ejpmr, 2021, 8(5), 305-319

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SARCOPENIC OBESITY – A CLINICAL REVIEW

[1]Shaista Sumayya, [1]Siddiqua Parveen, [1]Meraj Fatima, [1]Ameena Begum, [2]Syed Jaffer, [2*]S. P. Srinivas Nayak and [3]Anupama Koneru

[1]PharmD, Sultan-ul-Uloom College of Pharmacy, JNTUH, Telangana, India – 500075.
[2]Assistant Professor, Dept. of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, JNTUH, Telangana, India – 500075.
[3]Principal, Sultan-ul-Uloom College of Pharmacy, JNTUH, Telangana, India – 500075.

***Corresponding Author: Dr. S. P. Srinivas Nayak**

Assistant Professor, Dept. of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, JNTUH, Telangana, India – 500075.

Article Received on 08/03/2021 **Article Revised on 29/03/2021** **Article Accepted on 18/04/2021**

ABSTRACT

Purpose of review: Sarcopenic obesity is a chronic condition, which is due to progressively aging populations, the increasing incidence of obesity, and lifestyle changes. The increasing prevalence of sarcopenic obesity in elderly has augmented interest in identifying the most effective treatment. This article aims at highlighting potential pathways to muscle impairment in obese individuals, the consequences that joint obesity and muscle impairment may have on health and disability, recent progress in management with attention on lifestyle management and pharmacologic therapy involved in reversing sarcopenic obesity. **Recent findings:** It has been suggested that a number of disorders affecting metabolism, physical capacity, and quality of life may be attributed to sarcopenic obesity. Excess dietary intake, physical inactivity, low-grade inflammation, insulin resistance and hormonal changes may lead to the development of sarcopenic obesity. Weight loss and exercise independently reverse sarcopenic obesity. Optimum protein intake appears to have beneficial effects on net muscle protein accretion in older adults. Myostatin inhibition causes favourable changes in body composition. Testosterone and growth hormone offer improvements in body composition but the benefits must be weighed against potential risks of therapy. GHRH-analog therapy is effective but further studies are needed in older adults. **Summary:** Lifestyle changes involving both diet-induced weight loss and regular exercise appear to be the optimal treatment for sarcopenic obesity. It is also advisable to maintain adequate protein intake. Ongoing studies will determine whether pharmacologic therapy such as myostatin inhibitors or GHRH-analogs have a role in the treatment of sarcopenic obesity.

KEYWORDS: sarcopenic obesity, myostatin inhibitors, exercise, weight loss, elderly, testosterone.

I. INTRODUCTION

Obesity

Obesity is defined as abnormal or extensive fat accumulation that negatively affects health.[1] According to the World Health Organization[1], obesity is defined as Body Mass Index (BMI) ≥ 30 kg/m ^{2} and central obesity as a waist circumference greater than 102 cm in men and 88 cm in women. Whether these criteria are appropriate for older individuals has been questioned. Obesity is a disease characterized by increased adiposity with negative impact on patient health, and it is commonly diagnosed by body mass index (BMI) above 30 kg/m 2 (or above 27.5 kg/m 2 in specific ethnic groups). Its prevalence has rapidly increased worldwide over the last three decades, largely due to combined genetic predisposition and profound lifestyle changes including sedentary habits and high-calorie dietary intake.[2] In many parts of the world, overweight (BMI > 25 kg/m 2) and obese individuals currently account for a majority of the population[3]; the proportion is substantially higher in middle- and elderly age groups.[4]Obesity is a strong risk factor for metabolic diseases such as metabolic syndrome and type 2 diabetes as well as atherosclerosis and cardiovascular events. In addition, obese individuals are at higher risk for many chronic and acute diseases involving end-stage organ failures, cancer, and infections.[5] For example, overweight and obese patients carry an at least 70% higher risk for coronary disease and a 20–50% higher risk of developing wound infections after colorectal surgery compared to normal-weight patients.[6] Liver steatosis, cirrhosis, and cancer becomes a raising challenge for patients with long-standing obesity.[7]

Sarcopenia and Sarcopenic obesity

The term sarcopenia comes from the Greek words sarx (meaning flesh) and penia (meaning loss) was originally meant to represent age-related loss of muscle mass with aging.[8] Baumgartner et al.[9] defined sarcopenia as "appendicular skeletal muscle mass divided by body

height squared in meters (muscle mass index)" two standard deviations or more below reference values from young, healthy individuals measured with dual X-ray absorptiometry (DXA). In spite of the limitation discussed above, most of the literature focuses on the obesity/low muscle mass combination, appropriately defined as sarcopenic obesity. Like sarcopenia, sarcopenic obesity was first defined by Baumgartner[10] as a muscle mass index less than 2 SD below the sex-specific reference for a young, healthy population.

COMPARISON OF DIFFERENT SARCOPENIC OBESITY DEFINITIONS AND PREVALENCE

Table 1: shows the definitions of sarcopenic obesity given by New Mexico Ageing Process Study[10], NHANES III[20] and Zoico et al[21] and their prevalence respectively.

	New Mexico Aging Process Study	NHANES III	Zoico et al
Definition of sarcopenic obesity	Sarcopenia: skeletal muscle mass -2 SD below mean of young population or < 7.26 kg/m^2 in men and < 5.45 kg/m^2 in women. Obesity: percentage body fat greater than median or > 27% in men and 38% in women.	Sarcopenia: two lower quintiles of muscle mass (<9.12 kg/m^2 in men and <6.53 kg/m^2 in women). Obesity: two highest quintiles of fat mass (>37.16% in men and > 40.01% in women).	Sarcopenia: two lower quintiles of muscle mass (<5.7 kg/m^2) Obesity: two highest quintiles of fat mass (>42.9%)
Prevalence	M: 4.4% F: 3.0%	M: 4.4% F: 3.0%	F: 12.4%

Prevalence of Sarcopenic Obesity

Accurate estimation of the prevalence of sarcopenic obesity is limited due to not only the lack of a universally adopted definition of sarcopenia but also the use of different body composition assessment techniques.[11] In a 14-year prospective study of older adults (n = 4,652) more than 60 years of age by the National Health and Nutrition Examination Survey (NHANES) III, the prevalence rates of sarcopenic obesity were 18.1% in women and 42.9% in men.[12] The study defined sarcopenia using the BIA-derived sex-specific cutoffs for ALM/ht^2, as proposed by Janssen et al.[13] (men: ≤ 10.75 kg/m^2 and women: ≤ 6.75 kg/m^2). Obesity was based on the percentage of body fat (men: ≥27%, women: ≥38%). Previous studies in Korea have assessed the prevalence rates of sarcopenic obesity using information from the Korean NHANES (KNHANES) IV[14] database, which measured skeletal muscle mass using DXA. The prevalence rate of sarcopenic obesity was 7.6% for men and 9.1% for women based on ALM/weight (%). However, the rate was nearly zero for men and women using the ALM/ht^2 definition in the elderly population aged ≥65 years. The prevalence of sarcopenia in patients attending geriatric clinics was high.[15] Sarcopenic obesity was defined as class II sarcopenia with central obesity (WC: ≥90 cm for men and ≥85 cm for women).[16] Another study in Koreans (n = 2,221) aged over 60 years that used the same definition of sarcopenic obesity (ALM/weight (%)<2 SD from the reference values of young adult and central obesity) reported a prevalence rate of sarcopenic obesity of 6.1% for men and 7.3% for women.[17]

II. HEALTH CONSEQUENCES OF SARCOPENIC OBESITY

Sarcopenic obesity is associated with disability. In a cohort study of 451 elderly men and women, subjects with sarcopenic obesity, defined according to ALM/ht2 and percent body fat, had a 2.5-fold increased risk of disability during an 8-year follow-up period than individuals without sarcopenic obesity[18]; however, sarcopenia or obesity alone were not significantly associated with disability. The Concord Health and Aging Project reported that elderly men with sarcopenic obesity had a 2-fold higher risk of frailty and an ~1.5-fold increased risk of disability during the 7 years of follow-up.[19] Sarcopenia was associated with poor functional outcomes while obesity alone was not associated with any adverse outcomes. However, several cross-sectional studies reported opposite or mixed results. Sarcopenia or sarcopenic obesity (low muscle mass and high % body fat) was not related to disability in people aged 70 years and older from the NHANES, although obesity was associated with an increased risk of functional limitation in both men and women.[20] Another study reported that elderly women with sarcopenia only or with sarcopenic obesity did not have increased risks of disability, whereas those with obesity showed a 3-fold increased risk of disability.[21] Growing evidence indicates that muscle strength is a better indicator of aging-related functional decline than muscle mass. A meta-analysis of the relationship between body composition and muscle strength measures and functional decline in older men and women reported an association between dynapenia and obesity and long-term functional decline, respectively.[22] A cross-sectional study from China found that dynapenic obesity (low handgrip strength and elevated BMI) was associated

with increased risks of disability and slow gait speed compared to either dynapenia or obesity alone in an older Asian population.[23] Another prospective cohort study of Health ABC participants showed increased risks of functional limitation and mortality in participants with slow gait speed.[24] Furthermore, other tests of lower extremity function such as chair stand and standing balance showed comparable prognostic value for adverse health events. Each component of sarcopenia has a different association with institutionalization. A large observational study using data from Health ABC participants found that low muscle mass was not independently associated with an increased risk of hospitalization.[25] However, low muscle strength and poor physical performance were associated with increased risks of hospitalization.[26] Moreover, physical performance measures such as gait speed have been associated with future hospitalization and institutionalization in a variety of populations.[27] However, the association between obesity and hospitalization or institutionalization is more obvious. For instance, participants with obesity (BMI ≥30 kg/m2) in the NHANES showed a higher likelihood of nursing facility use[28] A longitudinal observation study reported midlife obesity to be associated with an increased risk of nursing home admission in late life[29], an association that persists in older adults with obesity.[30]

Mortality

Several prospective studies have investigated the relationship between sarcopenic obesity and the risk of mortality. The British Regional Heart Study, a 6-year prospective study of 4,252 men aged 60–79 years, reported a 55% higher risk of mortality in men with a high WC (>102 cm) and low midarm muscle circumference (sarcopenic obesity) than in those without sarcopenia or obesity.[31] Another prospective study of 4,652 participants aged ≥60 years from the NHANES III with a 14-year follow-up showed higher risks of all-cause mortality in women with sarcopenia and sarcopenic obesity than in women without sarcopenia or obesity.[32] Meanwhile, women with obesity were not at a high risk of mortality, and no significant difference was observed in mortality risk in male participants with sarcopenia, obesity, and sarcopenic obesity. However, individuals with sarcopenic obesity showed the lowest survival rate.[33] Interestingly, low physical performance (measured using walking speed) was significantly associated with increased mortality in older adults.[33] Measures of muscle strength, both knee extension and grip, were strong and independent predictors of mortality in older adults.[34] The magnitude of association for both quadriceps and grip strength were similar.[34] Although leg strength was more strongly associated with age itself than has grip strength[35], grip strength is currently much easier to measure, thus has greater potential for incorporating into clinic practice. A growing body of evidence indicates that muscular strength, as measured using grip strength, is associated with a variety of health outcomes including mortality in older adults.[36] A similar observation was reported in a 33-year follow-up study that included 3,594 men and women aged 50–91 years from the Mini-Finland Health Examination Survey. In this study, among participants aged ≥70 years, the risk of mortality was higher in participants with dynapenic obesity and dynapenia alone than in participants without dynapenia or obesity.[37] Moreover, the English Longitudinal Study of Aging reported minimal differences in all-cause mortality between patients with dynapenic obesity and those with dynapenia alone.[38] In this study, weight loss combined with low muscle strength had the greatest risk of mortality. Likewise, recent studies have shown an association between overweight or obesity and a lower risk of CVD or CVD-associated death, whereas being underweight is associated with an increased risk of CVD, a phenomenon known as the obesity paradox.[39] Older people with weight loss lose a greater percentage of lean mass than fat mass[40], which could contribute to the increased risk of CVD events after weight loss. Slow walking speed in older people was associated with an increased risk of cardiovascular mortality in a cohort of 3,208 older men and women.[41] Short Physical Performance Battery (SPPB) score is a group of physical performance measures including gait speed, chair rises, and balance test, and it was associated with an increased risk of all-cause mortality in a meta-analysis.[42] However, there is no study that evaluated the synergistic effects of low physical performance and obesity.

Metabolic Diseases

Both sarcopenia and obesity are associated with metabolic disorders.[43] Thus, sarcopenic obesity may have a greater impact on metabolic diseases and CVD-associated mortality than either sarcopenia or obesity alone.[44] In a large cross-sectional analysis of 14,528 adults from the NHANES III, the sarcopenic obesity group showed the highest risk of insulin resistance and dysglycemia.[45] The Korean Sarcopenic Obesity Study (KSOS) cohort study showed that sarcopenic obesity was associated with insulin, inflammation (C-reactive protein level), and vitamin D deficiency.[46] A cross-sectional study of 2,943 participants aged 60 years or older from KNHANES also reported that sarcopenic obesity was associated with insulin resistance, metabolic syndrome, dyslipidemia, and vitamin D deficiency.[47] Lim et al. observed a higher risk of metabolic syndrome among adults with sarcopenic obesity in a cross-sectional study of 565 participants aged ≥65 years from the Korean Longitudinal Study on Health and Aging.[48] Several cross-sectional studies of Korean populations of older adults from the KNHANES database reported sarcopenic obesity to be more strongly associated with increased risks of hypertension, dyslipidemia, and diabetes than sarcopenia or obesity alone.[49] The risk of hypertension was higher in the sarcopenia, and sarcopenic obesity groups than in the non-sarcopenia non-obesity group. Furthermore, individuals with sarcopenic obesity had a higher risk of dyslipidemia than men in the obesity and sarcopenia groups.[49] Recent studies have investigated

the relationship between low muscle strength and metabolic diseases. Relative handgrip strength, defined as handgrip strength normalized for BMI, was strongly negatively correlated with metabolic syndrome[50], hypertension[51], and dyslipidemia.[52] Handgrip strength normalized by body weight was inversely associated with insulin resistance and type 2 diabetes[53] Furthermore, lower handgrip strength was associated with non-alcoholic fatty liver disease[54] and all-cause and CVD mortality.[55] The risk of CVD increased by 23% in the dynapenia and obesity groups. Chronic medical conditions such as hypertension, diabetes mellitus, and dyslipidemia were associated with lower walking speed and greater decline in walking speed in older people.[56] All these results indicated that midlife cardiovascular risk factors likely contribute to poor physical function and disability in the elderly.

III. METABOLIC AND LIFESTYLE CHANGES

Primary Metabolic Abnormalities

Clustered metabolic derangements including systemic and muscle oxidative stress, inflammation and insulin resistance may occur in obesity[57] due to various causes that primarily include i) excess nutrient availability and tissue delivery, particularly saturated fat[58] and glucose[59] as well as ii) adipose tissue dysfunction upon activation of maladaptive responses in the presence of enhanced demand for lipid storage.[60] These alterations are at least in part causally interrelated and have a strong muscle-catabolic potential[61]; they can also promote a typical ‘anabolic resistance’ state in skeletal muscle, meaning that the response of muscle protein synthesis to nutrients is blunted.[62]

Ectopic Muscle Fat Accumulation

Muscle lipid accumulation commonly occurs[60] as a result of insufficient adipose tissue expansion in the face of excess lipid availability[63]; convincing evidence has long demonstrated the close association of skeletal muscle lipid content with tissue and systemic insulin resistance.[60] Mechanisms mediating metabolic lipotoxicity are complex and appearto include direct pro-oxidative and inflammatory activities[64] as well as accumulation of metabolically toxic lipid moieties such as diacylglycerol and ceramides.[65] Recent evidences show that ectopic lipid deposition may also compromise muscle protein turnover.[66]

Mitochondrial Dysfunction

Mitochondrial changes are not invariably observed in obese skeletal muscle until relatively late stages.[67] Their onset may however exacerbate oxidative stress and related metabolic cascades leading to insulin resistance and catabolism.[67] Potential reduction in ATP production may also directly result in low muscle strength and endurance capacity.

Stem Cell Dysfunction

Functionally altered muscle stem cells that may undergo adipocyte differentiation are increasingly described in the context of complicated obesity and muscle fat accumulation[68], and their potential relevant role in limiting skeletal muscle mass maintenance has been proposed.

Physical Inactivity

Low physical activity is one fundamental contributor to positive energy balance.[69] Progressive reduction of physical activity is further observed with disease progression due to worsening obesity and its joint and musculoskeletal complications[69], with direct negative impact on muscle protein turnover and muscle oxidative and performance capacity.[70]

IV. COMORBIDITIES

Cardiometabolic Complications

Complications such as metabolic syndrome or overt type 2 diabetes and hyperglycemia are associated with enhanced oxidative stress, pro-inflammatory changes, and mitochondrial dysfunction[71] that commonly cause catabolic abnormalities and may independently further muscle alterations.Altered tissue perfusion in the presence or absence of clinically relevant atherosclerotic disease as well as epicardial fat enlargement may also cause metabolic complications by enhancing ROS production and their negative metabolic impact.[72]

Chronic and Acute Complications

Obesity directly enhances the risk for, or may be associated with chronic organ failure syndromes and chronic diseases (including chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, and cancer) as well as their acute complications.[73] All of the above events and conditions may result in heterogeneous sources of inflammation and oxidative stress[74] while impairing spontaneous physical activity, thereby synergistically enhancing muscle loss and dysfunction.[75]

V. PATHWAYS TO THE OBESITY/MUSCLE IMPAIRMENT SYNDROME

Age-related changes in body composition

Longitudinal studies have shown that fat mass increases with age and is higher among later birth cohorts peaking at about age 60-75 years[76], whereas muscle mass and strength starts to decline progressively around the age of 30 years with a more accelerated loss after the age of 60.[77] Visceral fat and intramuscular fat tend to increase, while subcutaneous fat in other regions of the body declines.[78] Furthermore, fat infiltration into muscle is associated with lower muscle strength and leg performance capacity.[79] The increase in body weight and fatness are probably due to progressive decline in total energy expenditure stemming from decreased physical activity and reduced basal metabolic rate[80] in the presence of increased or stable caloric intake exceeding basal and activity-related needs. Aging is also associated with a decline in a variety of neural, hormonal and environmental trophic signals to muscle. Physical inactivity, hormonal changes, proinflammatory state,

malnutrition, loss of alpha-motor units in the central nervous system, and altered gene expression accelerate the loss of muscle mass and mass-specific strength.[81]

Physical activity

Sedentary life-style is an important risk factor for weight gain.[82] Obese persons also tend to be less physically active and this may contribute to decreased muscle strength.[83] Finally, muscle atrophy leads to reduction in metabolic rate both at rest and during physical activity and further aggravates the sedentary state, all of which can cause weight gain. Two recent studies have shown that weight loss intervention combining diet and exercise among older obese people improves muscle strength and muscle quality in addition to fat loss confirming the hypothesis about tight connection between adiposity and impaired muscle function.[84]

Inflammation

It is now evident that adipose tissue is an active metabolic tissue that secretes hormones and proteins. For example, in adipose tissue, either adipocytes directly or infiltrating macrophages produces pro-inflammatory cytokines, such as interleukin(IL)-6 and tumor necrosis factor (TNF)-α and adipokines, such as leptin and adiponectin, that up-regulate the inflammatory response[85], which, again, may contribute to muscle mass and strength decline.[86] Cesari et al.[87] reported that pro-inflammatory cytokines were positively associated with fat mass and negatively with muscle mass. In the InCHIANTI study, Schrager et al.[88] found that obese community-dwelling older persons with low muscle strength had elevated levels of CRP and IL-6 compared to those with normal strength. Thus, a pro-inflammatory state may be one of the key factors in creating a vicious cycle of decreased muscle strength among obese persons.

Insulin resistance

Studies in animals and humans have found that inflammatory molecules mediate obesityrelated insulin resistance through a cross-talk between cytokine receptors and insulin receptor signaling pathways.[89] It has been hypothesized that muscle fat infiltration causes insulin resistance in obese individuals[90] and this hypothesis has been partially confirmed in humans.[91] Since insulin is a powerful anabolic signal on proteins[92], insulin resistance in obese individuals may promote muscle catabolism. Studies have shown that insulin resistance is an independent correlate of poor muscle strength[93] and older diabetic patients show accelerated loss of leg muscle strength and quality.[94] Furthermore, resistance training improves insulin sensitivity and glycemic control.[95]

Growth hormone and testosterone

Increased adiposity is often associated with high circulating free fatty acids[96], which inhibit growth hormone production and decrease plasma insulin-like growth factor I (IGF-I).[97] Recent study showed that sarcopenic obese persons had depressed growth hormone secretion compared to obese persons.[98] Similarly, obese individuals tend to have lower testosterone.[99] Noteworthy, low levels of these anabolic hormones have been reported positively associated with low muscle strength[100] and may therefore contribute to muscle impairment in obese individuals.[101]

Malnutrition and weight loss

Weight gain results from the misbalance between energy intake and expenditure. Older persons tend to obtain too little proteins in their diet[102] which may impair protein muscle turnover, especially during periods of weight loss[103] which is often coincident with accelerated sarcopenia.

VI. DIAGNOSIS OF SARCOPENIC OBESITY

There is currently no consistent diagnosis of SO, nevertheless an adequate one should include the individual diagnosis of obesity and sarcopenia. According to the criteria of WHO, BMI ≥ 30 kg/m2 or wrist circumference (men ≥ 102 cm and women ≥ 88 cm) is considered as obesity. However, whether these criteria are appropriate for each individual has been questioned. Alternatively, cutoffs of BF% (Body Fat Percentage) or other adiposity indices have been regarded as useful outcomes measure of obesity.[104] European Working Group on Sarcopenia in Older People (EWGSOP) has proposed that (1) low muscle mass; (2) low muscle strength; (3) low physical performance are the three important parameters to define sarcopenia.[105]

Various techniques emerge for assessing muscle mass, among which, computed tomography (CT) and magnetic resonance imaging (MRI) are deemed as the gold standard to distinguish fat from other soft tissues, thereby, effectively estimating fat mass and muscle mass. However, it is hard to generalize CT and MRI due to the high cost, and the risk of radiation (for CT).[106] Therefore, another relatively inexpensive and low radiation method called dual-energy-X-ray absorptiometry (DXA) is recommended to estimate the lean and fat mass of the whole body or certain regions of body. Moreover, it also manifests strength in assessment of bone mass and density, thus simultaneously providing the conditions of bone, muscle, and fat.[107] In addition, as an affordable and available tool, bioelectrical impedance analysis (BIA) is used to measure muscle mass as well, whereas, the inaccuracy makes it unrecommended to diagnose sarcopenia.[108] An overestimation is accompanied with a poor distinction between extracellular and intracellular fluid.[109] Furthermore, air displacement plethysmography (ADP) measures body volume and body density and hence, total fat and lean tissue.[110] In spite of the widespread use of anthropometric measurements, such as mid-upper arm circumference, calf circumference, and skin fold thickness, they are inaccurate.[111]

Muscle strength can be assessed by handgrip strength, knee flexion/extension, and peak expiratory flow. Handgrip strength is a great predictor of extremity muscle power and mobility. Physical performance is defined by short physical performance battery (SPPB), usual gait speed, timed get-up-and-go test, and stair climb power test, which evaluate an individual's balance, gait, strength and endurance.[112]

VII. NONPHARMACOLOGICAL TEATMENT

Exercise and combined interventions

While aerobic and resistance exercises are core components in the treatment of sarcopenic obesity, the specific frequency, intensity, time and types (aerobic, resistance or both) should be considered. Longitudinal studies should verify whether weight loss plus combined aerobic and resistance training prolongs physical independence in sarcopenic obesity. Such studies might translate to older adults who have access to health membership benefits in community-based exercise centres.[113] Assessing aquatic therapies[114] or tai chi[115], in isolation or in tandem with other types of physical activities, might prove useful for treating patients with sarcopenic obesity. The addition of pharmacotherapy, such as testosterone supplementation, to progressive resistance training augmented the improvements in body composition, including reduced fat mass and improved lean mass[116] However, whether or not physical activity should be combined with novel and promising treatments requires systematic and further investigation.

Periodization strategies

Periodization, which is a systematic variation in physical training specificity, intensity and volume within periods, has emerged as a potential strategy to improve muscle performance.[117] Linear periodization reduces training volume while increasing training intensity or load between cycles.[118] Periodized resistance training in older adults demonstrated equal efficacy in physical function and physiological outcomes when compared with non-periodized resistance training.[119] In patients with sarcopenic obesity, no differences were observed in strength, power or short performance physical battery following a 10-week periodization strategy of strength and endurance training with concentric and eccentric movements.[120] Preliminary studies indicate that periodization results in increases in serum levels of irisin and decreases in IL-1β.[121] Leptin might also be reduced further with periodized resistance training.[122] While periodization could feasibly be prescribed in sedentary or frail older adults to improve physical function, it is premature to endorse this training as superior to non-periodized training.[123] Longer-term investigations in older populations with sarcopenic obesity are needed.

Whole-body vibration therapy

Whole-body vibration therapy is a novel therapy that could increase muscle contraction efficiency and function with similar efficacy to resistance training, though data on its efficacy are mixed. This safe and convenient technique is associated with a low risk of injury.[124] Whole-body vibration therapy uses the transmission of mechanical stimuli through the person's body[125] to activate the primary ends of muscle spindles, which leads to neuromuscular activation.[126] The participant stands on a vibrating platform where electrical signals are delivered through the body, and thus primary endings of muscle spindles are activated. Summative effects of the combination of whole body vibration therapy and resistance exercises[127] or of whole-body vibration therapy and vitamin D367 are mixed. Others hypothesize that pathways contributing to weight loss as a result of whole-body vibration therapy could inhibit adipogenesis, increase energy expenditure and reduce muscle mass.[128] Augmenting existing squatting exercises with whole-body vibration therapy failed to improve muscle mass in younger men aged 18–30 years.[129] Future research should focus on type, frequency and duration of treatment.[130]

Bariatric surgery

Bariatric surgery improves weight and metabolic outcomes and reduces mortality. In carefully selected patients, this could be considered a treatment for sarcopenic obesity in older adults ≥65 years.[131] Its safety and efficacy in sarcopenic obesity is unknown other than one study that evaluated the influence of sarcopenic obesity on gastric bypass and sleeve gastrectomy results.[132] Bariatric surgery leads to loss of fat mass[133], alters gut hormones[134] and can exacerbate weight loss-induced sarcopenia[135] and osteoporosis.[136] Carefully designed studies are needed before promoting this intervention.

VIII. PHARMACOLOGICAL THERAPY

Myostatin inhibitors

Myostatin inhibition may result in favorable changes in both adiposity and lean body mass. A member of the TGF-β superfamily of secreted growth factors, myostatin is produced by skeletal muscle and adipose tissue, functioning as a negative regulator of muscle mass.[137] Its clinical relevance has been confirmed in rodent models whereby myostatin infusion has resulted in marked muscle wasting.[138] Moreover, myostatin influences adipocyte differentiation with substantial evidence to suggest myostatin-mediated crosstalk between muscle and adipose tissue.[139] Indeed, myostatin has proven to be a biomarker of sarcopenia in the elderly, correlating inversely with muscle mass, with higher levels being observed in frail older adults compared to younger adults.[140] In contrast, observations of myostatin deficiency in nature have shed light on the implications of myostatin inhibition, with exceptional muscularity and scarce adiposity being well-described in myostatin-deficient cattle.[141] Similarly, a homozygous mutation in the myostatin gene has been described in a human child with increased muscle strength and phenotypic features overlapping those described in myostatin-deficient livestock.[142] Further, inhibition of myostatin by the administration of myostatin antibodies or introduction of

inhibitory propeptides in mice has been associated with improved muscle mass and function[143], increased intramuscular satellite cell function and IGF-1 signaling , enhanced thermogenesis, and resistance to obesity.[144] In one phase I/II trial of a myostatin antibody, no improvement in muscle strength or function was observed in muscular dystrophy patients, although the study was not powered for efficacy.[145] Further uncertainties regarding the effects of myostatin inhibition on muscle function stem from observations in individuals with the K153R polymorphism in the myostatin gene, a variant reported to reduce the ability of myostatin to modulate muscle mass and strength.[146] While this variant may contribute to exceptional longevity[147], there are also reports of diminished muscle force in some.[148], but not all[149] affected individuals. There are other unanswered questions regarding the long-term cardiovascular safety of myostatin inhibition given the evidence of myocardial expression of myostatin and its role in the development of heart failure.[150] For these reasons, long-term data are needed to elucidate the role myostatin inhibition may have in the prevention or treatment of sarcopenic obesity, with current studies ongoing in healthy adults.

Testosterone

A predictable decline in testosterone with aging parallels both the loss in lean body mass and the gain in fat mass which lead to sarcopenic obesity.[151] The beneficial effects of testosterone replacement on body composition and muscle strength in hypogonadal men have been well documented in a recent review.[152] Hildreth et al recently investigated the effects of 12 months of testosterone therapy or placebo in healthy older adults randomized to progressive resistance training versus no exercise.[153] In those subjects randomized to exercise, testosterone therapy was associated with improvements in fat mass and fat-free mass; however, no differences were observed in physical function or muscle strength compared to placebo. In contrast, upper body strength improved in the non-exerciser subjects treated with testosterone although no improvements were noted in physical function. Similarly, other studies in healthy older men have reported favorable effects of testosterone therapy on body composition.[154] Evidence suggests that testosterone therapy in healthy older men exerts beneficial effects on body composition which may be protective against sarcopenic obesity; however, there is need for careful monitoring for potential adverse events such as erythrocytosis, growth of subclinical prostate cancer, worsening of obstructive sleep apnea, and fluid retention.. The 2010 Endocrine Society Guidelines suggest treatment in older adults only if clinical and biochemical evidence of hypogonadism are present and after an informed discussion regarding the risks and benefits of therapy.[155]

Other therapies

Aging is associated with a progressive decline in growth hormone (GH) secretion and IGF-1 production[152], which is felt to be responsible in part for the decline in lean body mass and increase in fat mass that contribute to sarcopenic obesity.[156] Thus, GH therapy has been studied as an anti-aging agent and, in healthy older adults, reverses these changes in body composition.[157] Unfortunately, treatment has also been associated with significant adverse events such as arthralgias, edema, and glucose intolerance, and for this reason a systematic review in 2007 concluded that GH should not be used as anti-aging therapy.[158] The growth hormone secretagogue capromorelin improved body composition and physical function in healthy older adults but was associated with aggravation of glucose homeostasis.[159] On the other hand, Makimura et al recently reported the effects of a GHRH analog which reduced fat mass and increased lean body mass in obese individuals yet was not associated with abnormalities in glucose homeostasis or other adverse events compared to placebo.[160] The role for androgenic therapies aside from testosterone in improving body composition has also been evaluated. While there are conflicting data pertaining to the use of dehydroepiandrosterone (DHEA) alone on muscle mass and strength, we have demonstrated that DHEA supplementation potentiates the anabolic effects of heavy resistance exercise in older adults.[161] A recent meta-analysis of double blind placebo controlled trials in elderly men showed that DHEA supplementation can induce a small but significant positive effect on body composition, which is dependent on DHEA conversion to androgens or estrogens.[162] Treatment of elderly men with the synthetic anabolic androgen, oxandrolone, was associated with improvements in lean body mass, fat mass, and muscle strength.[163], but significant reductions in high-density lipoprotein (HDL) cholesterol were also observed.[164] Other treatments currently in development include inhibitors of transcription factor nuclear factor kappa B (NF-κB) for protection against cancer-related cachexia. Early studies demonstrate favorable effects of NF-κB inhibition on cancer-related cachexia and provide further insight into the pathogenesis of this disorder, offering promise for continued progress in the development of targeted therapies for muscle wasting disorders.[165]

IX. ALTERNATIVE TREATMENTS FOR SARCOPENIC OBESITY

Herbal Medicine and Derivative

With the growing of popularity of herbal medicine, many studies have indicated that herbal medicine or related derivatives may be effective methods to treat SO .A study has reported two cases about using wild ginseng complex (WGC) on two patients who only wanted to lose abdominal fat, but not in other parts of body. After 3 weeks of WGC intervention, the two patients had an increase in muscle mass, protein content, and basal metabolic rate. Therefore, WGC intervention may be a new alternative treatment for age-related sarcopenic obesity but more studies using larger samples are required to support this.[166]

Acupuncture

Acupuncture has been used in diabetes for a long time in Asian countries and recent studies have also suggested that acupuncture may alleviate SO.[167] A randomized controlled trial, using electrical acupuncture coupled with essential amino acid supplementation to treat SO in male older people, has indicated that both electrical acupuncture with oral essential amino acids group and oral essential amino acids alone group can decrease BF% and increase ASM/H2, with the combination group being more effective than another group. Moreover, the combination group can increase muscle mass in a shorter time.[168] Besides, a meta-analysis of randomized controlled trials has confirmed that acupuncture should be recommended as a complementary treatment in T2D control, particularly with obesity or other metabolic disorders.[169]

X. CONCLUSION

The increasing prevalence of obesity in elderly coupled with the decline in muscle mass resulting in sarcopenia act synergistically to maximize disability, morbidity, and mortality. It is necessary to provide effective treatment in the elderly. The primary treatment for sarcopenic obesity is lifestyle interventions. Though weight loss and exercise independently result in reversal of sarcopenic obesity, an intervention strategy incorporating combined weight loss and exercise has proven to be the most effective treatment for this disorder. Optimim protein intake also has beneficial effects. With regard to pharmacologic therapies for sarcopenic obesity, we do not believe that the data as of yet support testosterone therapy in the absence of symptomatic hypogonadism. On the other hand, there is promising, albeit limited data pertaining to the use of myostatin inhibitors and GHRH-analogs for sarcopenic obesity.

REFERENCES

1. WHO Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894; Geneva, Switzerland, 2000.
2. Branca F, Nikogosian H, Lobstein T eds; The Challenge of Obesity in the WHO European Region and the Strategies for Response: Summary. Copenhagen, WHO Regional Office for Europe, 2007.
3. NCD Risk Factor Collaboration NCD-RisC; Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19. 2 million participants. Lancet, 2016; 387: 1377–1396.
4. Ruesten A, Steffen A, Floegel A, Van der A DL, Masala G, Tjonneland A, et al: Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. PLoS One, 2011; 6: e27455.
5. Fruhbeck G, Toplak H, Woodward E, et al: Obesity: the gateway to ill health – an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts, 2013 6: 117–20.
6. Gurunathan U, Ramsay S, Mitrić G, Way M, Wockner L, Myles P: Association between obesity and wound infection following colorectal surgery: systematic review and meta-analysis. J Gastrointest Surg, 2017; 21: 1700–1712.
7. Michelotti GA, Machado MV, Diehl AM: NAFLD, NASH and liver cancer. Nat Rev Gastroenterol Hepatol, 2013; 10: 656–665.
8. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr, 1997; 127: 990S–991S.
9. Baumgartner R, Koehler K, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol, 1998; 147: 755–763.
10. Baumgartner RN. Body composition in healthy aging. Ann N Y Acad Sci. 2000; 904: 437–448.
11. Prado C, Wells J, Smith S, Stephan B, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr, 2012; 31: 583–601. doi:10.1016/j.clnu.2012.06.010.
12. Batsis JA, Mackenzie TA, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity, and functional impairments in older adults: national health and nutrition examination surveys 1999-2004. Nutr Res, 2015; 35: 1031–9. doi:10.1016/j. nutres.2015.09.003.
13. Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol, 2004; 159: 413–21. doi:10.1093/aje/kwh058.
14. Kim Y-S, Lee Y, Chung Y-S, Lee D-J, Joo N-S, Hong D, et al. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the fourth Korean National health and nutritional examination surveys. J Gerontol A Biol Sci Med Sci, 2012; 67: 1107–13. doi:10.1093/gerona/gls071.
15. Nguyen TN, Nguyen TN, Nguyen AT, et alPrevalence of sarcopenia and its associated factors in patients attending geriatric clinics in Vietnam: a cross-sectional studyBMJ Open, 2020; 10: e037630. doi:10.1136/bmjopen-2020-037630.
16. Lee SY, Park HS, Kim DJ, Han JH, Kim SM, Cho GJ, et al. Appropriate waist circumference cutoff points for central obesity in Korean adults. Diabetes Res Clin Pract, 2007; 75: 72–80. doi:10.1016/j.diabres.2006.04.013.
17. wang B, Lim J-Y, Lee J, Choi N-K, Ahn Y-O, Park B-J. Prevalence rate and associated factors of sarcopenic obesity in Korean elderly population. J Korean Med Sci, 2012; 27: 748–55. doi:10.3346/jkms. 2012.27.7.748.
18. 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. doi:10. 1038/oby. 2004. 250.
19. Hirani V, Naganathan V, Blyth F, Le Couteur DG, Seibel MJ, Waite LM, et al. Longitudinal

associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: the concord health and ageing in men project. Age Ageing, 2017; 46: 413–20. doi: 10. 1093/ageing/afw214.
20. 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: 1802–1809. doi: 10. 1046/j. 1532-5415. 2002. 50508. x.
21. Zoico E, Di Francesco V, Guralnik J, Mazzali G, Bortolani A, Guariento S, et al. Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. Int J Obes Relat Metab Disord, 2004; 28: 234–241. doi: 10. 1038/sj. ijo. 0802552.
22. Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. Epidemiol Rev, 2013; 35: 51–65. doi: 10. 1093/epirev/mxs006.
23. Yang M, Jiang J, Hao Q, Luo L, Dong B. Dynapenic obesity and lower extremity function in elderly adults. J Am Med Dir Assoc, 2015; 16: 31–6. doi: 10. 1016/j. jamda. 2014. 06. 019.
24. Cesari M, Kritchevsky SB, Newman AB, Simonsick EM, Harris TB, Penninx BW, et al. Added value of physical performance measures in predicting adverse health-related events: results from the health, aging and body composition study. J Am Geriatr Soc, 2009; 57: 251–9. doi: 10. 1111/j. 1532-5415. 2008. 02126. x.
25. Cawthon PM, Fox KM, Gandra SR, Delmonico MJ, Chiou CF, Anthony MS, et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc, 2009; 57: 1411–9. doi: 10. 1111/j. 1532-5415. 2009. 02366. x.
26. Cawthon PM, Fox KM, Gandra SR, Delmonico MJ, Chiou CF, Anthony MS, et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc, 2009; 57: 1411–9. doi: 10. 1111/j. 1532-5415. 2009. 02366. x.
27. Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc, 2003; 51: 314–22. doi: 10. 1046/j. 1532-5415. 2003. 51104. x.
28. Zizza CA, Herring A, Stevens J, Popkin BM. Obesity affects nursing-care facility admission among whites but not blacks. Obes Res, 2002; 10: 816–23. doi: 10. 1038/oby. 2002. 110.
29. Elkins JS, Whitmer RA, Sidney S, Sorel M, Yaffe K, Johnston SC. Midlife obesity and long-term risk of nursing home admission. Obesity. 2006; 14: 1472–8. doi: 10. 1038/oby. 2006. 167.
30. Valiyeva E, Russell LB, Miller JE, Safford MM. Lifestyle-related risk factors and risk of future nursing home admission. Arch Intern Med, 2006; 166: 985–90. doi: 10. 1001/archinte. 166. 9. 985.
31. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. Am J Clin Nutr, 2007; 86: 1339–46. doi: 10. 1093/ajcn/86. 5. 1339.
32. Batsis J, Mackenzie T, Barre L, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the national health and nutrition examination survey III. Eur J Clin Nutr, 2014; 68: 1001–7. doi: 10. 1038/ejcn. 2014. 117.
33. Cesari M, Pahor M, Lauretani F, Zamboni V, Bandinelli S, Bernabei R, et al. Skeletal muscle and mortality results from the InCHIANTI study. J Gerontol A Biol Sci Med Sci, 2009; 64: 377–84. doi: 10. 1093/gerona/gln031.
34. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci, 2006; 61: 72–7. doi: 10. 1093/gerona/61. 1. 72.
35. Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, et al. Strength and muscle quality in a well-functioning cohort of older adults: the health, aging and body composition study. J Am Geriatr Soc, 2003; 51: 323–30. doi: 10. 1046/j. 1532-5415. 2003. 51105. x.
36. Ling CH, Taekema D, De Craen AJ, Gussekloo J, Westendorp RG, Maier AB. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study, CMAJ. 2010; 182: 429–35. doi: 10. 1503/cmaj. 091278.
37. Stenholm S, Mehta NK, Elo IT, Heliövaara M, Koskinen S, Aromaa A. Obesity and muscle strength as long-term determinants of all-cause mortality—a 33-year follow-up of the mini-finland health examination survey. Int J Obes, 2014; 38: 1126–32. doi: 10. 1038/ijo. 2013. 214.
38. Hamer M, O'Donovan G. Sarcopenic obesity, weight loss, and mortality: the english longitudinal study of ageing. Am J Clin Nutr, 2017; 106: 125–9. doi: 10. 3945/ajcn. 117. 152488.
39. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia cohort consortium. BMJ, 2013; 347: f5446. doi: 10. 1136/bmj. f5446.
40. Miller S, Wolfe RR. The danger of weight loss in the elderly. J Nutr Health Aging, 2008; 12: 487–91. doi: 10. 1007/BF02982710.
41. Dumurgier J, Elbaz A, Ducimetiere P, Tavernier B, Alperovitch A, Tzourio C. Slow walking speed and cardiovascular death in well-functioning older

adults: prospective cohort study. BMJ, 2009; 339: b4460. doi: 10. 1136/bmj. b4460.
42. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, et al. Short physical performance battery and all-cause mortality: systematic review and meta-analysis. BMC Med, 2016; 14: 215. doi: 10. 1186/s12916-016-0763-7.
43. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. Nutr Metab Cardiovasc Dis. 2008; 18: 388–95. doi: 10. 1016/j. numecd, 2007. 10. 002.
44. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc, 2015; 74: 405–12. doi: 10. 1017/S002966511500169X.
45. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National health and nutrition examination survey III. PLoS ONE, 2010; 5: e10805. doi: 10. 1371/journal. pone. 0010805.
46. 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, 2013; 78: 525–32. doi: 10. 1111/j. 1365-2265. 2012. 04433. x.
47. Chung J-Y, Kang H-T, Lee D-C, Lee H-R, Lee Y-J. Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. Arch Gerontol Geriatr, 2013; 56: 270–8. doi:10.1016/j.archger.2012.09.007.
48. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean longitudinal study on health and aging KLoSHA; . Diabetes Care, 2010; 33: 1652–4. doi:10.2337/dc10-0107.
49. Baek S, Nam G, Han K, Choi S, Jung S, Bok A, et al. Sarcopenia and sarcopenic obesity and their association with dyslipidemia in Korean elderly men: the 2008–2010 Korea National health and nutrition examination survey. J Endocrinol Invest, 2014; 37: 247–60. doi:10.1007/s40618-013-0011-3.
50. Yi D, Khang AR, Lee HW, Son SM, Kang YH. Relative handgrip strength as a marker of metabolic syndrome: the Korea National health and nutrition examination survey KNHANES; VI 2014–2015; Diabetes Metab Syndr Obes, 2018; 11: 227–40. doi:10.2147/DMSO. S166875.
51. Ji C, Zheng L, Zhang R, Wu Q, Zhao Y. Handgrip strength is positively related to blood pressure and hypertension risk: results from the National Health and nutrition examination survey. Lipids Health Dis, 2018; 17: 86. doi:10.1186/s12944-018-0734-4.
52. Li D, Guo G, Xia L, Yang X, Zhang B, Liu F, et al. Relative handgrip strength is inversely associated with metabolic profile and metabolic disease in the general population in China. Front Physiol, 2018; 9: 59. doi:10.3389/fphys.2018.00059.
53. Lee M-R, Jung SM, Bang H, Kim HS, Kim YB. Association between muscle strength and type 2 diabetes mellitus in adults in Korea: data from the Korea national health and nutrition examination survey KNHANES; VI. Medicine, 2018; 97: e10984. doi:10.1097/MD.0000000000010984.
54. Kim B-J, Ahn SH, Lee SH, Hong S, Hamrick MW, Isales CM, et al. Lower hand grip strength in older adults with non-alcoholic fatty liver disease: a nationwide population-based study. Aging, 2019; 11: 4547–60. doi: 10. 18632/aging. 102068.
55. Kim GR, Sun J, Han M, Park S, Nam CM. Impact of handgrip strength on cardiovascular, cancer and all-cause mortality in the Korean longitudinal study of ageing. BMJ Open, 2019; 9: e027019. doi: 10. 1136/bmjopen-2018-027019.
56. Dumurgier J, Elbaz A, Dufouil C, Tavernier B, Tzourio C. Hypertension and lower walking speed in the elderly: the three-City study. J Hypertens, 2010; 28: 1506–14. doi: 10. 1097/HJH. 0b013e328338bbec.
57. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I: Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest, 2004; 114: 1752–1761.
58. Barazzoni R, Zanetti M, Gortan Cappellari G, Semolic A, Boschelle M, Codarin E, Pirulli A, Cattin L, Guarnieri G: Fatty acids acutely enhance insulin-induced oxidative stress and cause insulin resistance by increasing mitochondrial reactive oxygen species ROS; generation and nuclear factor-κB inhibitor IκB; -nuclear factor-κB NFκB; activation in rat muscle, in the absence of mitochondrial dysfunction. Diabetologia, 2012; 55: 773–782.
59. Barazzoni R, Deutz NEP, Biolo G, Bischoff S, Boirie Y, Cederholm T, Cuerda C, Delzenne N, Leon Sanz M, Ljungqvist O, Muscaritoli M, Pichard C, Preiser JC, Sbraccia P, Singer P, Tappy L, Thorens B, Van Gossum A, Vettor R, Calder PC: Carbohydrates and insulin resistance in clinical nutrition: recommendations from the ESPEN expert group. Clin Nutr, 2017; 36: 355–363.
60. Czech MP: Insulin action and resistance in obesity and type 2 diabetes. Nat Med, 2017; 23: 804–814.
61. Powers SK, Morton AB, Ahn B, Smuder AJ: Redox control of skeletal muscle atrophy. Free Radic Biol Med, 2016; 98: 208–217.
62. Guillet C, Delcourt I, Rance M, Giraudet C, Walrand S, Bedu M, Duche P, Boirie Y: Changes in basal and insulin and amino acid response of whole body and skeletal muscle proteins in obese men. J Clin Endocrinol Metab, 2009; 94: 3044–3050.
63. Cuthbertson DJ, Steele T, Wilding JP, Halford JC, Harrold JA, Hamer M, Karpe F: What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to

obesity and metabolic complications? Int J Obes, 2017; 41: 853–865.
64. Barazzoni R, Zanetti M, Gortan Cappellari G, Semolic A, Boschelle M, Codarin E, Pirulli A, Cattin L, Guarnieri G: Fatty acids acutely enhance insulin-induced oxidative stress and cause insulin resistance by increasing mitochondrial reactive oxygen species ROS; generation and nuclear factor-κB inhibitor IκB; -nuclear factor-κB NFκB; activation in rat muscle, in the absence of mitochondrial dysfunction. Diabetologia, 2012; 55: 773–782.
65. Lipina C, Hundal HS: Lipid modulation of skeletal muscle mass and function. J Cachexia Sarcopenia Muscle, 2017; 8: 190–201.
66. Tardif N, Salles J, Guillet C, Tordjman J, Reggio S, Landrier JF, Giraudet C, Patrac V, Bertrand-Michel J, Migne C, Collin ML, Chardigny JM, Boirie Y, Walrand S: Muscle ectopic fat deposition contributes to anabolic resistance in obese sarcopenic old rats through eIF2α activation. Aging Cell, 2014; 13: 1001–1111.
67. Dahlmans D, Houzelle A, Schrauwen P, Hoeks J: Mitochondrial dynamics, quality control and miRNA regulation in skeletal muscle: implications for obesity and related metabolic disease. Clin Sci, 2016 130: 843–852.
68. Vettor R, Milan G, Franzin C, Sanna M, De Coppi P, Rizzuto R, Federspil G: The origin of intermuscular adipose tissue and its pathophysiological implications. Am J Physiol Endocrinol Metab, 2009 297: E987–E998.
69. Strasser B: Physical activity in obesity and metabolic syndrome. Ann N Y Acad Sci, 2013; 1281: 141–159.
70. Biolo G, Agostini F, Simunic B, Sturma M, Torelli L, Preiser JC, Deby-Dupont G, Magni P, Strollo F, di Prampero P, Guarnieri G, Mekjavic IB, Pisot R, Narici MV: Positive energy balance is associated with accelerated muscle atrophy and increased erythrocyte glutathione turnover during 5 wk of bed rest. Am J Clin Nutr, 2008; 88: 950–958.
71. Dahlmans D, Houzelle A, Schrauwen P, Hoeks J: Mitochondrial dynamics, quality control and miRNA regulation in skeletal muscle: implications for obesity and related metabolic disease. Clin Sci, 2016 130: 843–852.
72. Hoppeler H, Vogt M, Weibel ER, Fluck M: Response of skeletal muscle mitochondria to hypoxia. Exp Physiol, 2003; 88: 109–119.
73. Fruhbeck G, Toplak H, Woodward E, et al: Obesity: the gateway to ill health – an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts, 2013; 6: 117–20.
74. Barazzoni R, Biolo G, Zanetti M, Bernardi A, Guarnieri G: Inflammation and adipose tissue in uremia. J Ren Nutr, 2006; 16: 204–207.
75. Brocca L, Cannavino J, Coletto L, Biolo G, Sandri M, Bottinelli R, Pellegrino MA: The time course of the adaptations of human muscle proteome to bed rest and the underlying mechanisms. J Physiol, 2012; 590: 5211–5230.
76. Rissanen A, Heliövaara M, Aromaa A. Overweight and anthropometric changes in adulthood: a prospective study of 17,000 Finns. Int J Obes, 1988; 12: 391–401.
77. Rantanen T, Masaki KT, Foley D, et al. Grip strength changes over 27 yr in Japanese-American men. J Appl Physiol, 1998; 85: 2047–2053.
78. Beaufrere B, Morio B. Fat and protein redistribution with aging: metabolic considerations. Eur J Clin Nutr, 2000; 54(3): S48–53.
79. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol, 2001; 90: 2157–2165.
80. Elia M, Ritz P, Stubbs RJ. Total energy expenditure in the elderly. Eur J Clin Nutr, 2000; 54: S92– S103.
81. Marcell TJ. Sarcopenia: causes, consequences, and preventions. J Gerontol A Biol Sci Med Sci, 2003; 58: M911–916.
82. LaMonte MJ, Blair SN. Physical activity, cardiorespiratory fitness, and adiposity: contributions to disease risk. Curr Opin Clin Nutr Metab Care, 2006; 9: 540–546.
83. Duvigneaud N, Matton L, Wijndaele K, et al. Relationship of obesity with physical activity, aerobic fitness and muscle strength in Flemish adults. J Sports Med Phys Fitness, 2008; 48: 201–210.
84. Wang X, Miller GD, Messier SP, Nicklas BJ. Knee strength maintained despite loss of lean body mass during weight loss in older obese adults with knee osteoarthritis. J Gerontol A Biol Sci Med Sci, 2007; 62: 866–871.
85. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol, 2005; 115: 911– 919. quiz 920.
86. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-α with muscle mass and muscle strength in elderly men and women: The Health ABC Study. J Gerontol A Biol Sci Med Sci, 2002; 57A: M326–M332.
87. Cesari M, Kritchevsky SB, Baumgartner RN, et al. Sarcopenia, obesity, and inflammation - results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study. Am J Clin Nutr, 2005; 82: 428–434.
88. Schrager MA, Metter EJ, Simonsick E, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. J Appl Physiol, 2007; 102: 919–925.
89. Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw, 2006; 17: 4–12.
90. Goodpaster BH, Brown NF. Skeletal muscle lipid and its association with insulin resistance: what is

the role for exercise? Exerc Sport Sci Rev, 2005; 33: 150–154.
91. Goodpaster BH, Krishnaswami S, Resnick H, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. Diabetes Care, 2003; 26: 372–379.
92. Biolo G, Declan Fleming RY, Wolfe RR. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J Clin Invest, 1995; 95: 811– 819.
93. Nomura T, Ikeda Y, Nakao S, et al. Muscle strength is a marker of insulin resistance in patients with type 2 diabetes: a pilot study. Endocr J, 2007; 54: 791–796.
94. Park SW, Goodpaster BH, Strotmeyer ES, et al. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: The Health, Aging, and Body Composition Study. Diabetes Care, 2007; 30: 1507–1512.
95. Goodpaster BH, Brown NF. Skeletal muscle lipid and its association with insulin resistance: what is the role for exercise? Exerc Sport Sci Rev, 2005; 33: 150–154.
96. Campbell PJ, Carlson MG, Nurjhan N. Fat metabolism in human obesity. Am J Physiol, 1994; 266: E600–605.
97. Van Dam PS, Smid HE, de Vries WR, et al. Reduction of free fatty acids by acipimox enhances the growth hormone GH; responses to GH-releasing peptide 2 in elderly men. J Clin Endocrinol Metab, 2000; 85: 4706–4711.
98. Waters DL, Qualls CR, Dorin RI, et al. Altered growth hormone, cortisol, and leptin secretion in healthy elderly persons with sarcopenia and mixed body composition phenotypes. J Gerontol A Biol Sci Med Sci, 2008; 63: 536–541.
99. Allan CA, Strauss BJ, McLachlan RI. Body composition, metabolic syndrome and testosterone in ageing men. Int J Impot Res, 2007; 19: 448–457.
100. Ceda GP, Dall'Aglio E, Maggio M, et al. Clinical implications of the reduced activity of the GHIGF-I axis in older men. J Endocrinol Invest, 2005; 28: 96–100.
101. Chu L-W, Tam S, Kung AWC, et al. Serum Total and Bioavailable Testosterone Levels, Central Obesity, and Muscle Strength Changes with Aging in Healthy Chinese Men. J Am Geriatr Soc, 2008in press. DOI:10.1111/j.1532-5415.2008.01746.x.
102. Morley JE. Anorexia of aging: physiologic and pathologic. Am J Clin Nutr, 1997; 66: 760–773.
103. Dreyer HC, Volpi E. Role of protein and amino acids in the pathophysiology and treatment of sarcopenia. J Am Coll Nutr, 2005; 24: 140S–145S.
104. Weir CB, Jan A. BMI Classification Percentile And Cut Off Points. Treasure Island, FL: StatPearls, StatPearls Publishing, 2020.
105. Yakabe M, Hosoi T, Akishita M, Ogawa S. Updated concept of sarcopenia based on muscle-bone relationship. J Bone Mineral Metab, 2020; 38: 7–13. 10. 1007/s00774-019-01048-2.
106. Donini LM, Busetto L, Bauer JM, Bischoff S, Boirie Y, Cederholm T, et al. . Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review. Clin Nutr, 2020; 39: 2368–88. 10. 1016/j. clnu. 2019. 11. 024.
107. Ilich JZ, Kelly OJ, Inglis JE. Osteosarcopenic obesity syndrome: what is it and how can it be identified and diagnosed? Curr Gerontol Geriatr Res, 2016; 2016: 1–7. 10. 1155/2016/7325973.
108. Bosy-Westphal A, Jensen B, Braun W, Pourhassan M, Gallagher D, Müller MJ. Quantification of whole-body and segmental skeletal muscle mass using phase-sensitive 8-electrode medical bioelectrical impedance devices. Eur J Clin Nutr, 2017; 71: 1061–7. 10. 1038/ejcn. 2017. 27.
109. Yu S, Alice P, Kareeann K, Renuka V. The performance of five bioelectrical impedance analysis prediction equations against dual x-ray absorptiometry in estimating appendicular skeletal muscle mass in an adult australian population. Nutrients, 2016; 8: 189. 10. 3390/nu8040189.
110. Kuriyan R. Body composition techniques. Indian J Med Res, 2018; 148: 648–58. 10. 4103/ijmr. IJMR_1777_18.
111. Choi KM. Sarcopenia and sarcopenic obesity. Korean J Inter Med, 2016; 31: 1054–60. 10. 3904/kjim. 2016. 193.
112. 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. 10. 1093/ageing/afq034.
113. Nguyen HQ et al. Health care use and costs associated with use of a health club membership benefit in older adults with diabetes. Diabetes Care, 2008; 31: 1562–1567.
114. Bergamin M et al. Water-versus land-based exercise in elderly subjects: effects on physical performance and body composition. Clin. Interv. Aging, 2013; 8: 1109–1117.
115. Li F et al. An evaluation of the effects of Tai Chi exercise on physical function among older persons: a randomized contolled trial. Ann. Behav. Med, 2001; 23: 139–146.
116. Hildreth KL et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J. Clin. Endocrinol. Metab, 2013; 98: 1891–1900.
117. Strohacker K, Fazzino D, Breslin WL & Xu X The use of periodization in exercise prescriptions for inactive adults: a systematic review. Prev. Med. Rep, 2015; 2: 385–396.
118. Steele J Intensity; in-ten-si-ty; noun. 1. Often used ambiguously within resistance training. 2. Is it time to drop the term altogether? Br. J. Sports Med, 2014; 48: 1586–1588.

119. Conlon JA et al. Periodization strategies in older adults: impact on physical function and health. Med. Sci. Sports Exerc, 2016; 48: 2426–2436.
120. Vasconcelos KS et al. Effects of a progressive resistance exercise program with high-speed component on the physical function of older women with sarcopenic obesity: a randomized controlled trial. Braz. J. Phys. Ther, 2016; 20: 432–440.
121. Prestes J et al. Understanding the individual responsiveness to resistance training periodization. Age Dordr, 2015; 37: 9793.
122. Botero JP et al. Effects of long-term periodized resistance training on body composition, leptin, resistin and muscle strength in elderly postmenopausal women. J. Sports Med. Phys. Fitness, 2013; 53: 289–294.
123. Strohacker K, Fazzino D, Breslin WL & Xu X The use of periodization in exercise prescriptions for inactive adults: a systematic review. Prev. Med. Rep, 2015; 2: 385–396.
124. Ebersbach G, Edler D, Kaufhold O & Wissel J Whole body vibration versus conventional physiotherapy to improve balance and gait in Parkinson's disease. Arch. Phys. Med. Rehabil, 2008; 89: 399–403.
125. Rogan S, Hilfiker R, Herren K, Radlinger L & de Bruin ED Effects of whole-body vibration on postural control in elderly: a systematic review and meta-analysis. BMC Geriatr, 2011; 11: 72.
126. Verschueren SM et al. The effects of whole-body vibration training and vitamin D supplementation on muscle strength, muscle mass, and bone density in institutionalized elderly women: a 6-month randomized, controlled trial. J. Bone Miner Res, 2011; 26: 42–49.
127. Bemben DA, Palmer IJ, Bemben MG & Knehans AW Effects of combined whole-body vibration and resistance training on muscular strength and bone metabolism in postmenopausal women. Bone, 2010; 47: 650–656. Batsis and Villareal Page 46.
128. Cristi-Montero C, Cuevas MJ & Collado PS Whole-body vibration training as complement to programs aimed at weight loss. Nutr. Hosp, 2013; 28: 1365–1371.
129. Lamont HS et al. Effects of a 6-week periodized squat training with or without whole-body vibration upon short-term adaptations in squat strength and body composition. J. Strength Cond. Res, 2011; 25: 1839–1848.
130. Wei N, Pang MY, Ng SS & Ng GY Optimal frequency/time combination of whole-body vibration training for improving muscle size and strength of people with age-related muscle loss sarcopenia; : a randomized controlled trial. Geriatr. Gerontol. Int, 2017; 17: 1412–1420.
131. Batsis JA & Dolkart KM Evaluation of older adults with obesity for bariatric surgery: geriatricians' perspective. J. Clin. Gerontol. Geriatr, 2015; 6: 45–53.
132. Mastino D et al. Bariatric surgery outcomes in sarcopenic obesity. Obes. Surg, 2016; 26: 2355–2362.
133. Cole AJ et al. Long-term body composition changes in women following roux-en-Y gastric bypass surgery. JPEN J. Parenter. Enteral Nutr, 2017; 41: 583–591.
134. Anderwald CH et al. Alterations in gastrointestinal, endocrine, and metabolic processes after bariatric Roux-en-Y gastric bypass surgery. Diabetes Care, 2012; 35: 2580–2587.
135. Lyytinen T, Liikavainio T, Paakkonen M, Gylling H & Arokoski JP Physical function and properties of quadriceps femoris muscle after bariatric surgery and subsequent weight loss. J. Musculoskelet. Neuronal Interaa, 2013; 13: 329–338.
136. Coates PS, Fernstrom JD, Fernstrom MH, Schauer PR & Greenspan SL Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. J. Clin. Endocrinol. Metab, 2004; 89: 1061–1065.
137. Schirwis E, Agbulut O, Vadrot N, Mouisel E, Hourde C, Bonnieu A, Butler-Browne G, Amthor H, Ferry A. The beneficial effect of myostatin deficiency on maximal muscle force and power is attenuated with age. Exp. Gerontol, 2013; 48: 183–190.
138. Zimmers TA, Davies MV, Koniaris LG, Haynes P, Esquela AF, Tomkinson KN, McPherron AC, Wolfman NM, Lee SJ. Induction of cachexia in mice by systemically administered myostatin. Science, 2002; 296: 1486–1488.
139. Argiles JM, Orpi M, Busquets S, Lopez-Soriano FJ. Myostatin: more than just a regulator of muscle mass. Drug Discov. Today, 2012; 17: 702–709.
140. Yarasheski KE, Bhasin S, Sinha-Hikim I, Pak-Loduca J, Gonzalez-Cadavid NF. Serum myostatin-immunoreactive protein is increased in 60–92 year old women and men with muscle wasting. J Nutr. Health Aging, 2002; 6: 343–348.
141. Grobet L, Martin LJ, Poncelet D, Pirottin D, Brouwers B, Riquet J, Schoeberlein A, Dunner S, Menissier F, Massabanda J, Fries R, Hanset R, Georges M. A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. Nat. Genet, 1997; 17: 71–74.
142. Schuelke M, Wagner KR, Stolz LE, Hubner C, Riebel T, Komen W, Braun T, Tobin JF, Lee SJ. Myostatin mutation associated with gross muscle hypertrophy in a child. N. Engl. J. Med, 2004; 350: 2682–2688.
143. Zhang L, Rajan V, Lin E, Hu Z, Han HQ, Zhou X, Song Y, Min H, Wang X, Du J, Mitch WE. Pharmacological inhibition of myostatin suppresses systemic inflammation and muscle atrophy in mice with chronic kidney disease. FASEB J, 2011; 25: 1653–1663.
144. Zhang C, McFarlane C, Lokireddy S, Masuda S, Ge X, Gluckman PD, Sharma M, Kambadur R. Inhibition of myostatin protects against diet-induced

obesity by enhancing fatty acid oxidation and promoting a brown adipose phenotype in mice. Diabetologia, 2012; 55: 183–193.
145. Wagner KR, Fleckenstein JL, Amato AA, Barohn RJ, Bushby K, Escolar DM, Flanigan KM, Pestronk A, Tawil R, Wolfe GI, Eagle M, Florence JM, King WM, Pandya S, Straub V, Juneau P, Meyers K, Csimma C, Araujo T, Allen R, Parsons SA, Wozney JM, Lavallie ER, Mendell JR. A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy. Ann. Neurol, 2008; 63: 561–571.
146. Gonzalez-Freire M, Rodriguez-Romo G, Santiago C, Bustamante-Ara N, Yvert T, Gomez-Gallego F, Serra Rexach JA, Ruiz JR, Lucia A. The K153R variant in the myostatin gene and sarcopenia at the end of the human lifespan. Age Dordr, 2010; 32: 405–409.
147. Garatachea N, Pinos T, Camara Y, Rodriguez-Romo G, Emanuele E, Ricevuti G, Venturini L, Santos-Lozano A, Santiago-Dorrego C, Fiuza-Luces C, Yvert T, Andreu AL, Lucia A. Association of the K153R polymorphism in the myostatin gene and extreme longevity. Age Dordr, 2013.
148. Santiago C, Ruiz JR, Rodriguez-Romo G, Fiuza-Luces C, Yvert T, Gonzalez-Freire M, Gomez-Gallego F, Moran M, Lucia A. The K153R polymorphism in the myostatin gene and muscle power phenotypes in young, non-athletic men. PLoS. ONE, 2011; 6: e16323.
149. Ferrell RE, Conte V, Lawrence EC, Roth SM, Hagberg JM, Hurley BF. Frequent sequence variation in the human myostatin GDF8; gene as a marker for analysis of muscle-related phenotypes. Genomics, 1999; 62: 203–207.
150. Gruson D, Ginion A, Lause P, Ketelslegers JM, Thissen JP, Bertrand L. Urotensin II and urocortin trigger the expression of myostatin, a negative regulator of cardiac growth, in cardiomyocytes. Peptides, 2012; 33: 351–353.
151. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J. Sex Med, 2013; 10: 245–284.
152. Giannoulis MG, Martin FC, Nair KS, Umpleby AM, Sonksen P. Hormone replacement therapy and physical function in healthy older men. Time to talk hormones? Endocr. Rev, 2012; 33: 314–377.
153. Hildreth KL, Barry DW, Moreau KL, Vande GJ, Meacham RB, Nakamura T, Wolfe P, Kohrt WM, Ruscin JM, Kittelson J, Cress ME, Ballard R, Schwartz RS. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J. Clin. Endocrinol. Metab, 2013; 98: 1891–1900.
154. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J. Clin. Endocrinol. Metab, 1999; 84: 2647–2653.
155. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab, 2010; 95: 2536–2559.
156. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. N. Engl. J. Med, 1990; 323: 1–6.
157. Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD, Stewart KJ, Cottrell E, St CC, Pabst KM, Harman SM. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA, 2002; 288: 2282–2292.
158. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, Hoffman AR. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann. Intern. Med, 2007; 146: 104–115.
159. White HK, Petrie CD, Landschulz W, MacLean D, Taylor A, Lyles K, Wei JY, Hoffman AR, Salvatori R, Ettinger MP, Morey MC, Blackman MR, Merriam GR. Effects of an oral growth hormone secretagogue in older adults. J. Clin. Endocrinol. Metab, 2009; 94: 1198–1206.
160. Makimura H, Feldpausch MN, Rope AM, Hemphill LC, Torriani M, Lee H, Grinspoon SK. Metabolic effects of a growth hormone-releasing factor in obese subjects with reduced growth hormone secretion: a randomized controlled trial. J. Clin. Endocrinol. Metab, 2012; 97: 4769–4779.
161. Villareal D, Holloszy JO. DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. Am J Physiol Endocrinol Metab, 2006: 00100.
162. Corona G, Rastrelli G, Giagulli VA, Sila A, Forti G, Mannucci E, Maggi M. Dehydroepiandrosterone supplementation in elderly men: a meta-analysis study of placebo controlled trials. J Clin Endocrin Metab, 2013.
163. Schroeder ET, Zheng L, Yarasheski KE, Qian D, Stewart Y, Flores C, Martinez C, Terk M, Sattler FR. Treatment with oxandrolone and the durability of effects in older men. J Appl. Physiol, 2004; 96: 1055–1062.
164. Schroeder ET, Zheng L, Ong MD, Martinez C, Flores C, Stewart Y, Azen C, Sattler FR. Effects of androgen therapy on adipose tissue and metabolism in older men. J Clin Endocrinol. Metab, 2004; 89: 4863–4872.
165. Der-Torossian H, Wysong A, Shadfar S, Willis MS, McDunn J, Couch ME. Metabolic derangements in the gastrocnemius and the effect of Compound A therapy in a murine model of cancer cachexia. J Cachexia. Sarcopenia. Muscle, 2013; 4: 145–155.
166. Hwang JH, Jung HW. Effects of pharmacopuncture with wild ginseng complex in 2 elderly patients with

obesity: case report. Medicine Baltimore; . 2018; 97: e11534. doi:10. 1097/MD. 0000000000011534.

167. Zhou X, Xing B, He G, Lyu X, Zeng Y. The effects of electrical acupuncture and essential amino acid supplementation on sarcopenic obesity in male older adults: a randomized control study. Obes Facts, 2018; 11: 327–34. doi:10. 1159/000491797.
168. Zhou X, Xing B, He G, Lyu X, Zeng Y. The effects of electrical acupuncture and essential amino acid supplementation on sarcopenic obesity in male older adults: a randomized control study. Obes Facts, 2018; 11: 327–34. doi:10. 1159/000491797.
169. Hwang JH, Jung HW. Effects of pharmacopuncture with wild ginseng complex in 2 elderly patients with obesity: case report. Medicine Baltimore, 2018; 97: e11534. doi:10. 1097/MD. 0000000000011534