

Review Article

Sarcopenic Obesity and Endocrinal Adaptation with Age

Kunihiro Sakuma¹ and Akihiko Yamaguchi²

¹ *Research Center for Physical Fitness, Sports and Health, Toyohashi University of Technology, 1-1 Hibarigaoka, Tenpaku-cho, Toyohashi 441-8580, Japan*

² *School of Dentistry, Health Sciences University of Hokkaido, Kanazawa, Ishikari-Tobetsu, Hokkaido 061-0293, Japan*

Correspondence should be addressed to Kunihiro Sakuma; ksakuma@las.tut.ac.jp

Received 29 November 2012; Accepted 1 March 2013

Academic Editor: Marco A. Minetto

Copyright © 2013 K. Sakuma and A. Yamaguchi. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In normal aging, changes in the body composition occur that result in a shift toward decreased muscle mass and increased fat mass. The loss of muscle mass that occurs with aging is termed sarcopenia and is an important cause of frailty, disability, and loss of independence in older adults. Age-related changes in the body composition as well as the increased prevalence of obesity determine a combination of excess weight and reduced muscle mass or strength, recently defined as sarcopenic obesity. Weight gain increases total/abdominal fat, which, in turn, elicits inflammation and fatty infiltration in muscle. Sarcopenic obesity appears to be linked with the upregulation of TNF- α , interleukin (IL)-6, leptin, and myostatin and the downregulation of adiponectin and IL-15. Multiple combined exercise and mild caloric restriction markedly attenuate the symptoms of sarcopenic obesity. Intriguingly, the inhibition of myostatin induced by gene manipulation or neutralizing antibody ameliorates sarcopenic obesity via increased skeletal muscle mass and improved glucose homeostasis. In this review, we describe the possible influence of endocrinal changes with age on sarcopenic obesity.

1. Introduction

Skeletal muscle contractions power human body movements and are essential for maintaining stability. Skeletal muscle tissue accounts for almost half of the human body mass and, in addition to its power-generating role, is a crucial factor in maintaining homeostasis. Given its central role in human mobility and metabolic function, any deterioration in the contractile, material, and metabolic properties of skeletal muscle has an extremely important effect on human health. Aging is associated with a progressive decline of muscle mass, quality, and strength, a condition known as sarcopenia [1]. The term sarcopenia, coined by I. H. Rosenberg, originates from the Greek words *sarx* (flesh) and *penia* (loss). Although this term is applied clinically to denote loss of muscle mass, it is often used to describe both a set of cellular processes (denervation, mitochondrial dysfunction, inflammatory, and hormonal changes) and a set of outcomes such as decreased muscle strength, decreased mobility and function [2], increased fatigue, a greater risk of falls [3], and reduced energy needs [4]. In addition, reduced muscle mass in aged

individuals has been associated with decreased survival rates following critical illness [5]. In most countries, there has been a rapid and continuing increase in life expectancy. By the year 2030, 20% of the adult USA population will be older than 65 years [6]. In the 27 member states of the EU, the percentage of people aged 65 years and older will rise from 17.1 in 2008 to 25.4 in 2035 and to 30 in 2060 [7]. The estimated direct healthcare costs attributable to sarcopenia in the USA in 2000 were \$18.5 billion (\$10.8 billion in men and \$7.7 billion in women), which represented about 1.5% of total healthcare expenditures for that year [8]. Therefore, age-related losses in skeletal muscle mass and function present an extremely important current and future public health issue.

Lean muscle mass generally contributes up to ~50% of total body weight in young adults but declines with aging to be 25% at 75–80 years old [9, 10]. The loss of muscle mass is typically offset by gains in fat mass. The loss of muscle mass is most notable in the lower limb muscle groups, with the cross-sectional area of the vastus lateralis being reduced by as much as 40% between the age of 20 and 80 years [11]. On a muscle fiber level, sarcopenia is characterized by specific type II

muscle fiber atrophy, fiber necrosis, and fiber-type grouping [11–13]. In elderly men, Verdijk et al. [13] showed a reduction in type II muscle fiber satellite cell content with aging. Although various investigators showed very contradicting results for age-dependent changes of satellite cell numbers [13–16], most studies point to an age-dependent reduction in muscle regenerative capacity due to reduced satellite cell proliferation and differentiation.

Another morphologic aspect of sarcopenia is the infiltration of muscle tissue components by lipids because of the increased frequency of adipocyte or lipid deposition [17, 18] within muscle fibers. As with precursor cells in bone marrow, liver, and kidney, muscle satellite cells that can express an adipocytic phenotype increase with age [19], although this process is still relatively poorly understood in terms of its extent and spatial distribution. Lipid deposition, often referred to as intramyocellular lipid, may result from a net buildup of lipids due to the reduced oxidative capacity of muscle fibers with aging [17, 20].

Several possible mechanisms for age-related muscle atrophy have been described; however, the precise contribution of each is unknown. Age-related muscle loss is a result of reductions in the size and number of muscle fibers [21] possibly due to a multifactorial process that involves physical activity, nutritional intake, oxidative stress, and hormonal changes [3, 22]. The specific contribution of each of these factors is unknown, but there is emerging evidence that the disruption of several positive regulators (Akt and serum response factor) of muscle hypertrophy with age is an important feature in the progression of sarcopenia [23, 24].

Obesity is currently epidemic in the USA, with almost 70% of Americans overweight and one of three obese [25]. Obesity is associated with increased morbidity and mortality, and there is unchallenged evidence that obesity increases the risk for the development of hypertension, dyslipidemia, type 2 diabetes mellitus, sleep apnea, cancers of the breast, prostate, and colon, and all-cause mortality [26–28]. This review introduces the relationship between endocrinal changes with age and sarcopenic obesity.

2. Sarcopenic Obesity

Aging is associated with important changes in body composition and metabolism [29, 30]. Between the age of 20 and 70 years, there is a progressive decrease of fat-free mass (mainly muscle) of about 40% and a rise in fat mass. There is a relatively greater decrease in peripheral compared to central fat-free mass. After the age of 70 years, fat-free mass and fat mass decrease in parallel. Fat distribution changes with age such that there is an increase in visceral fat, which is more marked in women than in men. Also, fat is increasingly deposited in skeletal muscle and in the liver. The higher visceral fat is the main determinant of impaired glucose tolerance in the elderly. Increased intramuscular and intrahepatic fat contribute to impaired insulin action through locally released adipokines and fat-free fatty acids. Increased pancreatic fat with declining β -cell function also plays a role [31].

Due to the loss of skeletal muscle, the basal metabolic rate declines by 2%–3% per decade after the age of 20 years, by 4% per decade after the age of 50 years, equating approximately 150 kcal per day, and overall by 30% between the age of 20 and 70 years [32]. This, together with decreased intensity and duration of physical activity as well as decreased postprandial energy expenditure due to a decreased fat oxidation, accounts for the decreased energy expenditure seen with aging. Medical complications of obesity in the elderly are mainly concentrated around the metabolic syndrome (with glucose intolerance, hypertension, dyslipidaemia, and cardiovascular disease). The metabolic syndrome peaks at the age of 50–70 years in males and of 60–80 years [33]. The metabolic syndrome is a recognized risk factor for stroke but is also related to subclinical ischaemic brain lesions, placing the subjects at risk for future cognitive impairment [34]. Obesity also increases the risk of heart failure, and estimates suggest that having a body mass index (BMI) > 30 kg/m² doubles the risk [35]. Other obesity-related disorders are osteoarthritis, pulmonary dysfunction such as the obstructive sleep apnoea syndrome, certain cancer types, reduced cognitive skills, and urinary incontinence [6, 36, 37].

The obesity elderly are also likely to have functional limitations because of the decreased muscle mass and strength and increased joint dysfunction, disabilities of activities of daily living, frailty, chronic pain, and impaired quality of life [6, 38]. Indeed, Baumgartner [39] observed that men and women older than 60 years of age with sarcopenic obesity showed, respectively, an 8- and 11-fold higher risk of having three or more physical disabilities. More importantly, it was observed that the association with functional status impairment was stronger for sarcopenic obesity than for either obesity or sarcopenia alone. Unintentional injuries such as sprains and strains occur more often [40]. Obesity is an important risk for frailty either through increased levels of inflammatory markers or through sarcopenia [41].

Interestingly, the proposed mechanism involved in sarcopenic obesity could be the increased production from adipose tissue of different substances, such as tumor necrosis factor- α (TNF- α) and leptin, which are known to influence insulin resistance and growth hormone (GH) secretion [42]. This hypothesis has been confirmed by Schragger et al. [43] who observed in a large-scale sample of men and women that the degree of obesity, as evaluated by BMI and its distribution, and by waist circumference, directly affected inflammation which in turn contributed to the development and progression of sarcopenia. Further increases in leptin, at least partially depending on the age-related fat mass increase, may lead to leptin resistance and thus to a reduction of fatty acid oxidation in muscles, contributing to ectopic fat deposition in organs such as the liver, heart, and muscles [44] and, in turn, to the loss of muscle quality in obese older subjects.

Studies in both humans and animals demonstrate that obesity is a state of low-grade, chronic inflammation, characterized by elevated circulating proinflammatory molecules produced predominantly from enlarged adipocytes and activated macrophages in adipose tissue [45, 46]. Lipocalin-2 would be a possible candidate regulating the amount of

adipose tissue under chronic inflammation and insulin resistance. Lipocalin-2 is abundantly produced by adipocytes [47, 48]. Expression of lipocalin-2 in adipose tissue is elevated in various experimental models of obesity and in obese humans [49–51]. Its expression can be induced by various inflammatory stimuli, including lipopolysaccharides and interleukin (IL)-1 β [52, 53]. Intriguingly, lipocalin-2 deficiency in mice elicits marked decreases in the expression and the activity of 12-lipoxygenase, an enzyme responsible for metabolizing arachidonic acid, and the production of TNF- α , a critical insulin resistance-inducing factor [54]. It remains to be elucidated whether lipocalin-2 levels increase with normal aging and further with sarcopenic obesity in mammals.

3. Endocrinal Adaptation with Age

3.1. GH and Testosterone. Testosterone increases muscle protein synthesis [55], and its effects on muscle are modulated by several factors including genetic background, nutrition, and exercise [56]. In males, levels of testosterone decrease by 1% per year and those of bioavailable testosterone by 2% per year from age 30 [57, 58]. In women, testosterone levels drop rapidly from 20 to 45 years of age [59].

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 [60]. GH secretion occurs in a pulsatile manner with a major surge at the onset of a slow-wave sleep and less conspicuous secretory episodes a few hours after meals [61]. The secretion of GH is maximal at puberty accompanied by very high circulating insulin-like growth factor-I (IGF-I) levels [62], with a gradual decline during adulthood. Indeed, circulating GH levels decline progressively after 30 years of age at a rate of ~1% per year [63]. In aged men, daily GH secretion is 5- to 20-fold lower than that in young adults [64]. Therefore, many researchers have indicated age-related endocrine defects such as decreases in anabolic hormones. Although hormonal supplementation for the elderly has been conducted on a large scale, it was found not to be effective against sarcopenia and to have minor side effects [64–67].

Increased adiposity is often associated with high circulating levels of free fatty acids [68, 69], which inhibit GH production and decrease plasma levels of IGF-I [70, 71]. A recent study showed that sarcopenic obese persons had depressed GH secretion compared to obese persons [72]. Similarly, obese individuals tend to have lower testosterone levels [73]. Of note, low levels of these anabolic hormones have been reported to be positively associated with low muscle strength [74, 75] and may therefore contribute to muscle impairment in obese individuals [76].

3.2. Insulin. Insulin is a powerful anabolic signal in proteins [77]. Insulin was infused directly into the femoral artery to increase the leg insulin levels to approximate postprandial values while avoiding systemic hypoaminoacidemia. Insulin significantly stimulated muscle protein synthesis in young but not older subjects. There was no significant change in muscle

protein breakdown as measured by two- and three-pool modeling. The increase in synthesis in young subjects resulted in a shift from a negative to positive protein net balance across the leg-indicating overall net protein accretion during the clamp in young subjects. In the older subjects, however, the net muscle protein balance remained negative. Insulin resistance has been long recognized as a characteristic of aging in humans and rodents [78]. Blood flow was lower in older as compared to younger subjects at baseline and during the clamp and tended to increase from baseline in young adults only during the clamp. As hypothesized by Timmerman and Volpi [79], this effect was likely mediated through insulin-induced vasodilation. Insulin is a potent stimulator of the endothelial-derived vasodilator and nitric oxide [80]. In a subsequent study, they reported that this age-related insulin resistance of muscle protein synthesis could be overcome by increasing insulin levels to approximately double the postprandial levels via improvements in mammalian target of rapamycin signaling [81].

Available experimental evidence points to the development of adiposity as the main cause of the decreased insulin action in old rats [82] and elderly humans [83, 84]. Studies in rats have demonstrated that fat mass accretion occurs at early aging and is paralleled by a marked decrease of insulin action in visceral fat tissue.

3.3. TNF- α , IL-6, and C-Reactive Protein (CRP). Inflammation may negatively influence skeletal muscle through direct catabolic effects or through indirect mechanisms (i.e., decreases in GH and IGF-I concentrations, induction of anorexia, etc.) [85]. There is growing evidence that higher levels of inflammatory markers are associated with physical decline in older individuals, possibly through the catabolic effects of these markers on muscle. In an observational study of more than 2000 men and women, TNF- α showed a consistent association with declines in muscle mass and strength [86]. The impact of inflammation on the development of sarcopenia is further supported by a recently published animal study showing that a reduction in low-grade inflammation by ibuprofen in old (20 months) animals resulted in a significant decrease in muscle mass loss [87]. An age-related disruption of the intracellular redox balance appears to be a primary causal factor for a chronic state of low-grade inflammation. More recently, Chung et al. [88] hypothesized that abundant nuclear factor- κ B (NF- κ B) protein-induced age-related increases in IL-6 and TNF- α . Moreover, reactive oxygen species (ROS) also appear to function as second messengers for TNF- α in skeletal muscle, activating NF- κ B either directly or indirectly [89]. Indeed, marked production of ROS has been documented in muscle of the elderly [90, 91]. However, it is not clear whether NF- κ B signaling is enhanced with age. Despite some evidence supporting enhanced NF- κ B signaling in type I fibers of aged skeletal muscle, direct evidence for increased activation and DNA binding of NF- κ B is lacking [92, 93]. For example, Philips and Leeuwenburgh [93] found that neither p65 protein expression nor the binding activity of NF- κ B was significantly altered in the vastus lateralis muscles of

26-month-old rats despite the marked upregulation of TNF- α expression in both blood and muscle. Upregulated TNF- α expression in serum and muscle seems to enhance apoptosis in mitochondria resulting in a loss of muscle fibers [93–95]. It has been shown that TNF- α is one of the primary signals inducing apoptosis in muscle.

IL-6 and CRP, known as “geriatric cytokines”, are multifunctional cytokine produced in situations of trauma, stress, and infection. During the aging process, levels of both IL-6 and CRP in plasma become elevated. The natural production of cytokines is likely beneficial during inflammation, but the overproduction and the maintaining of an inflammatory state for long periods of time, as seen in elderly individuals, is detrimental [96, 97]. A number of authors have demonstrated that a rise in plasma levels of proinflammatory cytokines, especially IL-6, and proteins under acute conditions is associated with a reduction in mobility as well as a reduced capacity to perform daily activities, the development of fragility syndrome, and increased mortality rates [96–98]. In older men and women, higher levels of IL-6 and CRP were associated with a two- to three-fold greater risk of losing more than 40% of grip strength over 3 years [99]. In contrast, there were no longitudinal associations between inflammatory markers and changes in grip strength among high functioning elderly participants from the MacArthur Study of Successful Aging [100]. More recently, Hamer and Molloy [101] demonstrated, in a large representative community-based cohort of older adults (1,926 men and 2,260 women (aged 65.3 ± 9.0 years)), that CRP was associated with poorer hand grip strength and chair stand performance in women but only chair stand performance in men. In addition, Haddad et al. [102] demonstrated atrophy in the tibialis anterior muscle of mice following the injection of relatively low doses of IL-6. In a recent randomized trial that employed aerobic and strength training in a group of elderly participants, significant reductions in various inflammatory markers (IL-6, CRP, and IL-18) were observed for aerobic but not strength training [103]. In contrast, combined resistance and aerobic training that increased strength by 38% resulted in significant reductions in CRP [104].

3.4. Myostatin. Myostatin was first discovered during screening for novel members of the transforming growth factor- β superfamily and shown to be a potent negative regulator of muscle growth [105]. Mutations in myostatin can lead to massive hypertrophy and/or hyperplasia in developing animals, as evidenced by knockout experiments in mice. Myostatin levels increase with muscle atrophy due to unloading in mice and humans [106, 107] and with severe muscle wasting in HIV patients [108]. Administration of myostatin *in vivo* to adult mice induces profound muscle loss analogous to that seen in human cachexia syndromes [109]. Together, these studies suggest that increased levels of myostatin lead to muscle wasting.

Many researchers have conducted experiments to inhibit myostatin in models of muscle disorders such as Duchenne muscular dystrophy, ALS, and cancer cachexia [23]. In addition, several investigators examined the effect of inhibiting

myostatin to counteract sarcopenia using animals [110, 111]. More recently, Murphy et al. [111] showed, by way of one-weekly injections, that a lower dose of PF-354 (10 mg/Kg) significantly increased the fiber cross-sectional area (by 12%) and *in situ* muscle force (by 35%) of aged mice.

Skeletal muscle is the primary site of insulin-mediated glucose disposal, the largest reservoir of glycogen in the human body, and a key determinant of energy expenditure. Hence, several recent studies have also investigated the effects of genetic and pharmacological inhibition of myostatin, and the resultant resistance-trained phenotype, on the prevention and treatment of obesity and type 2 diabetes mellitus [112, 113]. Similar to these results, Zhang et al. [114] demonstrated that the inhibition of myostatin increased skeletal muscle mass and reduced body weight, fat mass, and circulating concentrations of triacylglycerol caused by a high-fat diet. Postnatal blockade of myostatin with a neutralizing antibody in obese insulin-resistant mice significantly improved glucose homeostasis, lowered circulating triacylglycerols, and increased circulating concentrations of the adipose tissue-derived cytokine and adiponectin [115, 116]. These findings highlight the therapeutic potential of antibody-directed myostatin inhibition for sarcopenic obesity. Although many researchers expect myostatin levels to be increased not only in muscle but also in serum, blood myostatin levels have not been shown to increase with age [117].

3.5. Adiponectin and Leptin. Adipose tissue itself generates a myriad of hormones and other bioactive proteins, including leptin (in normal concentrations induces satiety and regulates body composition) and adiponectin (anti-inflammatory and antiatherogenic) [118]. Adiponectin is an abundant plasma protein. Structurally, adiponectin contains a carboxyl-terminal globular domain and an amino-terminal collagenous domain and also shares extensive sequence homology with collagen VIII and X [119]. Adiponectin circulates in serum as a range of multimers from low-molecular weight trimers to high-molecular weight dodecamers [120]. With the exception of severe cases of undernutrition [121] and in the newborn [122], there is a strong negative correlation between plasma adiponectin concentrations in humans and fat mass [119], with obesity reducing adiponectin levels and weight reduction increasing them [45, 123].

Adiponectin has been shown to improve a whole-body insulin sensitivity in models of genetic and diet-induced obesity [124, 125]. Adiponectin stimulates fatty acid oxidation and glucose uptake in skeletal muscle [126] and adipose tissue [127], effects which are dependent on AMP-activated protein kinase (AMPK) signaling. The activation of adiponectin is dependent on signaling through adiponectin receptor AdipoR1 and AdipoR2. A study in human skeletal muscle [128] and in primary myotubes [129] suggested that skeletal muscle contains abundant levels of both AdipoR1 and AdipoR2 but that liver primarily expresses AdipoR2. Adiponectin's activation of AMPK signaling is blunted in obesity [130], despite similar AdipoR1 and AdipoR2 expression. Adiponectin levels also decline with age [131]. Adiponectin activates AMPK and inhibits NF- κ B signaling, decreasing monocyte,

macrophage, and dendritic cell production of TNF- α and interferon (IFN)- γ while increasing the production of anti-inflammatory cytokines, IL-10, and IL-1R α [45]. Adiponectin directly inhibits natural killer (NK) cells by preventing IL-2-stimulated cytotoxicity and IFN- γ production [132].

In contrast to adiponectin levels, serum leptin levels reflect overall adipose mass [45]. Leptin is an adipokine that regulates energy balance and glucose homeostasis [133]. Leptin acts mainly through the central nervous system, binding to specific hypothalamic receptors and regulating appetite, neuroendocrine pathways, and the autonomic nerves which bring about effects on peripheral tissues [134]. Nevertheless, leptin receptor expression has been reported to occur in pancreatic β -cells, muscle, liver, and fat, among other peripheral tissues, suggesting the existence of a direct effect of leptin in addition to its central action [135]. With the exception of fat tissue [136, 137], *in vivo* treatment with leptin has an insulin-sensitizing effect on peripheral tissue. In skeletal muscle, chronic peripheral leptin administration induces an increase of glucose uptake under euglycemic-hyperinsulinemic conditions [137, 138], and the same has been observed after the microinjection of leptin into the ventromedial hypothalamus [136]. In addition, leptin is largely proinflammatory because leptin increases TNF- α , IL-6, and IL-12 production by monocytes [45, 118]. Serum leptin levels and hypothalamic leptin resistance increase with age [139].

Interestingly, in obese but not in lean rats, leptin administration has been proven to decrease insulin signaling in liver [140]. Since obese rats show central leptin resistance and hyperleptinemia similar to aged rats [141], it can be speculated that during aging, the direct effects of leptin on peripheral tissues could prevail over its central action and contribute to the development and maintaining of a state of insulin resistance.

3.6. IL-10 and IL-15. Serum IL-10 may be positively correlated with obesity in middle aged humans [142]. Exercise releases IL-10 into the circulation, implying production by skeletal muscle [143]. Macrophage IL-10 production increases in old mice [144, 145]. Two recent studies showed marked increase in serum IL-10 in elderly humans [146], although an earlier study did not show a significant difference between middle-aged and very old humans [147]. IL-10 is broadly anti-inflammatory, inhibiting antigen presentation and suppressing release of TNF- α , IL-2, IFN- γ , IL-4, and other cytokines [148]. Indeed, mice homozygous for targeted deletion of the IL-10 gene had elevated levels of TNF- α , IL-6, IFN- γ , and IL-1 β in serum particularly at a later age (between 72 and 90 weeks) [149]. In addition, these mice had higher mortality rates when compared to age and sex-matched B6 control mice. On the other hand, IL-10 stimulated NK cell proliferation, cytotoxicity, and cytokine secretion *in vitro* when combined with IL-1 [150]. In murine cytomegalovirus-infected mice, IL-10 promoted NK cell cytotoxic granule release but increased NK cell activation-induced cell death [151]. In the elderly cohort, BMI correlated inversely with the percentage of NK cells and correlated directly with the NK cell apoptosis rate [152]. Therefore, serum IL-10 levels may

regulate the amount of adipose tissue by modulating several inflammatory cytokines and/or recruiting immune cells (e.g., NK cells).

IL-15 mRNA is expressed in many tissues [153], but IL-15 biosynthesis is very complex, and RNA levels do not necessarily indicate protein secretion. IL-15 isoforms have alternative signal peptides of 21 and 48 amino acids. Importantly, IL-15 requires the presence of IL-15R α for efficient biosynthesis and secretion [154, 155]. Like IL-15, IL-15R α synthesis is widespread within and outside of lymphoid tissues. Skeletal muscle tissue produces very high levels of IL-15 and expresses IL-15R α [156]. IL-15 levels are reported to increase transiently immediately following resistance [157] and aerobic [158] exercise, suggesting that IL-15 is indeed released from muscle tissue. In mice, muscle and serum IL-15 protein levels decline progressively with advanced age [159]. A study of aging rats showed that a longevity-promoting regimen of calorie restriction prevented age-related declines in muscle IL-15 expression observed in ad libitum-fed rats [94]. In an intriguing brief report involving human subjects, Gangemi et al. [160] observed significantly elevated serum IL-15 levels in centenarians living independently, suggesting high expression of IL-15 conferred protection from both frailty and age-related disease. IL-15 also has important effects on adipose tissue. IL-15 inhibits adipocyte differentiation in culture and obese people have low-blood IL-15 levels [156, 161, 162]. IL-15-deficient mice become obese despite unaltered food consumption; IL-15 injections reversed both this obesity and diet-induced obesity, lowered glucose levels and increased insulin sensitivity [161, 163]. Figure 1 provides an overview of the action of dysregulated adipokines to various organs (e.g., hypothalamus and skeletal muscle) in sarcopenic obesity.

4. Therapeutic Application

4.1. Physical Exercise (Combination). Adipose tissue infiltration of skeletal muscle increases with age [164, 165]. Recent studies have demonstrated that mitochondrial damage occurs in obese individuals due to enhanced ROS and chronic inflammation caused by increased fatty acid load [166]. Specifically, in skeletal muscle, the expression of PGC-1 α drives not only mitochondrial biogenesis and the establishment of oxidative myofibers but also vascularization [167]. It was found that a high-fat diet or fatty acid treatment caused a reduction in the expression of PGC-1 α and other mitochondrial genes in skeletal muscle [168]. A recent study has also demonstrated that transgenic overexpression of PGC-1 α in skeletal muscle improved sarcopenia and obesity associated with aging in mice [169]. Therefore, the well-known sarcopenia-attenuating effects of endurance training may be attributable to the protection against mitochondrial disorders (apoptosis, oxidative damage, etc.) caused by an increase in the production of PGC-1 α [167].

The American College of Sports Medicine recommends a multicomponent training exercise programme (strength, endurance, balance, and flexibility) to improve and maintain physical function in older adults [170]. Resistance exercise has

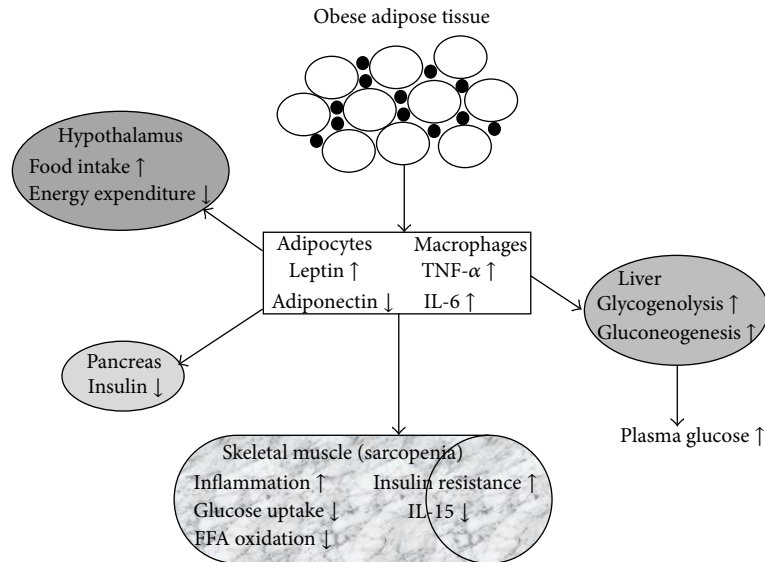


FIGURE 1: Obesity-induced changes in adipokine secretion and the development of insulin resistance in sarcopenic muscle. Expansion of adipose tissue in obesity leads to increased macrophage infiltration and inflammation with enhanced production of proinflammatory cytokines such as TNF- α and IL-6. This is accompanied by a dysregulated secretion of leptin and adiponectin. These adipocyte- and macrophage-derived adipokines elicit a variety of adverse effects on numerous tissues including the hypothalamus, liver, pancreas, and skeletal muscle. On the systemic level, altered adipokine secretion can lead to increased food intake and reduced energy expenditure through actions in the hypothalamus and to decreased muscle insulin sensitivity.

been investigated as an approach to counteract sarcopenia by stimulating protein synthesis and cause muscle hypertrophy with increased muscle strength and with improved physical performance [171]. Endurance training improves aerobic capacity. Most of the studies had a multicomponent program of 90-min sessions per week, consisting of 15 min of balance training, 15 min of flexibility, 30 min of aerobic exercise, and 30 min of high-intensity resistance training.

To study the impact of each exercise modality in more detail, Davidson et al. [172] randomized 60- to 80-year-old obese subjects into 4 groups: a control group, a group that had progressive resistance training, a group that performed aerobic exercise, and a group that combined progressive resistance training with aerobic exercise. After 6 months, body weight decreased by 0.6 kg in the resistance, by 2.8 kg in the aerobic, and by 2.3 kg in the combined exercise group. Abdominal fat and visceral fat decreased and endurance capacity improved significantly in the aerobic and combined exercise group. Skeletal muscle mass and muscle strength increased in the resistance and combined exercise groups only. Insulin resistance improved by 31% in the aerobic group and by 45% in the combined exercise group, whereas it did not change in the resistance training group. The combination of progressive resistance training and aerobic exercise is the optimal exercise strategy for simultaneous improvement of insulin resistance and functional limitations in the elderly. Aerobic exercise only is the second best choice.

4.2. Nutrition and Diet. Diet-induced weight loss results in a decrease in both fat mass and fat-free mass and so could

exacerbate the age-related loss of muscle mass and further impair physical function. Based on intensive research concerning sarcopenia and sarcopenic obesity, dietary guidelines were adjusted to prevent sarcopenic obesity and to guide the medical profession in managing weight loss in the presence of sarcopenic obesity [173, 174].

In the treatment of subjects with, or at risk of, sarcopenic obesity, the energy deficit should be more moderate than usual (range of 200–750 kcal) with emphasis on a higher intake of proteins (up to 1.5 g/Kg) of high biological quality, ensuring adequate renal function. When restricting energy intake, protein intake must be maintained or even increased as dietary protein, and amino acids are the most effective means to slow down or prevent muscle protein catabolism. In particular, Leucine is an important mediator of the response to amino acids. It increases muscle protein synthesis by modulating the activation of mammalian target of rapamycin complex 1 and signaling components of translation initiation [175]. In order to optimize the anabolic response to ingested high-quality proteins, certain peculiarities of old age have to be taken into account [173]. In contrast to younger people, the elderly have a diminished anabolic response to proteins when they are coingested with carbohydrates.

5. Conclusions and Perspectives

Obesity is a major public health problem. The population is growing older, and the prevalence of obesity in the elderly is rising. Aging and obesity are two conditions that present an important part of health costs. The impact of sarcopenic obesity on physical, metabolic, and cardiovascular functions

is becoming a primary concern amongst nutritionists, geriatricians, and public health officers. The etiopathogenesis of sarcopenic obesity is complex and multiple factors can interplay, including lifestyle, endocrine, and immunological factors [176, 177]. Decreased physical activity and energy expenditure with aging predispose to fat accumulation and fat redistribution but muscle loss. Sarcopenic obesity seems to be modulated by an age-related decrease in serum IL-15 and adiponectin and/or chronic inflammation (upregulation of TNF- α , IL-6, and myostatin).

Lifestyle intervention should be the first step, and its effects have been extensively in the obese elderly. Multicomponent exercise includes flexibility training, aerobic exercise, and resistance training. Obesity and specifically sarcopenic obesity, in the elderly, are potentially preventable, and should be tackled from younger ages and also during major later-life transitions such as retirement.

Abbreviations

AdipoR:	Adiponectin receptor
AMPK:	AMP-activated protein kinase
BMI:	Body mass index
CRP:	C-reactive protein
GH:	Growth hormone
IFN:	Interferon
IGF-I:	Insulin-like growth factor-I
IL:	Interleukin
NF- κ B:	Nuclear factor-kappa B
NK:	Natural killer
PGC-1 α :	Peroxisome proliferator-activated receptor γ coactivator 1 α
ROS:	Reactive oxygen species
TNF- α :	Tumor necrosis factor- α .

Acknowledgment

This work was supported by a research Grant-in-Aid for Scientific Research C (no. 23500578) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

- [1] D. G. Candow and P. D. Chilibeck, "Differences in size, strength, and power of upper and lower body muscle groups in young and older men," *The Journals of Gerontology A*, vol. 60, no. 2, pp. 148–156, 2005.
- [2] L. J. Melton III, S. Khosla, C. S. Crowson, M. K. O'Connor, W. M. O'Fallon, and B. L. Riggs, "Epidemiology of sarcopenia," *Journal of the American Geriatrics Society*, vol. 48, no. 6, pp. 625–630, 2000.
- [3] R. N. Baumgartner, D. L. Waters, D. Gallagher, J. E. Morley, and P. J. Garry, "Predictors of skeletal muscle mass in elderly men and women," *Mechanisms of Ageing and Development*, vol. 107, no. 2, pp. 123–136, 1999.
- [4] E. T. Poehlman, M. J. Toth, and T. Fonong, "Exercise, substrate utilization and energy requirements in the elderly," *International Journal of Obesity*, vol. 19, supplement 4, pp. S93–S96, 1995.
- [5] R. D. Griffiths, "Muscle mass, survival, and the elderly ICU patient," *Nutrition*, vol. 12, no. 6, pp. 456–458, 1996.
- [6] T. S. Han, A. Tajar, and M. E. J. Lean, "Obesity and weight management in the elderly," *British Medical Bulletin*, vol. 97, no. 1, pp. 169–196, 2011.
- [7] Population Projections 2008–2060.
- [8] I. Janssen, D. S. Shepard, P. T. Katzmarzyk, and R. Roubenoff, "The healthcare costs of sarcopenia in the United States," *Journal of the American Geriatrics Society*, vol. 52, no. 1, pp. 80–85, 2004.
- [9] K. R. Short and K. S. Nair, "The effect of age on protein metabolism," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 3, no. 1, pp. 39–44, 2000.
- [10] K. R. Short, J. L. Vittone, M. L. Bigelow, D. N. Proctor, and K. S. Nair, "Age and aerobic exercise training effects on whole body and muscle protein metabolism," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 286, no. 1, pp. E92–E101, 2004.
- [11] J. Lexell, "Human aging, muscle mass, and fiber type composition," *The Journals of Gerontology A*, vol. 50, pp. 11–16, 1995.
- [12] L. Larsson, "Morphological and functional characteristics of the ageing skeletal muscle in man. A cross-sectional study," *Acta Physiologica Scandinavica, Supplement*, vol. 457, pp. 1–36, 1978.
- [13] L. B. Verdijk, B. G. Gleeson, R. A. M. Jonkers et al., "Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men," *The Journals of Gerontology A*, vol. 64, no. 3, pp. 332–339, 2009.
- [14] I. M. Conboy, M. J. Conboy, G. M. Smythe, and T. A. Rando, "Notch-mediated restoration of regenerative potential to aged muscle," *Science*, vol. 302, no. 5650, pp. 1575–1577, 2003.
- [15] K. Day, G. Shefer, A. Shearer, and Z. Yablonka-Reuveni, "The depletion of skeletal muscle satellite cells with age is concomitant with reduced capacity of single progenitors to produce reserve progeny," *Developmental Biology*, vol. 340, no. 2, pp. 330–343, 2010.
- [16] A. J. Wagers and I. M. Conboy, "Cellular and molecular signatures of muscle regeneration: current concepts and controversies in adult myogenesis," *Cell*, vol. 122, no. 5, pp. 659–667, 2005.
- [17] J. Dubé and B. H. Goodpaster, "Assessment of intramuscular triglycerides: contribution to metabolic abnormalities," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 9, no. 5, pp. 553–559, 2006.
- [18] E. W. Kraegen and G. J. Cooney, "Free fatty acids and skeletal muscle insulin resistance," *Current Opinion in Lipidology*, vol. 19, no. 3, pp. 235–241, 2008.
- [19] G. Shefer, M. Wlekinski-Lee, and Z. Yablonka-Reuveni, "Skeletal muscle satellite cells can spontaneously enter an alternative mesenchymal pathway," *Journal of Cell Science*, vol. 117, no. 22, pp. 5393–5404, 2004.
- [20] M. T. Hamilton, E. Areiqat, D. G. Hamilton, and L. Bey, "Plasma triglyceride metabolism in humans and rats during aging and physical inactivity," *International Journal of Sport Nutrition and Exercise Metabolism*, vol. 11, pp. S97–S104, 2001.
- [21] J. Lexell, "Ageing and human muscle: observations from Sweden," *Canadian Journal of Applied Physiology*, vol. 18, no. 1, pp. 2–18, 1993.
- [22] R. Roubenoff and V. A. Hughes, "Sarcopenia: current concepts," *The Journals of Gerontology A*, vol. 55, no. 12, pp. M716–M724, 2000.

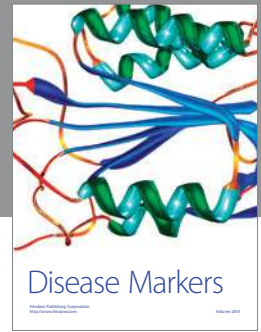
- [23] K. Sakuma and A. Yamaguchi, "Inhibitors of myostatin- and proteasome-dependent signaling for attenuating muscle wasting," *Recent Patent of Regenerative Medicine*, vol. 1, no. 3, pp. 284–298, 2011.
- [24] K. Sakuma and A. Yamaguchi, "Sarcopenia: molecular mechanisms and current therapeutic strategy," in *Cell Aging*, J. W. Perloft and A. H. Wong, Eds., pp. 93–152, Nova Science, New York, NY, USA, 2011.
- [25] K. M. Flegal, M. D. Carroll, C. L. Ogden, and L. R. Curtin, "Prevalence and trends in obesity among US adults, 1999–2008," *Journal of the American Medical Association*, vol. 303, no. 3, pp. 235–241, 2010.
- [26] T. M. Bellanger and G. A. Bray, "Obesity related morbidity and mortality," *The Journal of the Louisiana State Medical Society*, vol. 157, no. 1, pp. S42–S49, 2005.
- [27] S. Klein, L. E. Burke, G. A. Bray et al., "Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation," *Circulation*, vol. 110, no. 18, pp. 2952–2967, 2004.
- [28] E. E. Calle, M. J. Thun, J. M. Petrelli, C. Rodriguez, and C. W. Heath, "Body-mass index and mortality in a prospective cohort of U.S. adults," *The New England Journal of Medicine*, vol. 341, no. 15, pp. 1097–1105, 1999.
- [29] R. L. Kennedy, K. Chokkalingham, and R. Srinivasan, "Obesity in the elderly: who should we be treating, and why, and how?" *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 7, no. 1, pp. 3–9, 2004.
- [30] D. T. Villareal, C. M. Apovian, R. F. Kushner, and S. Klein, "Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society," *American Journal of Clinical Nutrition*, vol. 82, no. 5, pp. 923–934, 2005.
- [31] E. L. Lim, K. G. Hollingsworth, B. S. Aribisala, M. J. Chen, J. C. Mathers, and R. Taylor, "Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol," *Diabetologia*, vol. 54, no. 10, pp. 2506–2514, 2011.
- [32] D. Chau, L. M. Cho, P. Jani, and S. T. St Jeor, "Individualizing recommendations for weight management in the elderly," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 11, no. 1, pp. 27–31, 2008.
- [33] B. H. Goodpaster, S. Krishnaswami, T. B. Harris et al., "Obesity, regional body fat distribution, and the metabolic syndrome in older men and women," *Archives of Internal Medicine*, vol. 165, no. 7, pp. 777–783, 2005.
- [34] H. Bokura, S. Yamaguchi, K. Iijima, A. Nagai, and H. Oguro, "Metabolic syndrome is associated with silent ischemic brain lesions," *Stroke*, vol. 39, no. 5, pp. 1607–1609, 2008.
- [35] A. L. Bui, T. B. Horwich, and G. C. Fonarow, "Epidemiology and risk profile of heart failure," *Nature Reviews Cardiology*, vol. 8, no. 1, pp. 30–41, 2011.
- [36] J. Harrington and T. Lee-Chiong, "Obesity and aging," *Clinics in Chest Medicine*, vol. 30, no. 3, pp. 609–614, 2009.
- [37] K. M. McTigue, R. Hess, and J. Ziouras, "Obesity in older adults: a systematic review of the evidence for diagnosis and treatment," *Obesity*, vol. 14, no. 9, pp. 1485–1497, 2006.
- [38] L. H. McCarthy, M. E. Bigal, M. Katz, C. Derby, and R. B. Lipton, "Chronic pain and obesity in elderly people: results from the Einstein aging study," *Journal of the American Geriatrics Society*, vol. 57, no. 1, pp. 115–119, 2009.
- [39] R. N. Baumgartner, "Body composition in healthy aging," *Annals of the New York Academy of Sciences*, vol. 904, pp. 437–448, 2000.
- [40] D. R. Bouchard, W. Pickett, and I. Janssen, "Association between obesity and unintentional injury in older adults," *Obesity Facts*, vol. 3, no. 6, pp. 363–369, 2010.
- [41] C. S. Blaum, Q. L. Xue, E. Michelon, R. D. Semba, and L. P. Fried, "The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies," *Journal of the American Geriatrics Society*, vol. 53, no. 6, pp. 927–934, 2005.
- [42] R. Roubenoff, "Sarcopenic obesity: the confluence of two epidemics," *Obesity Research*, vol. 12, no. 6, pp. 887–888, 2004.
- [43] M. A. Schragger, E. J. Metter, E. Simonsick et al., "Sarcopenic obesity and inflammation in the InCHIANTI study," *Journal of Applied Physiology*, vol. 102, no. 3, pp. 919–925, 2007.
- [44] R. H. Unger, "Longevity, lipotoxicity and leptin: the adipocyte defense against feasting and famine," *Biochimie*, vol. 87, no. 1, pp. 57–64, 2005.
- [45] H. Tilg and A. R. Moschen, "Adipocytokines: mediators linking adipose tissue, inflammation and immunity," *Nature Reviews Immunology*, vol. 6, no. 10, pp. 772–783, 2006.
- [46] K. E. Wellen and G. S. Hotamisligil, "Inflammation, stress, and diabetes," *The Journal of Clinical Investigation*, vol. 115, no. 5, pp. 1111–1119, 2005.
- [47] I. Kratchmarova, D. E. Kalume, B. Blagoev et al., "A proteomic approach for identification of secreted proteins during the differentiation of 3T3-L1 preadipocytes to adipocytes," *Molecular & Cellular Proteomics*, vol. 1, no. 3, pp. 213–222, 2002.
- [48] Y. Lin, M. W. Rajala, J. P. Berger, D. E. Moller, N. Barzilai, and P. E. Scherer, "Hyperglycemia-induced production of acute phase reactants in adipose tissue," *The Journal of Biological Chemistry*, vol. 276, no. 45, pp. 42077–42083, 2001.
- [49] V. Catalán, J. Gómez-Ambrosi, A. Rodríguez et al., "Increased adipose tissue expression of lipocalin-2 in obesity is related to inflammation and matrix metalloproteinase-2 and metalloproteinase-9 activities in humans," *Journal of Molecular Medicine*, vol. 87, no. 8, pp. 803–813, 2009.
- [50] Q. W. Yan, Q. Yang, N. Mody et al., "The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance," *Diabetes*, vol. 56, no. 10, pp. 2533–2540, 2007.
- [51] J. Zhang, Y. Wu, Y. Zhang, D. Leroith, D. A. Bernlohr, and X. Chen, "The role of lipocalin 2 in the regulation of inflammation in adipocytes and macrophages," *Molecular Endocrinology*, vol. 22, no. 6, pp. 1416–1426, 2008.
- [52] J. B. Cowland, T. Muta, and N. Borregaard, "IL-1 β -specific up-regulation of neutrophil gelatinase-associated lipocalin is controlled by I κ B- ζ ," *Journal of Immunology*, vol. 176, no. 9, pp. 5559–5566, 2006.
- [53] L. A. Meheus, L. M. Franssen, J. G. Raymackers et al., "Identification by microsequencing of lipopolysaccharide-induced proteins secreted by mouse macrophages," *Journal of Immunology*, vol. 151, no. 3, pp. 1535–1547, 1993.
- [54] I. K. M. Law, A. Xu, K. S. L. Lam et al., "Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity," *Diabetes*, vol. 59, no. 4, pp. 872–882, 2010.
- [55] R. J. Urban, Y. H. Bodenbun, C. Gilkison et al., "Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 269, no. 5, pp. E820–E826, 1995.

- [56] S. Bhasin, L. Woodhouse, and T. W. Storer, "Proof of the effect of testosterone on skeletal muscle," *Journal of Endocrinology*, vol. 170, no. 1, pp. 27–38, 2001.
- [57] H. A. Feldman, C. Longcope, C. A. Derby et al., "Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 2, pp. 589–598, 2002.
- [58] J. E. Morley, F. E. Kaiser, H. M. Perry et al., "Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men," *Metabolism*, vol. 46, no. 4, pp. 410–413, 1997.
- [59] J. E. Morley and H. M. Perry, "Androgens and women at the menopause and beyond," *The Journals of Gerontology A*, vol. 58, no. 5, pp. M409–M416, 2003.
- [60] J. R. Florini, D. Z. Ewton, and S. A. Coolican, "Growth hormone and the insulin-like growth factor system in myogenesis," *Endocrine Reviews*, vol. 17, no. 5, pp. 481–517, 1996.
- [61] K. Y. Ho, J. D. Veldhuis, M. L. Johnson et al., "Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man," *The Journal of Clinical Investigation*, vol. 81, no. 4, pp. 968–975, 1988.
- [62] A. Moran, D. R. Jacobs, J. Steinberger et al., "Association between the insulin resistance of puberty and the insulin-like growth factor-I/growth hormone axis," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 10, pp. 4817–4820, 2002.
- [63] M. Hermann and P. Berger, "Hormonal changes in aging men: a therapeutic indication?" *Experimental Gerontology*, vol. 36, no. 7, pp. 1075–1082, 2001.
- [64] J. G. Ryall, J. D. Schertzer, and G. S. Lynch, "Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness," *Biogerontology*, vol. 9, no. 4, pp. 213–228, 2008.
- [65] S. Giovannini, E. Marzetti, S. E. Borst, and C. Leeuwenburgh, "Modulation of GH/IGF-1 axis: potential strategies to counteract sarcopenia in older adults," *Mechanisms of Ageing and Development*, vol. 129, no. 10, pp. 593–601, 2008.
- [66] R. Nass, G. Johannsson, J. S. Christiansen, J. J. Kopchick, and M. O. Thorner, "The aging population—is there a role for endocrine interventions?" *Growth Hormone and IGF Research*, vol. 19, no. 2, pp. 89–100, 2009.
- [67] K. Sakuma and A. Yamaguchi, "Molecular mechanisms in aging and current strategies to counteract sarcopenia," *Current Aging Science*, vol. 3, no. 2, pp. 90–101, 2010.
- [68] P. J. Campbell, M. G. Carlson, and N. Nurjhan, "Fat metabolism in human obesity," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 266, no. 4, pp. E600–E605, 1994.
- [69] K. F. Petersen, D. Befroy, S. Dufour et al., "Mitochondrial dysfunction in the elderly: possible role in insulin resistance," *Science*, vol. 300, no. 5622, pp. 1140–1142, 2003.
- [70] P. S. van Dam, H. E. C. Smid, W. R. de Vries et al., "Reduction of free fatty acids by acipimox enhances the growth hormone (GH) responses to GH-releasing peptide 2 in elderly men," *The Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 12, pp. 4706–4711, 2000.
- [71] A. Weltman, J. Y. Weltman, J. D. Veldhuis, and M. L. Hartman, "Body composition, physical exercise, growth hormone and obesity," *Eating and Weight Disorders*, vol. 6, no. 3, pp. 28–37, 2001.
- [72] D. L. Waters, C. R. Qualls, R. I. Dorin, J. D. Veldhuis, and R. N. Baumgartner, "Altered growth hormone, cortisol, and leptin secretion in healthy elderly persons with sarcopenia and mixed body composition phenotypes," *The Journals of Gerontology A*, vol. 63, no. 5, pp. 536–541, 2008.
- [73] C. A. Allan, B. J. G. Strauss, and R. I. McLachlan, "Body composition, metabolic syndrome and testosterone in ageing men," *International Journal of Impotence Research*, vol. 19, no. 5, pp. 448–457, 2007.
- [74] A. R. Cappola, K. Bandeen-Roche, G. S. Wand, S. Volpato, and L. P. Fried, "Association of IGF-I levels with muscle strength and mobility in older women," *The Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 9, pp. 4139–4146, 2001.
- [75] L. A. Schaap, S. M. F. Pluijm, J. H. Smitt et al., "The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women," *Clinical Endocrinology*, vol. 63, no. 2, pp. 152–160, 2005.
- [76] L. W. Chu, S. Tam, A. W. C. Kung et al., "Serum total and bioavailable testosterone levels, central obesity, and muscle strength changes with aging in healthy Chinese men," *Journal of the American Geriatrics Society*, vol. 56, no. 7, pp. 1286–1291, 2008.
- [77] A. M. Umpleby and D. L. Russell-Jones, "The hormonal control of protein metabolism," *Baillière's Clinical Endocrinology and Metabolism*, vol. 10, no. 4, pp. 551–570, 1996.
- [78] J. M. Carrascosa, A. Andrés, M. Ros et al., "Development of insulin resistance during aging: involvement of central processes and role of adipokines," *Current Protein and Peptide Science*, vol. 12, no. 4, pp. 305–315, 2011.
- [79] K. L. Timmerman and E. Volpi, "Endothelial function and the regulation of muscle protein anabolism in older adults," *Nutrition, Metabolism and Cardiovascular Diseases*, 2012.
- [80] M. A. Vincent, M. Montagnani, and M. J. Quon, "Molecular and physiologic actions of insulin related to production of nitric oxide in vascular endothelium," *Current Diabetes Reports*, vol. 3, no. 4, pp. 279–288, 2003.
- [81] S. Fujita, E. L. Glynn, K. L. Timmerman, B. B. Rasmussen, and E. Volpi, "Supraphysiological hyperinsulinaemia is necessary to stimulate skeletal muscle protein anabolism in older adults: evidence of a true age-related insulin resistance of muscle protein metabolism," *Diabetologia*, vol. 52, no. 9, pp. 1889–1898, 2009.
- [82] I. Gabriely, X. H. Ma, X. M. Yang et al., "Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process?" *Diabetes*, vol. 51, no. 10, pp. 2951–2958, 2002.
- [83] R. Basu, E. Breda, A. L. Oberg et al., "Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance," *Diabetes*, vol. 52, no. 7, pp. 1738–1748, 2003.
- [84] L. J. C. van Loon and B. H. Goodpaster, "Increased intramuscular lipid storage in the insulin-resistant and endurance-trained state," *Pflügers Archiv*, vol. 451, no. 5, pp. 606–616, 2006.
- [85] R. Roubenoff, "Catabolism of aging: is it an inflammatory process?" *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 6, no. 3, pp. 295–299, 2003.
- [86] L. A. Schaap, S. M. F. Pluijm, D. J. H. Deeg et al., "Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength," *The Journals of Gerontology A*, vol. 64, no. 11, pp. 1183–1189, 2009.
- [87] I. Rieu, H. Magne, I. Savary-Auzeloux et al., "Reduction of low grade inflammation restores blunting of postprandial muscle

- anabolism and limits sarcopenia in old rats," *The Journal of Physiology*, vol. 587, no. 22, pp. 5483–5492, 2009.
- [88] H. Y. Chung, M. Cesari, S. Anton et al., "Molecular inflammation: underpinnings of aging and age-related diseases," *Ageing Research Reviews*, vol. 8, no. 1, pp. 18–30, 2009.
- [89] M. B. Reid and Y. P. Li, "Tumor necrosis factor- α and muscle wasting: a cellular perspective," *Respiratory Research*, vol. 2, no. 5, pp. 269–272, 2001.
- [90] W. Aoi and K. Sakuma, "Oxidative stress and skeletal muscle dysfunction with aging," *Current Aging Science*, vol. 4, no. 2, pp. 101–109, 2011.
- [91] S. J. Meng and L. J. Yu, "Oxidative stress, molecular inflammation and sarcopenia," *International Journal of Molecular Sciences*, vol. 11, no. 4, pp. 1509–1526, 2010.
- [92] M. Bar-Shai, E. Carmeli, R. Coleman et al., "The effect of hindlimb immobilization on acid phosphatase, metalloproteinases and nuclear factor- κ B in muscles of young and old rats," *Mechanisms of Ageing and Development*, vol. 126, no. 2, pp. 289–297, 2005.
- [93] T. Phillips and C. Leeuwenburgh, "Muscle fiber specific apoptosis and TNF- α signaling in sarcopenia are attenuated by life-long calorie restriction," *The FASEB Journal*, vol. 19, no. 6, pp. 668–670, 2005.
- [94] E. Marzetti, C. S. Carter, S. E. Wohlgemuth et al., "Changes in IL-15 expression and death-receptor apoptotic signaling in rat gastrocnemius muscle with aging and life-long calorie restriction," *Mechanisms of Ageing and Development*, vol. 130, no. 4, pp. 272–280, 2009.
- [95] E. E. Pistilli, J. R. Jackson, and S. E. Alway, "Death receptor-associated pro-apoptotic signaling in aged skeletal muscle," *Apoptosis*, vol. 11, no. 12, pp. 2115–2126, 2006.
- [96] W. B. Ershler and E. T. Keller, "Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty," *Annual Review of Medicine*, vol. 51, pp. 245–270, 2000.
- [97] K. S. Krabbe, M. Pedersen, and H. Bruunsgaard, "Inflammatory mediators in the elderly," *Experimental Gerontology*, vol. 39, no. 5, pp. 687–699, 2004.
- [98] A. R. Cappola, Q. L. Xue, L. Ferrucci, J. M. Guralnik, S. Volpato, and L. P. Fried, "Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women," *The Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 5, pp. 2019–2025, 2003.
- [99] L. A. Schaap, S. M. F. Pluijm, D. J. H. Deeg, and M. Visser, "Inflammatory markers and loss of muscle mass (sarcopenia) and strength," *American Journal of Medicine*, vol. 119, no. 6, pp. 526.e9–526.e17, 2006.
- [100] D. R. Taaffe, T. B. Harris, L. Ferrucci, J. Rowe, and T. E. Seeman, "Cross-sectional and prospective relationships of interleukin-6 and c-reactive protein with physical performance in elderly persons: macArthur studies of successful aging," *The Journals of Gerontology A*, vol. 55, no. 12, pp. M709–M715, 2000.
- [101] M. Hamer and G. J. Molloy, "Association of C-reactive protein and muscle strength in the English Longitudinal Study of Ageing," *Age*, vol. 31, no. 3, pp. 171–177, 2009.
- [102] F. Haddad, F. Zaldivar, D. M. Cooper, and G. R. Adams, "IL-6-induced skeletal muscle atrophy," *Journal of Applied Physiology*, vol. 98, no. 3, pp. 911–917, 2005.
- [103] M. L. Kohut, D. A. McCann, D. W. Russell et al., "Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of β -blockers, BMI, and psychosocial factors in older adults," *Brain, Behavior, and Immunity*, vol. 20, no. 3, pp. 201–209, 2006.
- [104] L. K. Stewart, M. G. Flynn, W. W. Campbell et al., "The influence of exercise training on inflammatory cytokines and C-reactive protein," *Medicine and Science in Sports and Exercise*, vol. 39, no. 10, pp. 1714–1719, 2007.
- [105] A. C. McPherron, A. M. Lawler, and S. J. Lee, "Regulation of skeletal muscle mass in mice by a new TGF- β superfamily member," *Nature*, vol. 387, no. 6628, pp. 83–90, 1997.
- [106] K. Sakuma and A. Yamaguchi, "Sarcopenia and cachexia: the adaptations of negative regulators of skeletal muscle mass," *Journal of Cachexia, Sarcopenia and Muscle*, vol. 3, no. 2, pp. 77–94, 2012.
- [107] M. Wehling, B. Cai, and J. G. Tidball, "Modulation of myostatin expression during modified muscle use," *The FASEB Journal*, vol. 14, no. 1, pp. 103–110, 2000.
- [108] N. F. Gonzalez-Cadavid, W. E. Taylor, K. Yarasheski et al., "Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 25, pp. 14938–14943, 1998.
- [109] T. A. Zimmers, M. V. Davies, L. G. Koniaris et al., "Induction of cachexia in mice by systemically administered myostatin," *Science*, vol. 296, no. 5572, pp. 1486–1488, 2002.
- [110] N. K. LeBrasseur, T. M. Schelhorn, B. L. Bernardo, P. G. Cosgrove, P. M. Loria, and T. A. Brown, "Myostatin inhibition enhances the effects of exercise on performance and metabolic outcomes in aged mice," *The Journals of Gerontology A*, vol. 64, no. 9, pp. 940–948, 2009.
- [111] K. T. Murphy, R. Koopman, T. Naim et al., "Antibody-directed myostatin inhibition in 21-mo-old mice reveals novel roles for myostatin signaling in skeletal muscle structure and function," *The FASEB Journal*, vol. 24, no. 11, pp. 4433–4442, 2010.
- [112] D. L. Allen, D. S. Hittel, and A. C. McPherron, "Expression and function of myostatin in obesity, diabetes, and exercise adaptation," *Medicine and Science in Sports and Exercise*, vol. 43, no. 10, pp. 1828–1835, 2011.
- [113] N. K. LeBrasseur, K. Walsh, and Z. Arany, "Metabolic benefits of resistance training and fast glycolytic skeletal muscle," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 300, no. 1, pp. E3–E10, 2011.
- [114] C. Zhang, C. McFarlane, S. Lokireddy et al., "Inhibition of myostatin protects against diet-induced obesity through enhancing fatty acid oxidation and promoting brown adipose phenotype in mice," *Diabetologia*, vol. 55, no. 1, pp. 183–193, 2011.
- [115] I. Akpan, M. D. Goncalves, R. Dhir et al., "The effects of a soluble activin type IIB receptor on obesity and insulin sensitivity," *International Journal of Obesity*, vol. 33, no. 11, pp. 1265–1273, 2009.
- [116] B. L. Bernardo, T. S. Wachtmann, P. G. Cosgrove et al., "Postnatal PPARdelta activation and myostatin inhibition exert distinct yet complimentary effects on the metabolic profile of obese insulin-resistant mice," *PLoS one*, vol. 5, no. 6, Article ID e11307, 2010.
- [117] A. Ratkevicius, A. Joyson, I. Selmer et al., "Serum concentrations of myostatin and myostatin-interacting proteins do not differ between young and sarcopenic elderly men," *The Journals of Gerontology A*, vol. 66, no. 6, pp. 620–626, 2011.
- [118] S. E. Wozniak, L. L. Gee, M. S. Wachtel, and E. E. Frezza, "Adipose tissue: the new endocrine organ? a review article," *Digestive Diseases and Sciences*, vol. 54, no. 9, pp. 1847–1856, 2009.

- [119] E. Hu, P. Liang, and B. M. Spiegelman, "AdipoQ is a novel adipose-specific gene dysregulated in obesity," *The Journal of Biological Chemistry*, vol. 271, no. 18, pp. 10697–10703, 1996.
- [120] L. Barré, C. Richardson, M. F. Hirshman et al., "Genetic model for the chronic activation of skeletal muscle AMP-activated protein kinase leads to glycogen accumulation," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 292, no. 3, pp. E802–E811, 2007.
- [121] H. Iwahashi, T. Funahashi, N. Kurokawa et al., "Plasma adiponectin levels in women with anorexia nervosa," *Hormone and Metabolic Research*, vol. 35, no. 9, pp. 537–540, 2003.
- [122] R. S. Lindsay, J. D. Walker, P. J. Havel, B. A. Hamilton, A. A. Calder, and F. D. Johnstone, "Adiponectin is present in cord blood but is unrelated to birth weight," *Diabetes Care*, vol. 26, no. 8, pp. 2244–2249, 2003.
- [123] M. Matsubara, S. Maruoka, and S. Katayose, "Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women," *European Journal of Endocrinology*, vol. 147, no. 2, pp. 173–180, 2002.
- [124] T. P. Combs, A. H. Berg, S. Obici, P. E. Scherer, and L. Rossetti, "Endogenous glucose production is inhibited by the adipose-derived protein Acrp30," *The Journal of Clinical Investigation*, vol. 108, no. 12, pp. 1875–1881, 2001.
- [125] T. Yamauchi, J. Kamon, H. Waki et al., "The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity," *Nature Medicine*, vol. 7, no. 8, pp. 941–946, 2001.
- [126] T. Yamauchi, J. Kamon, Y. Minokoshi et al., "Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase," *Nature Medicine*, vol. 8, no. 11, pp. 1288–1295, 2002.
- [127] X. Wu, H. Motoshima, K. Mahadev, T. J. Stalker, R. Scalia, and B. J. Goldstein, "Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes," *Diabetes*, vol. 52, no. 6, pp. 1355–1363, 2003.
- [128] C. Debard, M. Laville, V. Berbe et al., "Expression of key genes of fatty acid oxidation, including adiponectin receptors, in skeletal muscle of type 2 diabetic patients," *Diabetologia*, vol. 47, no. 5, pp. 917–925, 2004.
- [129] H. Staiger, S. Kaltenbach, K. Staiger et al., "Expression of adiponectin receptor mRNA in human skeletal muscle cells is related to in vivo parameters of glucose and lipid metabolism," *Diabetes*, vol. 53, no. 9, pp. 2195–2201, 2004.
- [130] M. B. Chen, A. J. McAinch, S. L. Macaulay et al., "Impaired activation of AMP-kinase and fatty acid oxidation by globular adiponectin in cultured human skeletal muscle of obese type 2 diabetics," *The Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 6, pp. 3665–3672, 2005.
- [131] N. Vilarrasa, J. Vendrell, J. Maravall et al., "Distribution and determinants of adiponectin, resistin and ghrelin in a randomly selected healthy population," *Clinical Endocrinology*, vol. 63, no. 3, pp. 329–335, 2005.
- [132] K. Y. Kim, J. K. Kim, S. H. Han et al., "Adiponectin is a negative regulator of NK cell cytotoxicity," *Journal of Immunology*, vol. 176, no. 10, pp. 5958–5964, 2006.
- [133] C. Koch, R. A. Augustine, J. Steger et al., "Leptin rapidly improves glucose homeostasis in obese mice by increasing hypothalamic insulin sensitivity," *The Journal of Neuroscience*, vol. 30, no. 48, pp. 16180–16187, 2010.
- [134] B. B. Kahn and J. S. Flier, "Obesity and insulin resistance," *The Journal of Clinical Investigation*, vol. 106, no. 4, pp. 473–481, 2000.
- [135] R. B. Ceddia, H. A. Koistinen, J. R. Zierath, and G. Sweeney, "Analysis of paradoxical observations on the association between leptin and insulin resistance," *The FASEB Journal*, vol. 16, no. 10, pp. 1163–1176, 2002.
- [136] Y. Minokoshi, M. S. Haque, and T. Shimazu, "Microinjection of leptin into the ventromedial hypothalamus increases glucose uptake in peripheral tissues in rats," *Diabetes*, vol. 48, no. 2, pp. 287–291, 1999.
- [137] C. Pérez, C. Fernández-Galaz, T. Fernández-Agulló et al., "Leptin impairs insulin signaling in rat adipocytes," *Diabetes*, vol. 53, no. 2, pp. 347–353, 2004.
- [138] J. Rouru, I. Cusin, K. E. Zakrzewska, B. Jeanrenaud, and F. Rohner-Jeanrenaud, "Effects of intravenously infused leptin on insulin sensitivity and on the expression of uncoupling proteins in brown adipose tissue," *Endocrinology*, vol. 140, no. 8, pp. 3688–3692, 1999.
- [139] P. J. Scarpace, M. Matheny, and N. Tümer, "Hypothalamic leptin resistance is associated with impaired leptin signal transduction in aged obese rats," *Neuroscience*, vol. 104, no. 4, pp. 1111–1117, 2001.
- [140] G. Brabant, G. Müller, R. Horn, C. Anderwald, M. Roden, and H. Nave, "Hepatic leptin signaling in obesity," *The FASEB Journal*, vol. 19, no. 8, pp. 1048–1050, 2005.
- [141] C. Fernández-Galaz, T. Fernández-Agulló, C. Pérez et al., "Long-term food restriction prevents ageing-associated central leptin resistance in Wistar rats," *Diabetologia*, vol. 45, no. 7, pp. 997–1003, 2002.
- [142] K. Esposito, A. Pontillo, F. Giugliano et al., "Association of low interleukin-10 levels with the metabolic syndrome in obese women," *The Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 3, pp. 1055–1058, 2003.
- [143] B. K. Pedersen, "The diseasome of physical inactivity—and the role of myokines in muscle-fat cross talk," *The Journal of Physiology*, vol. 587, no. 23, pp. 5559–5568, 2009.
- [144] R. L. Chelvarajan, S. M. Collins, J. M. van Willigen, and S. Bonada, "The unresponsiveness of aged mice to polysaccharide antigens is a result of a defect in macrophage function," *Journal of Leukocyte Biology*, vol. 77, no. 4, pp. 503–512, 2005.
- [145] B. C. Chiu, V. R. Stolberg, and S. W. Chensue, "Mononuclear phagocyte-derived IL-10 suppresses the innate IL-12/IFN- γ axis in lung-challenged aged mice," *Journal of Immunology*, vol. 181, no. 5, pp. 3156–3166, 2008.
- [146] L. Álvarez-Rodríguez, M. López-Hoyos, P. Muñoz-Cacho, and V. M. Martínez-Taboada, "Aging is associated with circulating cytokine dysregulation," *Cell Immunology*, vol. 273, no. 2, pp. 124–132, 2012.
- [147] R. J. Forsey, J. M. Thompson, J. Ernerudh et al., "Plasma cytokine profiles in elderly humans," *Mechanisms of Ageing and Development*, vol. 124, no. 4, pp. 487–493, 2003.
- [148] S. Pestka, C. D. Krause, D. Sarkar, M. R. Walter, Y. Shi, and P. B. Fisher, "Interleukin-10 and related cytokines and receptors," *Annual Review of Immunology*, vol. 22, pp. 929–979, 2004.
- [149] F. Ko, Q.-Y. Xue, W. Yao et al., "Inflammation and mortality in a frail mouse model," *Age*, vol. 34, no. 3, pp. 705–715, 2012.
- [150] W. E. Carson, M. J. Lindemann, R. Baiocchi et al., "The functional characterization of interleukin-10 receptor expression on human natural killer cells," *Blood*, vol. 85, no. 12, pp. 3577–3585, 1995.

- [151] M. A. Stacey, M. Marsden, E. C. Wang, G. W. Wilkinson, and I. R. Humphreys, "IL-10 restricts activation-induced death of NK cells during acute murine cytomegalovirus infection," *Journal of Immunology*, vol. 187, no. 6, pp. 2944–2952, 2011.
- [152] C. T. Lutz and L. S. Quinn, "Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism," *Aging*, vol. 4, no. 8, pp. 535–546, 2012.
- [153] K. H. Grabstein, J. Eisenman, K. Shanebeck et al., "Cloning of a T cell growth factor that interacts with the β chain of the interleukin-2 receptor," *Science*, vol. 264, no. 5161, pp. 965–968, 1994.
- [154] C. Bergamaschi, M. Rosati, R. Jalah et al., "Intracellular interaction of interleukin-15 with its receptor α during production leads to mutual stabilization and increased bioactivity," *The Journal of Biological Chemistry*, vol. 283, no. 7, pp. 4189–4199, 2008.
- [155] E. Mortier, T. Woo, R. Advincola, S. Gozalo, and A. Ma, "IL-15R α chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans presentation," *Journal of Experimental Medicine*, vol. 205, no. 5, pp. 1213–1225, 2008.
- [156] L. S. Quinn, "Interleukin-15: a muscle-derived cytokine regulating fat-to-lean body composition," *Journal of Animal Science*, vol. 86, supplement 14, pp. E75–E83, 2008.
- [157] S. E. Riechman, G. Balasekaran, S. M. Roth, and R. E. Ferrell, "Association of interleukin-15 protein and interleukin-15 receptor genetic variation with resistance exercise training responses," *Journal of Applied Physiology*, vol. 97, no. 6, pp. 2214–2219, 2004.
- [158] Y. Tamura, K. Watanabe, T. Kantani, J. Hayashi, N. Ishida, and M. Kaneki, "Upregulation of circulating IL-15 by treadmill running in healthy individuals: is IL-15 an endocrine mediator of the beneficial effects of endurance exercise?" *Endocrine Journal*, vol. 58, no. 3, pp. 211–215, 2011.
- [159] L. S. Quinn, B. G. Anderson, L. Strait-Bodey, and T. Wolden-Hanson, "Serum and muscle interleukin-15 levels decrease in aging mice: correlation with declines in soluble interleukin-15 receptor alpha expression," *Experimental Gerontology*, vol. 45, no. 2, pp. 106–112, 2010.
- [160] S. Gangemi, G. Basile, D. Monti et al., "Age-related modifications in circulating IL-15 levels in humans," *Mediators of Inflammation*, vol. 2005, no. 4, pp. 245–247, 2005.
- [161] N. G. Barra, S. Reid, R. MacKenzie et al., "Interleukin-15 contributes to the regulation of murine adipose tissue and human adipocytes," *Obesity*, vol. 18, no. 8, pp. 1601–1607, 2010.
- [162] A. R. Nielsen, P. Hojman, C. Erikstrup et al., "Association between interleukin-15 and obesity: interleukin-15 as a potential regulator of fat mass," *The Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 11, pp. 4486–4493, 2008.
- [163] N. G. Barra, M. V. Chew, A. C. Holloway, and A. A. Ashkar, "Interleukin-15 treatment improves glucose homeostasis and insulin sensitivity in obese mice," *Diabetes and Obese Metabolism*, vol. 14, no. 2, pp. 190–193, 2012.
- [164] B. H. Goodpaster, C. L. Carlson, M. Visser et al., "Attenuation of skeletal muscle and strength in the elderly: the health ABC study," *Journal of Applied Physiology*, vol. 90, no. 6, pp. 2157–2165, 2001.
- [165] M. Y. Song, E. Ruts, J. Kim, I. Janumala, S. Heymsfield, and D. Gallagher, "Sarcopenia and increased adipose tissue infiltration of muscle in elderly African American women," *American Journal of Clinical Nutrition*, vol. 79, no. 5, pp. 874–880, 2004.
- [166] E. J. Anderson, M. E. Lustig, K. E. Boyle et al., "Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans," *The Journal of Clinical Investigation*, vol. 119, no. 3, pp. 573–581, 2009.
- [167] Z. Arany, S. Y. Foo, Y. Ma et al., "HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1 α ," *Nature*, vol. 451, no. 7181, pp. 1008–1012, 2008.
- [168] S. Crunkhorn, F. Dearie, C. Mantzoros et al., "Peroxisome proliferator activator receptor γ coactivator-1 expression is reduced in obesity: potential pathogenic role of saturated fatty acids and p38 mitogen-activated protein kinase activation," *The Journal of Biological Chemistry*, vol. 282, no. 21, pp. 15439–15450, 2007.
- [169] T. Wenz, S. G. Rossi, R. L. Rotundo, B. M. Spiegelman, and C. T. Moraes, "Increased muscle PGC-1 α expression protects from sarcopenia and metabolic disease during aging," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 48, pp. 20405–20410, 2009.
- [170] W. L. Haskell, I. M. Lee, R. R. Pate et al., "Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association," *Medicine and Science in Sports and Exercise*, vol. 39, no. 8, pp. 1423–1434, 2007.
- [171] C. J. Liu and N. K. Latham, "Progressive resistance strength training for improving physical function in older adults," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD002759, 2009.
- [172] L. E. Davidson, R. Hudson, K. Kilpatrick et al., "Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial," *Archives of Internal Medicine*, vol. 169, no. 2, pp. 122–131, 2009.
- [173] D. Paddon-Jones and B. B. Rasmussen, "Dietary protein recommendations and the prevention of sarcopenia," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 12, no. 1, pp. 86–90, 2009.
- [174] D. L. Waters, R. N. Baumgartner, P. J. Garry, and B. Vellas, "Advantages of dietary, exercise-related, and therapeutic interventions to prevent and treat sarcopenia in adult patients: an update," *Clinical Interventions in Aging*, vol. 5, pp. 259–270, 2010.
- [175] H. C. Dreyer, M. J. Drummond, B. Pennings et al., "Leucine-enriched essential amino acid and carbohydrate ingestion following resistance exercise enhances mTOR signaling and protein synthesis in human muscle," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 294, no. 2, pp. E392–E400, 2008.
- [176] S. Walrand, C. Guillet, J. Salles, N. Cano, and Y. Boirie, "Physiopathological mechanism of sarcopenia," *Clinics in Geriatric Medicine*, vol. 27, no. 3, pp. 365–385, 2011.
- [177] M. Zamboni, G. Mazzali, F. Fantin, A. Rossi, and V. di Francesco, "Sarcopenic obesity: a new category of obesity in the elderly," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 18, no. 5, pp. 388–395, 2008.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

