clinical comprehensive approach. For this review we used a narrative approach rather than meta-analyses or systematic reviews to summarize pharmaceutical therapies for counteracting sarcopenia that included testosterone, dehydroepiandrosterone, estrogen, growth hormone, ghrelin, vitamin D, angiotensin converting enzyme inhibitor, and eicosapentaenoic acid. Non-pharmaceutical therapies for sarcopenia including resistance training, protein and amino acid supplementation, and non-smoking are also reviewed. The two reviews focused on human studies.

The European Wording Group on Sarcopenia in Older People categorized sarcopenia into two types, as it may be useful in clinical practice [3]. 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 so that it may not be possible to characterize each individual as having primary or secondary sarcopenia [3]. Patients with disuse syndrome and deconditioning often complicate the diagnosis of not only activity-related sarcopenia, but also age-, disease-, and nutrition-related sarcopenia [14]. Patients with disease-related sarcopenia such as neuromuscular diseases, endocrine diseases, and Alzheimer's disease can complicate age-, activity-, and nutrition-related sarcopenia. In these cases a comprehensive approach can be the best way to treat sarcopenia. In this review, we address several pharmaceutical therapies, non-pharmaceutical therapies, and the comprehensive approach for inhibiting sarcopenia.

2. METHODS

We searched PubMed from 1989 through to February 2013 using combinations of the terms sarcopenia, muscle, drug therapy, exercise therapy, nutrition therapy, and smoking. Searches were limited to humans, English, and Japanese studies. Cross-referencing and hand searches of the reference lists of the retrieved studies were performed to identify additional relevant studies. Criteria for inclusion required meta-analyses, systematic reviews, and randomized clinical trials in human studies. If there were few meta-analyses, systematic reviews, or clinical trials, observational studies were included. Exclusion criteria were preclinical animal studies.

After the search, testosterone, dehydroepiandrosterone, estrogen, growth hormone, ghrelin, vitamin D, angiotensin converting enzyme inhibitors, and eicosapentaenoic acid were included in this review, as these areas included some human studies. On the other hand, myostatin inhibitors, ursolic acid, proteasome inhibitors, cyclophilin inhibitors, and peroxisome proliferator-activated receptor γ coactivator 1α were excluded as there were no clinical trials in humans.

3. PHARMACEUTICAL THERAPIES

3.1. Testosterone

Although the mechanisms by which testosterone increases skeletal muscle are poorly understood, testosterone has been shown to positively regulate insulin-like growth factor-1 and myostatin [8]. 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 [15]. 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 [15]. 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) [16]. The mean g-index of 0.53 indicates that androgen treatment produced an approximately 19.3% increase in muscle strength [16].

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 (weighted mean difference (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) [17]. No significant effect on mortality, prostate, or cardiovascular outcomes were observed in that study [17]. On the other hand, a testosterone gel was shown to be associated with an increased risk of cardiovascular adverse events (total risk odds ratio, 10.6; 95% CI, 1.3 to 84.5) in older men with limitations in mobility and a high prevalence of chronic disease [18].

Testosterone increases fat-free mass and muscle strength, and could be prescribed in sarcopenic elderly men for a few months with monitoring of side effects, if no contraindications for testosterone were encountered. Testosterone gel (1%) is applied once daily between 50 and 100 mg, while testosterone enanthate or testosterone cypionate is injected intramuscularly at a dose between 50 and 400 mg every 2 to 4 weeks.

3.2. Dehydroepiandrosterone

Dehydroepiandrosterone binds androgen receptors and displays tissue-selective activation of androgenic signaling. A cross-sectional study showed that low dehydroepiandrosterone levels were associated with a higher prevalence of frailty in older men and women [19]. However, a systematic review showed that the benefit of dehydroepiandrosterone on muscle strength and physical function in older adults remains inconclusive [20]. Of seven studies that examined measures of muscle strength, four showed improvement in handgrip strength, chest press, or knee extension and flexion, although a similar numbers of studies reported negative results for each of these endpoints [20]. Of five studies that examined measures of physical function and performance, only one study showed an improvement in physical performance [20]. Further large clinical trials are therefore necessary to recommend dehydroepiandrosterone supplementation to elderly sarcopenic patients.

3.3. Estrogen

In women accelerated rates of muscle strength loss are associated with menopause, which indicates that changes in ovarian hormones due to menopause contribute to muscle

weakness [21]. A meta-analysis that included 15 cross-sectional studies and 8 longitudinal studies showed that estrogen-based hormone therapy in postmenopausal women had a small beneficial effect on muscle strength (overall effect size = 0.23; p = 0.003), that equated to approximately 5% greater strength [21]. However, the overall health risks including coronary heart disease, breast cancer, stroke, and pulmonary embolism exceeded the benefits from use of combined estrogen plus progestin over an average 5.2-year follow-up in healthy postmenopausal US women participating in the Women's Health Initiative [22]. Estrogen is not indicated for primary or secondary prevention of cardio-vascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women [23]. The risk of endometrial and breast cancer after long-term use of systemic estrogen outweighs the benefits, especially in women with an intact uterus [24]. Therefore, estrogen-based hormone therapy is not recommended for preventing or treating sarcopenia.

3.4. 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. GH-induced muscle growth may be mediated in an endocrine manner by circulating insulin-like growth factor-I derived from the liver, and/or in an autocrine/paracrine manner by direct expression of insulin-like growth factor-I from target muscle *via* GH receptors on muscle membranes. 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 treated with GH [25]. However, subjects treated with GH were 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 as a consequence of its adverse effects [25].

After this systematic review, administration of the oral GH secretagogue, capromorelin, in healthy older adults was shown to improve body composition and physical function (lean body mass increased with capromorelin 1.4 kg vs. placebo 0.3 kg, P = 0.001). Adverse events included fatigue, insomnia, and small increases in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance [26]. Several randomized controlled trials using growth hormone and/or testosterone in healthy, elderly subjects also revealed that body composition and muscle performance were improved and enhanced with GH supplementation [27-30]. 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 [27]. GH therapy with or without testosterone had positive effects by improving body composition and muscle performance. However, GH therapy is still not recommended as sarcopenia treatment because of its adverse effects.

3.5. 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 (GHS-R) [31]. 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. Ghrelin inhibits the production of anorectic proinflammatory cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor-α (TNF-α). 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 the treatment of sarcopenia.

Oral administration of the ghrelin mimetic MK-677 at a dose of 25 mg once daily for 1 year in healthy older adults over the age of 60 years was shown to significantly increase 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) [32]. However, that study did not show a significant increase in strength or function in the ghrelin-mimetic treatment group, compared with the placebo group [32]. In 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, ghrelin treatment resulted in significant increases in lean body mass (P = 0.012) and decreases in fat mass (P = 0.017) [33]. In contrast, muscle strength and walking ability did not differ significantly [33].

The effect of ghrelin has been investigated in other diseases including chronic heart failure [34], chronic obstructive pulmonary disease [35, 36], end-stage renal disease [37, 38], and cancer [39-44]. Ghrelin improved lean body mass [34, 35], respiratory strength [36], energy intake [37-39, 42-44], appetite scores and loss of whole body mass [41]. Ghrelin appears to increase lean body mass in the elderly, although 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.

3.6. Vitamin D

Vitamin D deficiency is one cause of proximal myopathy and sarcopenia which improves with vitamin D supplementation [45, 46]. Vitamin D appears to down-regulate myostatin expression and up-regulate follistatin expression, an inhibitor of myostatin. The precise mechanism of the vitamin D receptor and vitamin D on muscle cells is, however, unknown. Because low vitamin D was shown to be associated with an increased risk of mobility limitation and disability in community-dwelling subjects [47], vitamin D supplementation appears a reasonable treatment option in sarcopenia, especially in the elderly with vitamin D deficiency. The association between low vitamin D and low muscle mass has been reported in some studies [48-51]. On the other hand, Marantes *et al.* [52] found the association between low vitamin D and low muscle mass 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 remains controversial [53]. 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 [53]. Four studies showed a significant effect on muscle strength, while this effect was not observed in three other studies [53]. 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 (standardized mean difference (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 [54]. However, pooled data from two studies in 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) [54].

Vitamin D would be expected to reduce the risk of falling and fracture in the elderly. Vitamin D combined with calcium reduces the risk of falls (OR, 0.83; 95% CI, 0.72 to 0.93), although subgroup analysis of meta-analyses showed the reduction in studies without calcium co-administration did not reach statistical significance (OR, 0.97; 95% CI, 0.84 to 1.11) [55]. In a recently updated Cochrane Database of Systematic Review on interventions for preventing falls in older people living in the community, vitamin D did not reduce the rate of falls (rate ratio (RR), 1.00; 95% CI, 0.90 to 1.11, 7 trials) or risk of falling (RR, 0.96; 95% CI, 0.89 to 1.03, 13 trials) [56]. However, vitamin D did reduce the rate of falls (RR, 0.57; 95% CI, 0.37 to 0.89, 2 trials) or risk of falling (RR, 0.70; 95% CI, 0.56 to 0.87, 4 trials) in people with lower vitamin D levels before treatment [56]. On the other hand, high-dose vitamin D supplementation (≥ 800 international units daily) was favorable for preventing hip fractures (HR, 0.70; 95% CI, 0.58 to 0.86) and any nonvertebral fracture (HR, 0.86; 95% CI, 0.76 to 0.96) in persons 65 years of age or older [57]. However, an annual high-dose of oral vitamin D resulted in an increased risk of falls (RR, 1.15; 95% CI, 1.02 to 1.30) and fractures (RR, 1.26; 95% CI, 1.00 to 1.59) [58]. Vitamin D supplementation is therefore recommended only in elderly subjects with vitamin D deficiency, for the purpose of increasing muscle strength and reducing the rate of falls and fractures. A dose of 800 international units of vitamin D daily is recommended as a maintenance dose for the elderly with vitamin D deficiency.

3.7. Angiotensin Converting Enzyme Inhibitor

Angiotensin-converting enzyme (ACE) inhibitors have long been used as a treatment for primary and secondary prevention of cardiovascular diseases. It has been suggested that ACE inhibitors may have a beneficial effect on skeletal muscle in the elderly without chronic heart failure. ACE inhibitors may improve muscle function by improving endothelial function, metabolic function, anti-inflammatory effects, and angiogenesis, thereby improving skeletal muscle blood flow. ACE inhibitors can increase the numbers of mitochondria and levels of insulin-like growth factor-I, thereby helping to counter sarcopenia. Observational studies have shown that the long-term use of ACE inhibitors was associated with a lower decline in muscle strength in elderly women with hypertension without chronic heart failure [59] and a larger lower extremity muscle mass in older people when compared with users of other antihypertensive agents [60]. In contrast, Gray *et al.* [61] found no association between the use of ACE inhibitors and a slower decline in physical performance or muscle strength in older women.

The effect of ACE inhibitors on physical function and muscle strength was investigated in three randomized controlled trials [62-64]. One study that investigated functionally impaired older people without heart failure showed that perindopril improved 6-minute walking distance (mean between-group difference, 31.4 m; 95% CI, 10.8 to 51.9) and maintained health-related quality of life (between-group difference, 0.09; 95% CI 0.00 to 0.17), but did not improve muscle function measured by the sit-to-stand test (between-group difference, -3.1 s; 95% CI -7.5 to 1.3) [62]. A study comparing the effects of nifedipine with ACE inhibitors (enalapril) in hypertensive, older people did not show a significant difference between treatments in fat free mass (enalapril; baseline 39.0 ± 6.8 kg, 4.5 month 38.7 ± 6.8 kg: nifedipine; baseline 38.7 ± 7.4 kg, 4.5 month 38.4 ± 6.9 kg, non-significant), muscle strength, walking distance, or functional performance [63]. Cesari *et al.* [64] found no significant modifications in physical performance assessed by the Short Physical Performance Battery total score (fosinopril 2.113 ± 0.284 vs. placebo 2.096 ± 0.298, P = 0.23) and grip strength (fosinopril 37.044 ± 12.993 kg vs. placebo 36.898 ± 13.178 kg, P = 0.57) after 6 months of fosinopril use in older persons with a high cardiovascular risk profile. ACE inhibitors may therefore have a possible effect by preserving muscle strength and function in older adults with sarcopenia. However, further evidence is required before recommending ACE inhibitors to counter the effects of sarcopenia.

3.8. Eicosapentaenoic Acid

Eicosapentaenoic acid (EPA) is a 20-carbon omega n-3 polyunsaturated fatty acid with anti-inflammatory properties, which is synthesized from ingested alphalinolenic acid, or alternatively is consumed in fish and fish oil. EPA has been shown to inhibit the proinflammatory transcription factor, nuclear factor kappa B, and to reduce TNF-α production by macrophages, and to prevent the damaging effects of TNF-α during skeletal muscle differentiation *in vitro*. An observational study in older men and women showed fatty fish consumption can have an important influence on muscle function [65]. An increase in grip strength of 0.43 kg (95% CI, 0.13 to 0.74) in men and 0.48 kg (95% CI, 0.24 to 0.72) in women was observed for each additional portion of fatty fish consumed per week [65]. Smith *et al.* [66] found that while omega-3 fatty acid supplementation had no effect on the basal rate of muscle protein synthesis it augmented the hyperaminoacidemia-hyperinsulinemia-induced increase in the rate of muscle protein synthesis. In a randomized, controlled trial strength-training program, elderly woman who received fish oil supplementation (2 g/day) achieved greater improvements in muscle strength and functional capacity than with strength training only [67]. However, there are no randomized controlled trials evaluating the effectiveness of EPA on muscle mass and muscle strength in the elderly without strength training.

The effect of EPA has been investigated more in cancer patients with cachexia than in the elderly with sarcopenia. Plasma omega-3 fatty acids have been reported to be depleted in patients with non-small cell lung cancer and sarcopenia and may contribute to accelerated rates of muscle loss [68]. The anti-inflammatory properties of omega-3 fatty acids would be expected to lead to a gain in lean body mass in cancer cachexia. However, a systematic review and meta-analysis revealed that there is insufficient evidence to support a net benefit of omega-3 fatty acids in cachexia in advanced cancer [69, 70]. As EPA produces few serious side effects, it may be a potentially useful therapeutic agent for the treatment and prevention of sarcopenia. Intervention research on a moderate dose of fish oil for older adults recovering from hip fracture is ongoing [71]. Further clinical trials are required to recommend EPA as sarcopenia treatment.

4. NON-PHARMACEUTICAL THERAPIES

4.1. Resistance Training

Resistance training has been shown to be the most promising among interventions aimed at 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 the elderly, identified five of six articles that concluded high-intensity resistance training resulted in significant increases in soft lean tissue and muscle mass [72]. On the other hand, the remaining three articles indicated that moderate-intensity resistance training did not affect soft lean tissue or muscle mass [72]. High-intensity resistance training with sufficient periods, 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 [73]. Strength increases ranged from 9.8 to 31.6 kg, while percent changes were 29 ± 2, 24 ± 2, 33 ± 3, and 25 ± 2 for leg presses, chest presses, knee extensions, and lateral pulls, respectively [73]. A Cochrane database systematic review reported progressive resistance strength training was also an effective intervention for improving physical functioning in older people by increasing muscle strength (SMD, 0.84; 95% CI, 0.67 to 1.00) and gait speed (mean difference (MD), 0.08 m/s; 95% CI, 0.04 to 0.12) in [74]. However, several studies [75, 76] have shown that excess intensive strength training in the elderly may impair the effective gain in muscle strength and mass, particularly in women. Careful attention should therefore be paid when determining the amount and frequency of resistance training in the elderly.

4.2. Protein and Amino Acids

Protein and amino acid supplementation can counteract sarcopenia, as low protein intake is known to be associated with declining muscle mass in older adults [77]. A Cochrane database of systematic review found that protein and energy supplementation produces 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) [78]. However, this review found no evidence of a reduction in the length of hospital stay with supplements (-0.8 days; 95% CI, -2.8 to 1.3) [78]. In a recent systematic review on the effectiveness of nutritional supplementation on muscle mass in the treatment of sarcopenia in old age, an improvement in muscle mass and muscle strength was proven [79]. Many essential acids including large amounts of leucine are needed to effectively counteract sarcopenia [9].

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 most effective for preventing and treating age-related muscle wasting and weakness [8-10]. Kim *et al.* [80] found that exercise and amino acid supplementation together may be 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 after prolonged resistance-type exercise training in both younger and older subjects [81]. Therefore, a comprehensive approach to sarcopenia treatment should include resistance training and protein and amino acid supplementation.

4.3. Non-smoking

Several cross-sectional studies have shown an association between cigarette smoking and lower levels of muscle mass and muscle strength in smokers. In the MINOS cohort, which included 845 men aged 45-85, smokers had lower relative appendicular skeletal muscle mass than men who had never smoked (-3.2%; $P < 0.003$) [82]. The Rancho Bernardo cohort, which examined the prevalence of sarcopenia and associated risk factors in 1,700 men and women aged 55-98, showed current smokers were more likely to have sarcopenia (men OR, 2.46; 95% CI, 0.87 to 7.00: women OR, 1.90; 95% CI, 0.83 to 4.34) [83]. Sarcopenia was also reported to be associated with cigarette smoking in 4,000 community-dwelling older Chinese men (MD, -0.19; 95% CI, -0.31 to -0.07) and women (MD, -0.3; 95% CI, -0.54 to -0.07) [84]. In addition, there is evidence cigarette smoking was negatively associated with muscle strength, especially grip strength (correlation coefficient between muscle strength and Brinkman index; right -0.208, left -0.197) in 4249 Japanese men aged 43.3 ± 13.9 years [85].

In a longitudinal cohort study, which included 963 men and women aged 30 to 73 yr at baseline, smoking predicted the decline in muscle strength over 22 years of follow-up (never smoked, β estimate -6.48; former smoker, β estimate -7.95, $P = 0.02$; current smoker, β estimate -8.81, $P < 0.001$) [86]. In addition, persistent smoking was associated with an accelerated decline in handgrip strength [86]. These epidemiological studies indicate that smoking is associated with sarcopenia and that non-smoking earlier in life may prevent sarcopenia in old age. Non-smoking can therefore be recommended for preventing and treating sarcopenia.

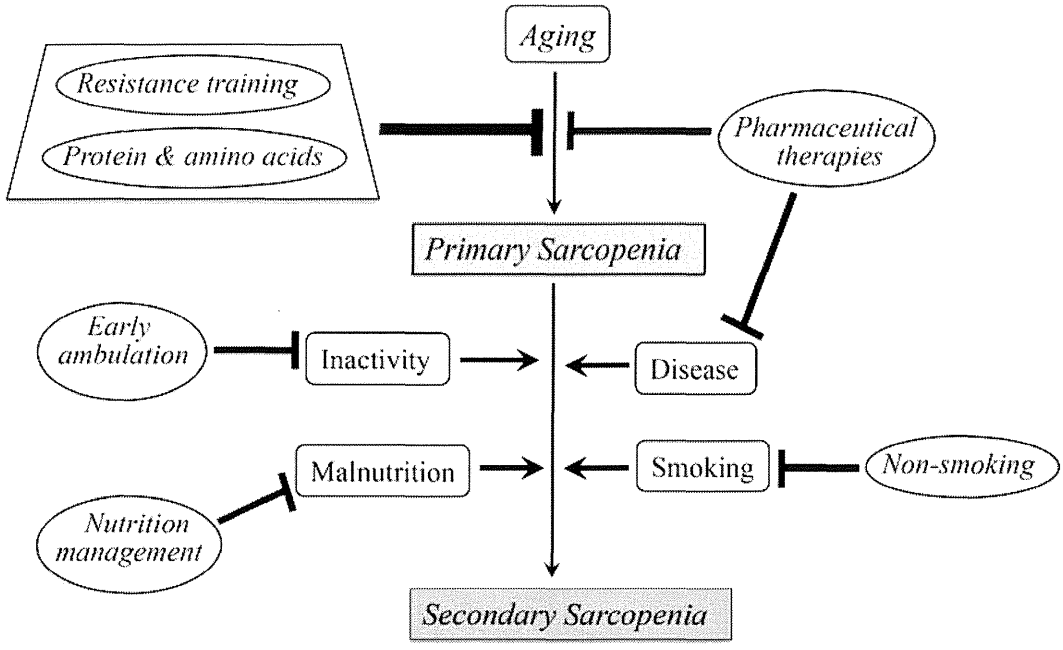

Fig. (2). Comprehensive approach to primary and secondary sarcopenia treatment. Resistance training combined with protein and amino acid supplements would be most effective to prevent and treat sarcopenia.

5. COMPREHENSIVE APPROACH

The comprehensive approach to age-related sarcopenia includes pharmaceutical therapies for primary sarcopenia, resistance training, protein and amino acid supplementation, and non-smoking. As the importance of skeletal muscle has been increasingly recognized in geriatric subspecialty rehabilitation disciplines, the term sarcopenia has also been applied widely to changes in muscle associated with chronic disease states and inactivity [87]. Because chronic illnesses, inactivity, and aging often coexist, a broad application of the term sarcopenia highlights the range of clinical populations at risk for loss of muscle mass and function [87]. A comprehensive approach to sarcopenia treatment should target not only primary sarcopenia but also secondary sarcopenia, such as activity-, disease-, or nutrition-related sarcopenia.

Activity-related sarcopenia can result from bed rest, a sedentary lifestyle, and deconditioning or zero-gravity conditions [3]. Avoiding bed rest, early ambulation, and exercise are important for preventing and treating activity-related sarcopenia. Ninety-one percent of patients with disuse syndrome and deconditioning were defined as being malnourished, and nutritional status was associated with rehabilitation outcome [11]. In an acute rehabilitation setting, underweight patients with deconditioning showed the smallest increases in functional independence measure scores, compared with either patients with a body mass index in the normal range or obesity [88]. Therefore, a combination of both rehabilitation therapy and appropriate nutrition management is important and may be associated with a better outcome in elderly subjects with activity-related sarcopenia [11].

Disease-related sarcopenia is associated with advanced organ failure (heart, lung, liver, kidney, and brain), inflammatory disease, malignancy, or endocrine disease [3]. Although the high prevalence of comorbid chronic diseases in sarcopenic older adults complicates the understanding of the underlying pathophysiology in an individual, such associations provide opportunities for investigating pharmacological interventions [87]. Pharmaceutical therapies for both age- and disease-related sarcopenia are important for inhibiting sarcopenia. Careful attention should be paid in cancer treatment, as the adverse effects of chemotherapy increase in cancer patients with sarcopenia [89-91].

Nutrition-related sarcopenia results from inadequate dietary intake of energy and/or protein associated with either malabsorption, gastrointestinal disorders, or use of medications that cause anorexia [3]. Resistance training cannot increase muscle mass in the elderly with starvation or nutrition-related sarcopenia, as substantial intake of energy and protein is necessary to promote muscle anabolism. A comprehensive approach to nutrition-related sarcopenia should include nutrition management. In contrast, some sarcopenic elderly subjects have sarcopenic obesity [92, 93]. Energy restriction and exercise are required for the elderly with sarcopenic obesity to improve sarcopenia and physical function [94, 95].

Age-, activity-, disease-, and nutrition-related sarcopenia often coexist in the elderly. A comprehensive approach to primary and secondary 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 the causes of sarcopenia.

6. CONCLUSION

The advances in our understanding of sarcopenia that have occurred over the years have led to new hopes for pharmaceutical therapies. Testosterone improves muscle mass and muscle strength but have several side effects, while the benefit of dehydroepiandrosterone on muscle strength and physical function remains inconclusive. GH is still not recommended as sarcopenia treatment due to its side effects. Ghrelin appears to increase lean body mass, although increased fat-free mass may not result in changes in muscle strength or physical function. Vitamin D supplementation is recommended only in the elderly with vitamin D deficiency. Non-pharmaceutical therapies including resistance training, protein and amino acid supplementation, and non-smoking can be recommended for preventing and treating sarcopenia. Because primary and secondary sarcopenia often coexist, 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 (Fig. **2**).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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