Prevalence and associated factors of dysphagia in nursing home residents. Geriatr Nurs 2013; 34: 212-217.
17. Nogueira D, Reis E. Swallowing disorders in nursing home residents: how can the problem be explained? Clin Interv Aging 2013; 8, 221-227.
18. Ney DM, Weiss JM, Kind AJ, Robbins J. Senescent swallowing: impact,

strategies, and interventions. Nutr Clin Pract 2009; 24: 395-413.
19. Rosenberg IH. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. Am J Clin Nutr 1989; 50: 1231-1233.
20. Rosenberg IH. Sarcopenia: Origins and clinical relevance. J Nutr 1997; 127: 990S-991S.
21. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010; 39: 412-423.
22. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011; 12: 249-256.
23. Wakabayashi H, Sashika H. Association of nutrition status and rehabilitation outcome in the disuse syndrome: a retrospective cohort study. General Med 2011; 12: 69-74.
24. Wakabayashi H, Sashika H. Malnutrition is associated with poor rehabilitation outcome in elderly inpatients with hospital-associated deconditioning: a prospective cohort study. J Rehabil Med, in press.
25. Tamura F, Kikutani T, Tohara T, Yoshida M, Yaegaki K. Tongue thickness relates to nutritional status in the elderly. Dysphagia 2012; 27: 556-561.
26. Feng X, Todd T, Lintzenich CR, et al. Aging-related geniohyoid muscle atrophy is related to aspiration status in healthy older adults. J Gerontol A Biol Sci Med Sci 2013; 68: 853-860.
27. Belafsky PC, Mouadeb DA, Rees CJ, et al. Validity and reliability of the Eating Assessment Tool (EAT-10). Ann Otol Rhinol Laryngol 2008; 117: 919-924.
28. Wakabayashi H, Kayashita J. Translation, reliability, and validity of the Japanese version of the 10-item Eating Assessment Tool (EAT-10) for the screening of dysphagia. J-JSPEN, in press [Japanese]
29. Kagaya H, Okada S, Shigeta R, et al. Dysphagia associated with unilateral vocal cord immobility after cardiovascular surgery. Am J Phys Med Rehabil 2011; 90: 901-907.
30. Bours GJ, Speyer R, Lemmens J, Limburg M, de Wit R. Bedside screening tests vs. videofluoroscopy or fibreoptic endoscopic evaluation of swallowing to detect dysphagia in patients with neurological disorders: systematic review. J Adv Nurs 2009; 65: 477-493.
31. Tamura BK, Bell CL, Masaki KH, Amella EJ. Factors associated with weight loss, low BMI, and malnutrition among nursing home patients: a systematic review of the literature. J Am Med Dir Assoc 2013; 14: 649-655.
32. Foley NC, Martin RE, Salter KL, Teasell RW. A review of the relationship between dysphagia and malnutrition following stroke. J Rehabil Med 2009; 41: 707-713.
33. White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Parenter Enteral Nutr 2012; 36: 275-283.
34. van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, Schols JM, de Baat C. Oral health care and aspiration pneumonia in frail older people: a systematic literature review. Gerodontology 2013; 30: 3-9.
35. Antunes EB, Lunet N. Effects of the head lift exercise on the swallow function: a systematic review. Gerodontology 2012; 29: 247-257.
36. Robbins J, Gangnon RE, Theis SM, Kays SA, Hewitt AL, Hind JA. The effects of lingual exercise on swallowing in older adults. J Am Geriatr Soc 2005; 53: 1483-1489.
37. Robbins J, Kays SA, Gangnon RE, et al. The effects of lingual exercise in stroke patients with dysphagia. Arch Phys Med Rehabil 2007; 88: 150-158.
38. Cichero JA, Steele CM, Duivestein JA, et al. The need for international terminology and definitions for texture-modified foods and thickened liquids used in dysphagia management: foundations of a global initiative. Curr Phys Med Rehabil Rep, Published online: DOI 10.1007/s40141-013-0024-z
39. Wakabayashi H, Sakuma K. Nutrition, exercise, and pharmaceutical therapies for sarcopenic obesity. J Nutr Ther 2013; 2: 100-111.
40. Wakabayashi H, Sakuma K. Comprehensive approach to sarcopenia treatment. Curr Clin Pharmacol, in press

Send Orders for Reprints to reprints@benthamscience.net

Current Clinical Pharmacology, 2014, *9*, 000-000

Comprehensive Approach To Sarcopenia Treatment

Hidetaka Wakabayashi[1,*] and Kunihiro Sakuma[2]

[1]*Department of Rehabilitation Medicine, Yokohama City University Medical Center;* [2]*Research Center for Physical Fitness, Sports and Health, Toyohashi University of Technology*

Abstract: Sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death. Primary sarcopenia is considered to be age-related when no other cause is evident, other than ageing itself. Secondary sarcopenia should be considered when one or more other causes are evident, such as activity-, disease-, or nutrition-related sarcopenia. In this narrative review that focused on human studies, we summarize the pharmaceutical therapies (testosterone, dehydroepiandrosterone, estrogen, growth hormone, ghrelin, vitamin D, angiotensin converting enzyme inhibitor, and eicosapentaenoic acid) and non-pharmaceutical therapies (resistance training, protein and amino acid supplementation, and non-smoking) for counteracting primary sarcopenia. Testosterone and growth hormone improve muscle mass and muscle strength, but have several side effects. Although there are some intriguing pharmaceutical therapies to combat sarcopenia, resistance training combined with supplements containing amino acids are the most effective for preventing and treating age-related muscle wasting and weakness. The etiology of sarcopenia in the elderly is multi-factorial. Patients with disuse syndrome and deconditioning often complicate the diagnosis, of not only activity-related sarcopenia, but also age-, disease-, and nutrition-related sarcopenia. In these cases a comprehensive approach to sarcopenia treatment should include pharmaceutical therapies for age-related sarcopenia and comorbid chronic diseases, resistance training, early ambulation, nutrition management, protein and amino acid supplementation, and non-smoking. The effect of pharmaceutical therapies for sarcopenia can be enhanced by this comprehensive approach. Future research on pharmaceutical therapies for counteracting sarcopenia should consider non-pharmaceutical therapies and also the causes of sarcopenia.

Keywords: Amino acids, ghrelin, growth hormone, non-smoking, rehabilitation, resistance training, sarcopenia, testosterone.

1. INTRODUCTION

Aging is associated with a progressive decline in muscle mass that may lead to decreased muscle quality and strength. The term sarcopenia was used by Rosenberg to describe this age-related decrease in muscle mass, and originates from the Greek words sarx (flesh) and penia (loss) [1, 2]. This term was initially applied clinically to denote loss of muscle mass. In 2010 the European Working Group on Sarcopenia in Older People described sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, associated with a risk of adverse outcomes such as physical disability, poor quality of life, and death [3]. In 2011, the International Working Group on Sarcopenia defined sarcopenia as an age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multi-factorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same [4]. Decreased muscle strength and physical function are also now included in the definition of sarcopenia.

*Address correspondence to this author at the Department of Rehabilitation Medicine, Yokohama City University Medical Center, 4-57 Urafune-chou, Minami ward, Yokohama city, Japan 232-0024; Tel: +81-45-261-5656; Fax: +81-45-253-9955; E-mail: noventurenoglory@gmail.com

In the elderly, sarcopenia increases the risk of adverse outcomes such as functional disability, risk of falls, and death [5-7]. Sarcopenia was shown to be associated independently with functional disability for 2 years in both men (odds ratio (OR), 45.1; 95% confidence interval (CI), 6.5 to 313.9) and women (OR, 10.4; 95% CI, 1.8 to 59.8) [5]. In the ilSIRENTE study, participants with sarcopenia evaluated using the European Wording Group on Sarcopenia in Older People algorithm had a higher risk of incident falls compared with non sarcopenic subjects during a follow-up period of 2 years (adjusted hazard ratio (HR), 3.23; 95% CI, 1.25 to 8.29) [6]. Sarcopenia assessed by this algorithm was also shown to be independently associated with mortality (HR, 2.39; 95% CI, 1.05 to 5.43) in a group of Mexican elderly subjects [7].

The prevalence of sarcopenia assessed by appendicular skeletal muscle mass (kg) / height^2 (m^2) is estimated to range between 13% to 24% in adults over 60 years of age, to more than 50% in people aged 80 and older [8]. There is also evidence that 33.6% of community-dwelling elderly subjects 70 years or older [9], and 32.8% aged 70 years and older living in nursing homes [10] were identified as having sarcopenia using the European Wording Group on Sarcopenia in Older People algorithm that measures gait speed, grip strength, and muscle mass [3]. The high prevalence of sarcopenia is therefore an extremely important current and future public health issue.

Several possible mechanisms for age-related muscle atrophy have been described. However, the precise

1574-8847/14 $58.00+.00

contribution of each is unknown. Age-related muscle loss results from a reduction in the size and number of muscle fibers, possibly due to a multifactorial process that involves physical activity, nutritional intake, oxidative stress, and hormonal changes [11-13]. The specific contribution of each of these factors is unknown, but there is emerging evidence that disruption of several positive regulators (Akt and serum response factor) and upregulation of negative regulators (Smad-2/3 and TNF-α) for muscle hypertrophy with age are important factors in the progression of sarcopenia (Fig. **1**).

A number of potential targets for pharmacological interventions to treat sarcopenia have been identified in both animal experiments and human studies [11-13]. For example, a myostatin inhibitor, ursolic acid, proteasome inhibitor, cyclophilin inhibitor, and peroxisome proliferator-activated receptor γ coactivator 1α are novel and intriguing strategies that have been shown to attenuate sarcopenia in animal studies [13]. Although preclinical animal studies are very important for developing sarcopenia treatments, results from human studies are necessary to formulate a

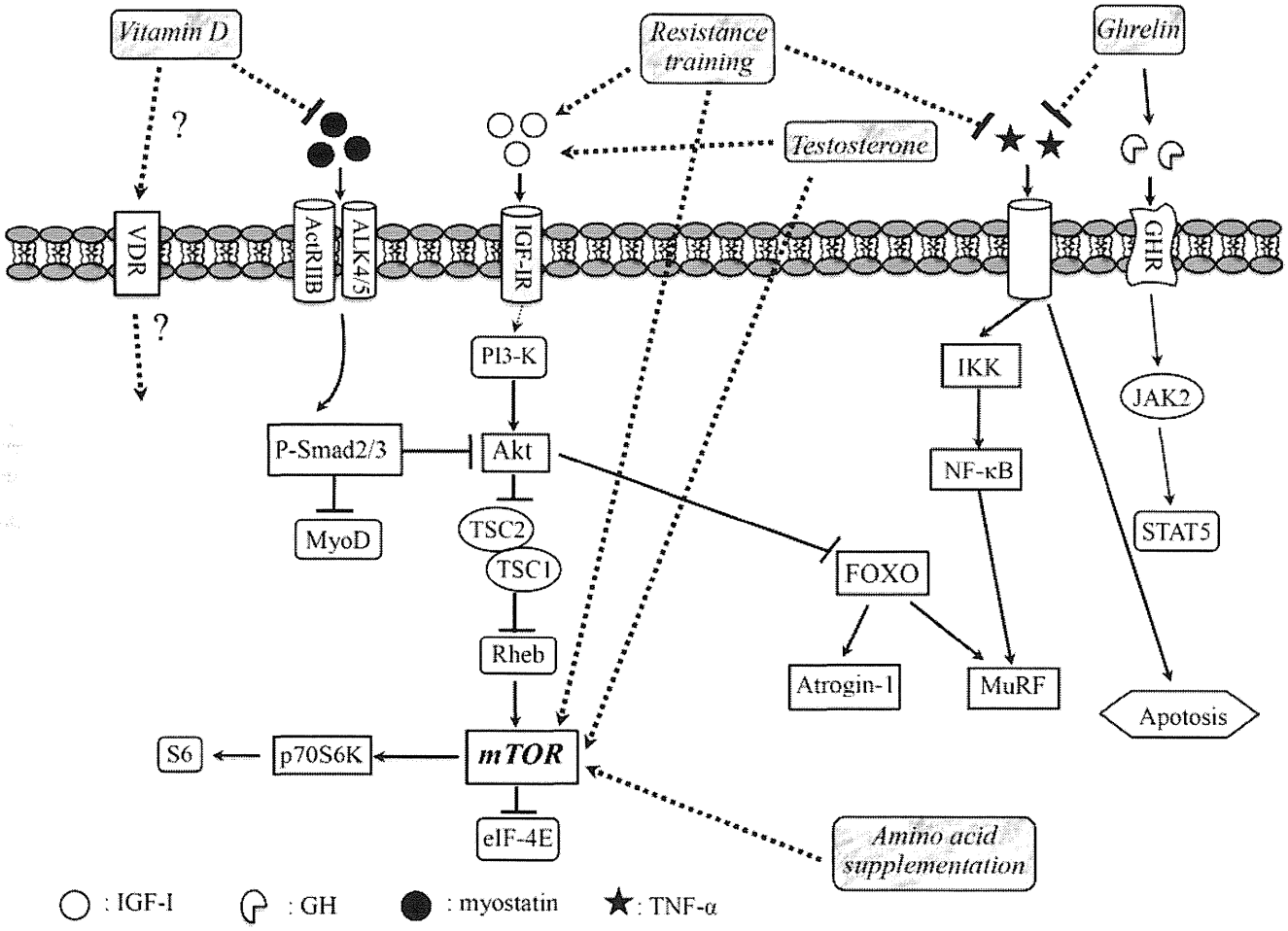


Fig. (1). Pathophysiological mechanisms of primary sarcopenia and treatment. In sarcopenic muscle, myostatin signals through ActRIIB, and the ALK4/5 heterodimer appears to activate Smad2/3 and block MyoD transactivation in an autoregulatory feedback loop. Abundant activated Smad2/3 inhibits protein synthesis probably due to blocking the functional role of Akt. The increased levels of blood TNF-α increases protein degradation through IKK/NF-κB signaling and enhances apoptosis. Lower serum levels of IGF-I, GH, and testosterone fail to activate signaling candidates (Akt, mTOR, STAT5, etc.) that enhance protein synthesis. The impaired regulation of FOXO by Akt results in abundant expression of Atrogin-1 and MuRF, resulting in consequent protein degradation in sarcopenic muscle. Testosterone and resistance training induce muscle expression of IGF-I and mTOR activation which stimulate muscle protein synthesis. Abundant serum GH, which is induced by ghrelin, activates JAK2-STAT5 signaling to promote muscle-specific gene transcription necessary for hypertrophy. Ghrelin and resistance training inhibit the production of TNF-α. Vitamin D appears to down-regulate myostatin expression and up-regulate follistatin expression, an inhibitor of myostatin. The precise mechanism of vitamin D receptor and vitamin D on muscle cell is unknown. Amino acid supplementation plays a role in the phosphorylation of eIF-4E and p70S6K, through an mTOR-mediated mechanism. ActRIIB, activin receptor IIB; ALK4/5, activin-like kinase 4/5; eIF-4E, eukaryotic initiation factor 4E; FOXO, Forkhead box O; GH, growth hormone; GHR, growth hormone receptor; IGF-I, insulin-like growth factor-I; IGF-IR, insulin-like growth factor-I receptor; IKK, inhibitor of κB kinase; JAK2, Janus kinase 2; mTOR, mammalian target of rapamycin; MuRF, muscle ring-finger protein; NF-κB, nuclear factor of kappa B; p70S6K, p70 ribosomal S6 kinase; PI3-K, phosphatidylinositol-3 kinase; p-Smad2/3, phosphorylated-Smad2/3; Rheb, Ras homolog enriched in brain; STAT5A, signal transducer and activator of transcription 5A; TNF-α, tumor necrosis factor-α; TSC, tumor suppressor complex; VDR, vitamin D receptor.