HHS Public Access

Author manuscript

Exp Gerontol. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Exp Gerontol. 2021 November ; 155: 111561. doi:10.1016/j.exger.2021.111561.

Aging, Obesity, Sarcopenia and the Effect of Diet and Exercise Intervention

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Abstract

The number of adults 65 years and older is increasing worldwide and will represent the 20% of the population by 2030. Half of them will suffer from obesity. The decline in muscle mass and strength, known as sarcopenia, is very common among older adults with obesity (sarcopenic obesity). Sarcopenic obesity is strongly associated with frailty, cardiometabolic dysfunction, physical disability, and mortality. Increasing efforts have been hence made to identify effective strategies able to promote healthy aging and curb the obesity pandemic. Among these, lifestyle interventions consisting of diet and exercise protocols have been extensively explored. Importantly, diet-induced weight loss is associated with fat, muscle, and bone mass losses, and may further exacerbate age-related sarcopenia and frailty outcomes in older adults. Successful approaches to induce fat mass loss while preserving lean and bone mass are critical to reduce the aging- and obesity-related physical and metabolic complications and at the same time ameliorate frailty. In this review article, we discuss the most recent evidence on the age-related alterations in adipose tissue and muscle health and on the effect of calorie restriction and exercise approaches for older adults with obesity and sarcopenia, emphasizing the existing gaps in the literature that need further investigation.

Keywords

Elderly; Sarcopenia; Frailty; Lifestyle Interventions; Exercise; Diet; Skeletal Muscle; Adipose Tissue

1. Obesity and sarcopenia in older adults

The number of older adults (age ≥ 65 years) is increasing worldwide. In 2017, the number of older adults accounted for 13% of the global population and is expected to reach 2.1 billion

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Conflict of interest: authors have nothing to disclose.

people by 2050 (Nations, 2017). Most chronic conditions exacerbate with aging, which is *per se* associated with profound body composition changes, *i.e.*, gain and redistribution of fat mass and loss of muscle and bone masses (Batsis and Villareal, 2018). Among the most common conditions, there is obesity (defined as a BMI of ≥ 30 kg/m^2), a complex, multifactorial and relapsing disease that has spread into a pandemic worldwide (Bray et al., 2017; WHO, 2018). In several countries, obesity prevalence reaches 30-40% of the population and its incidence is expected to further increase during the next decades (Bluher, 2019; Ward et al., 2019). Obesity is characterized by an excessive accumulation of white adipose tissue, not only in fat depots, but also ectopically, a phenomenon that significantly compromises physical function (Batsis and Villareal, 2018; Bray et al., 2017). It is thus not surprising that obesity is associated with over 200 medical complications and with an increased risk of morbidity and mortality, representing the fifth leading cause of death worldwide (Bluher, 2019; Bray et al., 2017). The decline in muscle mass and strength, known as sarcopenia, is very common among older adults with obesity (sarcopenic obesity, Figure 1) (Bluher, 2019; Bray et al., 2017) and is closely associated with frailty – a condition of impaired homeostatic reserve and stress tolerance, resulting in increased vulnerability to adverse health outcomes (Fielding et al., 2011). Sarcopenic obesity is therefore strongly related not only to cardiometabolic dysfunctions, but also to physical disability (Batsis and Villareal, 2018).

Older adults will represent the 20% of the population by 2030 and half of them will suffer from obesity (Flegal et al., 2016). Hence, although we are clearly experiencing a significant increase in overall life expectancy, the chronic conditions associated with aging which are exacerbated by obesity, profoundly burdens the quality of life during those “gained years”. Increasing efforts have hence been made to identify effective strategies able to promote healthy aging and curb the obesity pandemic. Among these, lifestyle interventions consisting of dietary and exercise protocols have been extensively explored (Armamento-Villareal et al., 2012; Batsis and Villareal, 2018; Colleluori et al., 2019; Colleluori et al., 2017; Villareal et al., 2017a; Villareal et al., 2011a; Villareal et al., 2017b; Weiss et al., 2017a). In this context, it is important to underline that diet-induced weight loss is associated with not only fat, but also muscle and bone losses and may further exacerbate age-related sarcopenia and frailty in older adults (Armamento-Villareal et al., 2012; Villareal et al., 2011a). Successful approaches able to induce fat mass loss while preserving muscle and bone mass are critical to reduce the aging- and obesity-related cardiometabolic risks and, at the same time, prevent or ameliorate frailty (Batsis and Villareal, 2018; Cartee et al., 2016; Egan and Zierath, 2013; Piccoli et al., 2020; Villareal et al., 2017a; Villareal et al., 2011a). In this review article, we first describe adipose tissue and skeletal muscle alterations occurring in the context of aging and obesity and then discuss the most recent evidence on the effects of different types of lifestyle protocols (combined exercise and calorie restriction) on such impairments, emphasizing the existing gaps in the literature worth further investigation.

2. Body composition changes in older adults with obesity

Human body composition undergoes considerable modifications with advancing age. Specifically, muscle and bone mass progressively decrease starting from the third decade of life, while fat mass increases up to the age of 70 and decreases afterwards (Fantin et

al., 2007; Santanasto et al., 2017). The age-related lean mass reduction is estimated to be ~0.5-1.0% per year (Cruz-Jentoft et al., 2019). Appendicular lean mass and skeletal muscle index (limb muscle mass in kg divided by the square of the height in meters) progressively decrease with aging (Rossi et al., 2021). Importantly, fat mass increase and lean mass decrease occurring with aging may be underestimated due to fat redistribution and skeletal muscle lipid infiltration. Such miscalculation often occurs when assessing body composition through dual energy x-ray absorptiometry (DXA) or bioimpedance which have limitations in distinguishing organs' fat infiltration. For this reason, magnetic resonance (MRI) (Figure 1) or computed tomography (CT) may provide a better estimation of the actual fat and muscle amount (Batsis and Villareal, 2018). In a study conducted on ~1800 older adults (70-79 years old), in fact, Santanasto and colleagues reported a reduction of total fat and lean mass, as well as visceral adipose tissue (VAT) and thigh muscle areas after five years of follow up, but an increase in intramuscular adipose tissue (IMAT) assessed by CT (Santanasto et al., 2017).

The age-related fat redistribution in favor of VAT depots (as opposed to subcutaneous) occurs independently of weight gain (Fantin et al., 2007; Hughes et al., 2004; Siervo et al., 2016), a phenomenon strongly contributing to the cardiometabolic risks (Ross et al., 2020). While the age-related fat redistribution is partly attributed to sex hormonal profile modifications (Aguirre et al., 2015; Colleluori et al., 2018a; Colleluori et al., 2018b; Kotani et al., 1994; Koutsari et al., 2009), the rise in relative fat amount is due to multiple factors. Aging is in fact associated with a reduction in lean mass which in turn leads to a significant decrease in resting metabolic rate, triggering a vicious cycle responsible for the muscle mass reduction and relative fat mass increase. This phenomenon is attributed in part to behavioral modifications typically observed in older adults such as for example: reduced levels of physical activity, lower consumption of high-quality proteins (*e.g.*, meat due to difficulties in chewing), along with an increased preference for highly palatable food rich in sugars and fat (Batsis and Villareal, 2018; Zamboni et al., 2014). In addition, physiologic hormonal changes occurring with aging, such as marked decrease in anabolic hormones (*i.e.*, testosterone and growth hormone/IGF-1 axis) strongly contribute to the deleterious body composition changes (Batsis and Villareal, 2018; Zamboni et al., 2014).

Importantly, not all adipose depots display the same age-related variations. Brown adipose tissue, for example, which has the main role to dissipate energy in the form of heat during the process of non-shivering thermogenesis, reduces with advancing age, partly contributing to the energy expenditure decrease (Cypess et al., 2009; Zingaretti et al., 2009). On the other hand, bone marrow adipose tissue, of which the specific functions have yet to be clarified, increases with aging, obesity, or calorie restriction, possibly affecting hematopoiesis and cytokine production (Blebea et al., 2007; Krings et al., 2012). Furthermore, due to recent advances in technology, including the use of *single cell* or *single nucleus RNAseq* approaches, different adipocyte subpopulations with specific functions within each adipose depot have been discovered and seem to be differently affected by diet (Sarvari et al., 2021; Schwalie et al., 2018; Wenfei, 2020). The advent of such novel experimental strategies has also allowed the identification of specialized age-related subpopulations within the skeletal muscle, paving the way to new unexplored areas of investigation (Kim et al., 2020; Petrany et al., 2020). Whether lifestyle factors, aging, and obesity influence such adipose

and/or skeletal muscle subpopulations has been only marginally investigated and represents a groundbreaking area of investigation.

3. Adipose tissue dysfunction in older adults with obesity

In contrast to subcutaneous adipose tissue (SAT), lipids deposition in VAT and IMAT (Figure 1) are associated with insulin resistance, dyslipidemia, chronic inflammation, hypertension, and physical dysfunction (Brinkley et al., 2012; Goodpaster et al., 2000; Siervo et al., 2016; Tchkonia et al., 2013), leading to a greater overall risk of mortality within every body mass index (BMI) category (Cerhan et al., 2014; de Hollander et al., 2012; Santanasto et al., 2017). Older adults display more systemic lipolysis and meal fat oxidation, but less lipid storage in SAT compared to younger adults according to one study using mCi [l-^{14}C] to trace meal fatty acids (Koutsari et al., 2009). SAT's inability to store excessive energy results in the deposition of lipids in VAT and other ectopic depots (*e.g.*, skeletal muscle, liver, pancreas, heart), the *primum movens* of lipotoxicity (Despres and Lemieux, 2006). Such phenomenon is further exacerbated by the chronic positive energy balance typical of obesity (Zamboni et al., 2014). Excessive calorie load follows adipose tissue expansion which can occur through adipocyte hypertrophy and hyperplasia (Kim et al., 2014). Human adipocyte volume is positively related to total fat mass, whereas adipocyte number is set during adolescence and remains constant throughout life (Spalding et al., 2008). Massive weight loss by bariatric surgery leads in fact to a reduction in adipocyte size but not number, which is higher among obese compared to lean individuals (Spalding et al., 2008). Accordingly, 16 weeks of weight gain resulted in adipocyte hypertrophy, but not hyperplasia in healthy adults (Salans et al., 1971). In contrast to what is observed during youth, adipocyte hyperplasia during adulthood occurs predominantly in VAT during sustained and chronic positive energy balance when adipocytes cannot further accommodate the energy surplus increasing their size (Kim et al., 2014; Wang et al., 2013). Paradoxically, the age-related inability to expand adipose tissue through *de novo* adipogenesis is at the core of the metabolic anomalies observed in conditions of obesity. Aging is therefore associated with a marked decline in homeostatic and obesity-related adipocyte plasticity and with a reduction in adipocyte progenitor self-renewal (Kim et al., 2014). Similarly, the preadipocyte dysfunction occurring with advancing age and obesity is responsible for the lower adipose tissue expandability, and results in obesity-related complications (lipotoxicity and ectopic fat deposition) (Guo et al., 2007; Sepe et al., 2011). SAT adipocyte hypertrophy is related to low adipocyte generation rate which predicts insulin resistance in humans and animal models (Arner et al., 2010; Kim et al., 2014; Spalding et al., 2008; Weyer et al., 2000). Interestingly, a specific adipocyte size threshold associated with type 2 diabetes and poor metabolic response to gastric bypass was identified in adults with obesity (Cotillard et al., 2014). Adipocytes within different depots have a peculiar *critical size* above which cells cannot further expand, display signs of stress, and die of *pyroptosis* (Cinti et al., 2005; Giordano et al., 2013). Hypertrophic and stressed adipocytes exhibit a deregulation of fatty acid flux and altered pattern of adipokines and chemokines expression (e.g., higher IL-6, TNF-α, and resistin and lower adiponectin), which attract pro-inflammatory immune cells and strongly contribute to inflammation and insulin resistance (Giordano et al., 2013; Lumeng et al., 2011). Adipocyte size and death are hence associated with the presence

of the so-called *crown like structures i.e.*, macrophages surrounding dead adipocytes and absorbing their remnants/debris discovered by the group of Cinti (Figure 2A and B) (Cinti et al., 2005; Murano et al., 2008). Crown like structures are more prevalent in obese than lean (Cinti et al., 2005) and their presence in the adipose tissue is associated with lower insulin disposition index and higher VAT, intrahepatic adipose tissue, IMAT, TNF-α, fasting insulin, and glucose in adults with obesity (Le et al., 2011). Adipocytes in VAT have a lower *critical death size* compared to those in SAT, a feature that partly explains the strict association between central obesity and the impaired metabolic profiles (Giordano et al., 2013; Murano et al., 2008). Pro-inflammatory macrophages (type 1) and T cells infiltrating the adipose tissue are increased with aging and obesity and establish the typical low-grade chronic inflammation observed in older adults (*inflammaging*) (Lumeng et al., 2011; Weisberg et al., 2003). Besides inflammation, obesity induced–adipocyte hypertrophy is associated with anomalies in tissue remodeling *i.e.*, overproduction of extracellular matrix components, reduced angiogenesis, fibrosis and hypoxia, which profoundly compromise tissue microenvironment and function (Cancello et al., 2005; Goossens et al., 2011; Sun et al., 2013). Interestingly, trained, older women with obesity display lower SAT inflammation and oxidative stress markers expression, and reduced infiltration of proinflammatory macrophages compared to their sedentary counterparts (Cizkova et al., 2020). Importantly, VAT directly discharges the excess of free fatty acids into the portal circulation, reason for which lipid overload riches *in primis* the liver (often causing *non-alcoholic fatty liver steatosis* or NASH) and then the skeletal muscle, leading to lipotoxicity and muscle dysfunction (Figure 2C and D). A longitudinal study conducted in 70-79 years old adults demonstrated that thigh muscle fat loss has a strong protective effect against mortality in weight stable men (Santanasto et al., 2017). It is therefore not surprising that the age-related body composition changes, such as muscle fat infiltration, are closely associated with frailty and disability (Batsis and Villareal, 2018). The specific changes occurring in the skeletal muscle in the context of aging and obesity are described in the next section.

4. Skeletal muscle dysfunction in older adults with obesity

The age-related reduction in muscle mass and strength adversely impacts health and is exacerbated by obesity. Skeletal muscle is in fact the most extended tissue in mammalians and plays various roles: not only allows locomotion and defines physical function, but also sets energy expenditure, insulin sensitivity, and whole-body metabolic health, besides representing the main body proteins reservoir. Considering its wide distribution, relatively small alterations in skeletal muscle tissue profoundly affects overall health.

4.1 Muscle mass

In older adults, thigh muscle reduction was recognized as the best predictor of mortality among numerous metabolic outcomes investigated (Santanasto et al., 2017). It is estimated that 10-20% of muscle mass is lost by the 7th decade of life (Janssen et al., 2000). For this reason, the understanding of the mechanisms responsible for muscle loss and identification of effective strategies to counteract such loss is extremely urgent.

4.1.1 Muscle protein synthesis—Contrary to what was previously thought, the age-related decline in muscle mass is not due to an augmented muscle protein breakdown, but to a blunted muscle protein synthesis (MPS response to anabolic stimuli (e.g., insulin, amino acids and exercise), as elegantly demonstrated by Volpi and colleagues who compared muscle protein turnover using stable isotope methodology in young and older volunteers (Rasmussen et al., 2006; Volpi et al., 2000). On the other hand, obesity is associated with a wide range of alterations in skeletal muscle protein kinetics (Beals et al., 2019). Although basal MPS is similar in obese and normo-weight adults (Beals et al., 2019), reduced mixed muscle protein turnover, lack of mitochondrial protein synthesis, and lower inhibition of whole-body proteolysis in response to anabolic stimuli have been described in adults with obesity compared to their normo-weight counterparts (Guillet et al., 2009; Tran et al., 2018). In addition, adults with obesity were reported to experience diminished myofibrillar MPS in response to food ingestion compared to controls (Beals et al., 2016). Such anomalies are not surprising considering the obesity-related impairments in macronutrient utilization, especially glucolipid metabolism and insulin sensitivity (Beals et al., 2019; Rasmussen et al., 2006). Nonetheless, not all studies on muscle protein kinetics in obesity report consistent findings possibly due to different experimental design (*e.g.*, type of anabolic stimulus used), comparison groups, and muscle subfractions investigated (mitochondria, mixed muscle, sarcoplasmic, or myofibrillar protein synthesis) (Beals et al., 2019).

4.1.2 Muscle fibers, capillarization and regeneration abilities—Fiber size, number, and relative type as well as muscle capillarization are affected by aging. Specifically, fiber size and number are reduced in older adults, which display a higher relative prevalence of type I fibers (slow twitch) with a concomitant decrease in capillary content (Morgan et al., 2020). Capillarization plays the crucial function of delivering oxygen, nutrients, and regulatory hormones to the muscle and its alteration contributes not only to the reduced muscle function, but also to the lower MPS response to anabolic stimuli described above (Batsis and Villareal, 2018; Rasmussen et al., 2006). Based on a study in older adults, the amount of muscle fiber capillarization predicts the hypertrophic response to resistance exercise (anabolic stimulus), with a lower amount related to a blunted muscle fiber size increase (Moro et al., 2019).

Fiber growth, repair, and regeneration are determined by satellite cells which allow proper muscle turnover and anabolic response. Satellite cell proliferation and function are impaired with aging and sarcopenia, and therefore, a blunted adaptive response of muscle fiber to exercise stimuli is observed in older compared to younger adults (Snijders et al., 2014). In addition, during aging exacerbated by obesity, mesenchymal cell progenitors in the skeletal muscle tend to give rise to adipocyte-like cells, further contributing to the ectopic lipids deposition (Sepe et al., 2011). Obesity is moreover characterized by a higher prevalence of the type II fiber subtype (fast twitch), which is associated with lower lipid oxidation abilities, impaired insulin sensitivity, and higher oxidative stress and metabolic impairments (Fisher et al., 2017; Tanner et al., 2002). A study conducted in adults with obesity revealed a positive relation between the baseline prevalence of type 1 fiber and the percentage of weight loss 12 months after gastric bypass, suggesting that fiber type may influence obesity susceptibility and/or response to weight loss, and not vice-versa, a topic worth further

exploration (Tanner et al., 2002) (for further details please see ref (Morgan et al., 2020)). Despite the differences in fiber type's prevalence occurring with aging and obesity, it is important to note that both are independently associated with muscle atrophy and reduced myogenesis (Morgan et al., 2020).

4.2 Muscle quality

The age-related loss of muscle strength is three times faster than the loss of muscle mass, which has led to extensive efforts exploring mechanisms that underlie the age-related decrease in muscle quality (Bell et al., 2016; Goodpaster et al., 2006; Romanello and Sandri, 2015). Muscle quality has been defined as muscle strength relative to a given quantity of muscle mass in previous studies (Cruz-Jentoft et al., 2019) with muscle strength assessed through distinct methods (e.g., one-repetition maximum, handgrip strength) (Batsis and Villareal, 2018). At the cellular and molecular level, the interplay of a multitude of mechanisms seems to be implicated in the reduction of muscle quality with aging and will be briefly described below.

4.2.1 Lipid infiltration and inflammation—Reduced muscle density due to lipid infiltration occurs with aging and obesity, and correlates with impaired physical function, e.g., decreases in gait speed, balance, and strength across different older populations (Scott et al., 2015; Visser et al., 2005). Lipid infiltrating muscle fibers (intramyocellular) and/or stored in adipocytes situated between fibers (extramyocellular) are associated with reduced improvements in strength and performance in response to resistance exercise in older individuals (Long et al., 2021). In addition, the excess fat may be stored in adipocytes occupying the space between muscles (IMAT) and such ectopic deposition is strongly associated with insulin resistance, disability, hospitalization, and reduced quality of life (Goodpaster et al., 2000; Trombetti et al., 2016; Visser et al., 2005). Muscle fat infiltration is closely related to local inflammation which in turn contributes to muscle wasting (Bell et al., 2016; Wu and Ballantyne, 2017). Furthermore, inflammatory cytokines reduce myocytes response to the insulin-like growth factor 1 (IGF1) hence impairing muscle anabolic pathways (Hamrick, 2017). Although myocytes are capable of secreting inflammatory cytokines (and myokines), obesity-associated local inflammation within the skeletal muscle is mainly attributed to the release of pro-inflammatory cytokines by resident adipocytes, a topic nicely described by Wu and colleagues elsewhere (Wu and Ballantyne, 2017). Similar to that observed in VAT, skeletal muscle immune cells tend to polarize to the pro-inflammatory state in the context of obesity (Wu and Ballantyne, 2017). Importantly, IMAT was associated with circulating monocyte chemoattractant protein 1 (MCP-1, pro-inflammatory cytokine) and with insulin resistance independent of VAT according to a cross-sectional study in women with obesity (Haam et al., 2016). Moreover, 10% weight gain induced by overfeeding in otherwise healthy adults led to a significant remodeling of the skeletal muscle extracellular matrix, local inflammation, and reduced insulin sensitivity, but not to significant alterations in SAT or to systemic inflammation (Tam et al., 2014). Taken together, this evidence points toward the early insult of skeletal muscle health during obesity, which may precede the VAT or SAT impairments resulting from nutrient excess. Notably, thigh muscle loss, and not VAT changes, was the best predictor of mortality in older adults, while thigh fat loss had a protective effect in weight stable individuals (Santanasto

et al., 2017), results that further underline the critical role of skeletal muscle health during aging and obesity.

4.2.2 Proteostasis, mitochondrial function and dynamics—The above-described phenomena result in high states of cellular stress, for which functional protein and organelle quality control mechanisms, able to identify, repair or remove damaged structures are highly needed in the context of aging and obesity (Bell et al., 2016; Cartee et al., 2016; Drey et al., 2013; Egan and Zierath, 2013; Romanello and Sandri, 2015). Among these processes are the autophagy and ubiquitin proteasome systems in which their hyper or hypoactivation cause muscle wasting and cellular malfunction, respectively. For this reason, genes regulating such pathways have been named *atrogens* (atrophy related genes, e.g., *ATG6, MURF1, MAFbx*). Similarly, mitophagy and mitochondrial fusion and fission dynamics are crucial to allow adequate mitochondrial function and respond to oxidative stress (Romanello and Sandri, 2015). A study comparing normal weight and overweight adults revealed a higher expression of autophagy-related genes due to the elevated inflammation and oxidative stress (Potes et al., 2017). Furthermore, young and lifelong trained senior adults displayed similarly lower skeletal muscle *atrogenes* expression compared to sedentary older adults, suggesting not only an increased cellular stress occurring with aging (requiring higher *atrogenes* activation), but also its attenuation through regular physical activity throughout life (Zampieri et al., 2015). Importantly, the age-related muscle atrophy is associated with elevated mitochondrial fission which ultimately leads to the activation of proteolytic pathways (Cartee et al., 2016; Romanello and Sandri, 2015). Such phenomenon is accompanied by reduced mitochondrial content and function and increased oxidative stress, features that characterize adults with obesity (He et al., 2001; Kelley et al., 1999; Morgan et al., 2020). In summary, older adults with obesity require a degree of activation of the above pathways that aging does not support and show blunted adaptation to exercise compared to younger adults (Cartee et al., 2016; Potes et al., 2017).

4.2.3 Neuromuscular junction—The age-related reduction in physical function and activity is also attributed to alterations in the neuromuscular junction function (Badawi and Nishimune, 2020; Batsis and Villareal, 2018; Drey et al., 2013). Based on studies conducted in human cadavers, aging is associated with a gradual loss of cervical and lumbar motor neurons, possibly due to impaired trophic signaling, local degeneration and/or feedback signals from dysfunctional muscle, a topic extensively detailed elsewhere (Badawi and Nishimune, 2020). Muscle denervation is among the numerous age-related events contributing to atrophy and degeneration, a phenomenon detectable by histochemical analyses through the progressive accumulation and clustering of small and angular fibers reflecting what has been called *disseminated neurogenic atrophy* (Badawi and Nishimune, 2020). Nevertheless, the role of neurodegenerative mechanism in the etiology of sarcopenia has only been marginally studied. Additionally, obesity is also associated with neuromuscular junction impairments – partially denervated synaptic sites, reduced synaptic area, abnormal acetylcholine receptors expression and distribution (Martinez-Pena and Akaaboune, 2020). However, only very few studies conducted in animal models are available on the topic, which makes further pre-clinical and clinical research necessary.

A schematic summary of skeletal muscle alterations occurring with obesity and aging is shown in Figure 3.

5. Lifestyle intervention in older adults with obesity

Different exercise or dietary protocols can be employed in the context of lifestyle interventions. Exercise interventions may include *i.* resistance training: exercises that make muscles work against a weight or force (*e.g.*, knee extensions, bench press) consisting of 1-3 sets of 8-12 repetitions performed at 60-80% of 1-repetition maximum for 2-3 days per week; *ii.* aerobic training: exercises that make the heart pump faster (*e.g.*, running, cycling) consisting of 20-60 minutes/session performed at 60-75% of the maximum heart rate for 3-7 days per week; iii. balance training: exercises that emphasize static and dynamic postures (*e.g.*, heel-to-toe walking, standing on one foot) consisting of 1-2 sets for 3-7 days per week {Izquierdo, 2021 #3314}{Aguirre, 2015 #2509} . Different exercise types may be performed in specific combinations and intensities. In our laboratory, we have found that the combination of aerobic and resistance training was the most effective in improving functional status of older adults with obesity while dieting (Villareal 2017a). Dietary interventions to treat obesity often involve calorie restriction necessary to achieve weight loss. The dietary protocol applied in our laboratory, in line with the *Joint Position Statement of the American Society for Nutrition and Obesity Society for Obesity in Older Adults* (Villareal et al., 2005), typically consists of a balanced (approximately 30% of energy as fat, 50% as carbohydrate, and 20% as protein or at least 1.0 g/kg protein/d) energy-restricted (deficit of 500-750 kcal per day) which results in a ~10% weight loss within 6 months (Villareal et al 2005, Villareal et al., 2011a). The dietary intervention is combined with behavioral strategies (*e.g.*, goal setting, self-monitoring) to modify eating habits. Multivitamin and mineral seements are provided to ensure that all daily requirements are met, including 1500 mg Ca/d and 1000 IU vitamin D/d (Villareal et al 2005). Such weight reduction has been associated with a decrease in cardiometabolic risks associated with obesity (Heymsfield and Wadden, 2017, Bouchonville 2014). Other dietary protocols (*e.g.*, intermittent calorie restriction, Mediterranean diet, high protein diet) can be adopted and are currently being studied. In the next section, we refer to the combination of different exercise modalities (aerobic, resistance, and balance) and calorie restriction (energy restriction as described above) unless otherwise specified. A comprehensive analysis of the effect of different dietary protocols on aging muscle has been reported elsewhere (Gielen et al., 2021; Hsu et al., 2019).

5.1 Body composition and frailty outcomes

In 2011, our group demonstrated that the combination of diet-induced weight loss and regular exercise may be the most effective lifestyle intervention for older adults with obesity. Diet plus exercise induces fat mass loss while minimizing weight loss–induced reduction of muscle and bone mass as compared to diet alone or exercise alone (Villareal et al., 2011a). Moreover, among the lifestyle interventions, diet plus exercise resulted in the greatest improvement in physical function and reduction in frailty (Villareal et al., 2011a). Interestingly, in older men with obesity and hypogonadism, the addition of testosterone to such lifestyle strategy results in a relative preservation of lean mass and bone mineral

density, without further improving physical function (Barnouin et al., 2021). In another randomized controlled trial (RCT) in 160 frail, older adults with obesity (*LITOE* study, Figure 4) we demonstrated that the combination of resistance and aerobic exercise during matched diet-induced weight loss leads to the greatest preservation of muscle and bone mass and improvement of physical function as compared aerobic or resistance exercise alone (Armamento-Villareal et al., 2020; Villareal et al., 2017a) (Figure 1B and C). Additionally, the combination exercise added to weight loss in this study population was found to be the most effective in improving ectopic fat deposition (VAT and IMAT) that translated into mitigation of aging- and obesity related physical and metabolic complications (Waters et al., 2021). Based on this evidence, it is recommended that diet-induced weight loss should always be accompanied by both resistance and aerobic training in frail, older adults with obesity, a lifestyle strategy that also results in the greatest improvement in frailty outcomes, muscle strength, and quality of life (Villareal et al., 2017a).

5.2 Adipose tissue dysfunction

Dietary calorie restriction and exercise cause fatty acid mobilization from adipose depots to other tissues which result in a healthier adipokine profiles (Bouchonville et al., 2014; Weiss et al., 2017b). Based on a recent study conducted in 25 older adults, 12 months of resistance training improved muscle strength and mass but did not alter VAT content (Ziegler et al., 2019). In the context of lifestyle interventions, calorie restriction is necessary to allow a significant VAT reduction and to improve cardiometabolic health. Older adults with obesity performing 12 months of diet and exercise, or diet alone, significantly reduced VAT, systemic inflammation, blood pressure and improved insulin sensitivity and lipid profile as compared to controls and to adults performing exercise alone (Bouchonville et al., 2014; Colleluori et al., 2017). Exercise *per se* usually induces only a modest (~2 kg) weight loss (Villareal et al., 2011a); in fact, the volume of exercise needed to achieve a significant weight reduction equivalent to that attained by diet is considerable (Villareal et al., 2006). Interestingly, a trial conducted in healthy, sedentary individuals losing equal ~10% of weight by exercise or calorie restriction demonstrated that exercise-induced weight loss resulted in a greater reduction in VAT and IMAT compared to that achieved by calorie restriction (Murphy et al., 2012), suggesting that physical activity may result in a healthier fat distribution. Furthermore, while insulin sensitivity improvements correlated with VAT reduction in the diet group, they correlated with IMAT loss in the exercise group (Murphy et al., 2012). Myokine secretion from exercising muscle are among the potential mediators for the exercise-induced changes in body composition (Bostrom et al., 2012; Palermo et al., 2015). A recent RCT conducted in adults with obesity demonstrated that the exercise-induced VAT reduction is mediated by the release of IL-6 by skeletal muscle (Wedell-Neergaard et al., 2019). Four months of exercise training reduced the relative content of immune cells and inflammatory characteristics in the SAT of non-obese older women (Cizkova et al., 2020). The same study revealed a reduction in the expression of *HIF1α* and *SOD* markers of hypoxia and oxidative stress respectively, suggesting an overall improvement in the adipose tissue function induced by exercise. Furthermore, based on the assessment performed on SAT explants, trained women exhibited a reduced adipocyte secretion of inflammatory cytokines such as TNF-α and IL-8, but not IL-6, and displayed improved systemic inflammation (Cizkova et al., 2020). Moreover, weight loss is associated

with reduced infiltration of inflammatory cells in the SAT of adults with obesity (Cancello et al., 2005). These results are consistent with another study in severely obese men and women following a lifestyle protocol of calorie restriction and moderate intensity aerobic exercise for 15 weeks (Bruun et al., 2006). The authors reported a significant reduction in systemic and SAT inflammation (macrophages infiltration, cytokines expression and release) which correlated with increasing adiponectin production and improvement in insulin sensitivity (Bruun et al., 2006). Interestingly, based on the results obtained from *vastus lateralis* biopsies, the skeletal muscle did not seem to significantly contribute to the systemic inflammatory status, which was mainly determined by adipose tissue (Bruun et al., 2006). A recent RCT conducted in women with obesity demonstrated that 12 weeks of aerobic plus resistance training led to a significant SAT increase of mitochondrial respiration and reduction of H_2O_2 content (marker of oxidative stress) compared to controls (Mendham et al., 2020). On the other hand, adipocyte hypertrophy occurring with aging was counteracted with calorie restriction based on recent preclinical evidence which showed attenuated adipocyte enlargement and lower decline in thermogenic BAT (Sheng et al., 2021), a finding that requires validation in humans.

5.2 Muscle dysfunction

The independent effects of diet and exercise on MPS in older adults with obesity has been extensively studied (Smith et al., 2012; Villareal et al., 2012; Villareal et al., 2011b). During acute weight loss, the MPS response to anabolic stimuli is greater than during weight maintenance (Villareal et al., 2011b), while exercise increases MPS during both the basal and fed state (Villareal et al., 2012). Our study conducted in a subgroup of participants in the LITOE trial (n:47, Figure 4) demonstrated that MPS response to anabolic stimuli (mixed meal), which is impaired with aging (Volpi et al., 2000), improves more when a resistance exercise component is included during diet-induced weight loss (Colleluori et al., 2019). Similarly, based on the same study, resistance exercise was required to preserve the expression of regulators of muscle regeneration (*MEF2A*), data consistent with the greater preservation of muscle mass reported among individuals performing resistance plus aerobic exercise or resistant exercise alone (Colleluori et al., 2019). Consistent with our results, Snijder and colleagues reported that 12 weeks of resistance exercise combined with aerobic exercise (high intensity interval training) significantly increased type I and II muscle fibers satellite cell content in older adults (Snijders et al., 2019). The increase in type II fiber satellite cells in the study population was associated with an increase in muscle capillarization (Snijders et al., 2019).

Exercise, but not diet, decreases skeletal muscle inflammation in frail older adults with obesity (Lambert et al., 2008). Specifically, the combination of aerobic and resistance exercise during weight loss led to a reduction in the expression of *atrogenes* (*LAMP2*), as well as of mitochondrial (*FIS1, PARL, OPA1*) and inflammatory (*TLR2*, *CD68*) stress markers in the *vastus lateralis* muscle, reflecting an attenuated myocellular stress due to the intervention (Colleluori et al., 2019). On other hand, a recent study conducted on older non-obese adults performing 12 months of resistance exercise (without calorie restriction), reported improvements in muscle strength and mass without alterations in *vastus lateralis* inflammation, suggesting that exercise training without weight loss in non-obese subjects

may have a different effect on muscle health (Ziegler et al., 2019). Diet plus aerobic exercise alone provoked a higher activation not only of mitochondrial function (consistent with higher improvements in VO_2peak), but also of mitophagy and mitochondrial fusion and fission regulators expression (*OPA1, MFF, DRP*) (Colleluori et al., 2019). Although aerobic exercise has been demonstrated to attenuate the decline in mitochondrial respiratory capacity experienced with advancing age (Cartee et al., 2016), it is possible that an elevated activation of the oxidative network in the context of weight loss, aging, and sarcopenia results in muscle mass reduction due to a greater catabolic stimulation (Colleluori et al., 2019). The described data provide a mechanistic explanation for the observed positive changes in body composition and frailty outcomes in the LITOE trial – participants performing the combination of aerobic and resistance exercise preserved the most muscle mass and experienced the greatest increase in physical function and muscle strength (Colleluori et al., 2019; Villareal et al., 2017a). The LITOE substudy could not detect variations in neuromuscular junction integrity as assessed by the measurements of circulating C-terminal agrin fragment (Montagnani et al.), which was demonstrated to be a reliable marker of neuromuscular junction degeneration and sarcopenia, elevated among older adults (Drey et al., 2013). Such finding is consistent with the results from the LIFE-P trail conducted on over 300 elderly undergoing exercise intervention (Bondoc et al., 2015). However, two recent smaller studies detected a significant reduction in circulating CAF among adults following different exercise interventions (Bigdeli et al., 2020; Willoughby et al., 2020). Furthermore, older adults practicing long-term high-level exercise were reported to experience lower loss of muscle strength, fewer denervated fiber, and preserved otherwise lost fibers compared to their sedentary counterparts assessed by histomorphology (Mosole et al., 2014). Accordingly, it is possible that the functional decline in the neuromuscular junction occurring with aging can be prevented with regular exercise practiced throughout life (Mosole et al., 2014).

A schematic representation of the effect of lifestyle intervention on myocellular function of the aging muscle is shown in Figure 5

6. Conclusions and future perspectives

The combination of aerobic and resistance exercise added to diet-induced weight loss significantly improves physical function and ameliorates frailty in older adults with obesity. Among the lifestyle interventions, this may be the most effective in improving myocellular quality and MPS response to anabolic stimuli thereby preserving muscle mass during dietary calorie restriction. Such lifestyle intervention can thus be considered an effective strategy to mitigate aging- and obesity-related metabolic and physical complications, with the ultimate goal to maintain the functional independence and quality of life of older adults with obesity. Therefore, healthcare providers should consider prescribing both resistance and aerobic exercise to counteract sarcopenic obesity, one of the major health care challenges of this century affecting an increasing proportion of older adults. Additional studies should be performed to further explore mechanisms as the bases for such clinical outcomes, with a particular focus on muscle-adipose tissue crosstalk in the context of exercise and weight loss.

Acknowledgment:

We thank Professor Saverio Cinti from Marche Polytechnic University for providing muscle samples shown in figure 2.

Funding:

This work was supported by the National Institutes of Health (R01-AG031176, RO1-DK109950) and the US Department of Veterans Affairs (101 CX00906 and CX002161). The contents do not represent the view of the United States Government or the US Department of Veterans Affairs.

Abbreviations:

SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue
DXA	dual x-ray absorptiometry
MRI	magnetic resonance imaging
CT	computed tomography
IMAT	intermuscular adipose tissue
MPS	muscle protein synthesis

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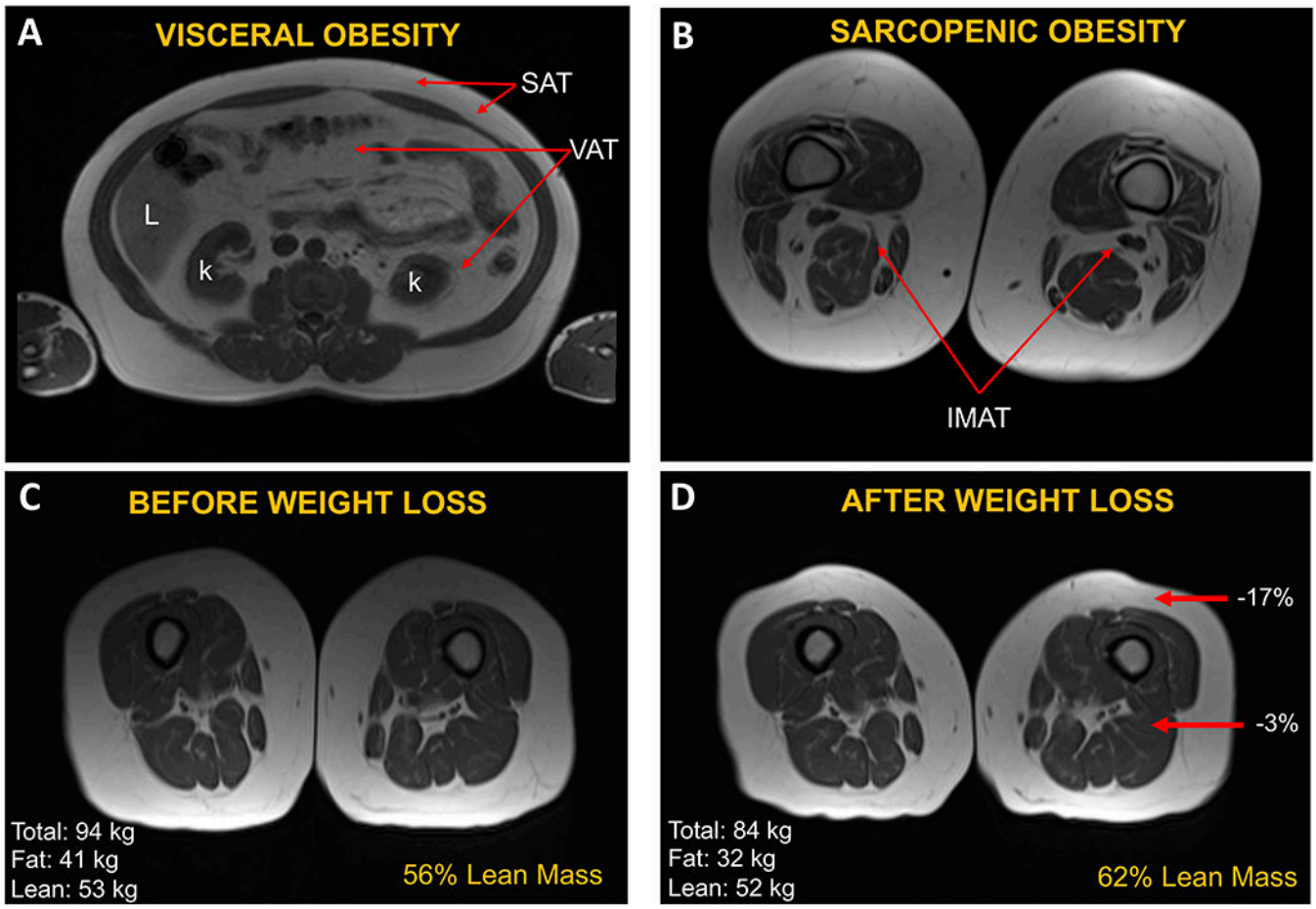

Figure 1: Skeletal muscle and adipose tissue in older adults suffering from obesity by MRI.

A. Abdominal MRI of an older adult with obesity; arrows indicate SAT: subcutaneous adipose tissue and VAT: visceral adipose tissue; L: liver; k: kidney. B. Thigh MRI of an older adult with obesity; arrows indicate intermuscular adipose tissue (IMAT). Thigh MRI of an older adult with obesity before (C) and after (D) diet-induced weight loss plus combined aerobic and resistance exercise training (6 months intervention). Total mass, fat mass and lean mass data refer to whole body composition assessed by dual energy x-ray absorptiometry.

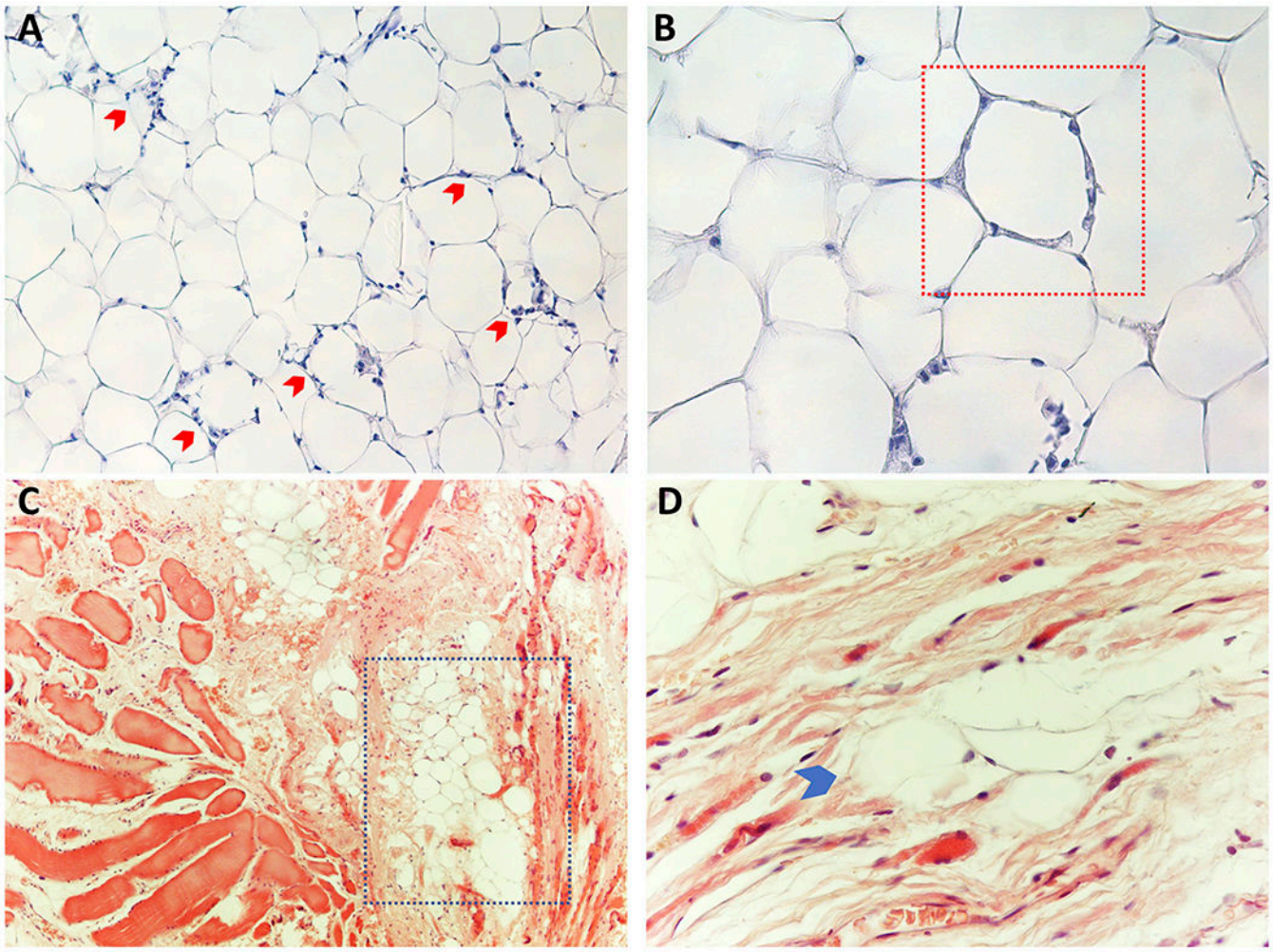

Figure 2: Adipose tissue and muscle dysfunction in obesity and aging

A and B (hematoxylin staining): light microscopy of visceral adipose tissue belonging to a 71-year-old woman with central obesity. A: elevated infiltration of inflammatory cells (partly indicated by arrowheads) often forming crown-like structures surrounding adipocytes; (20x magnification). B: squared area indicates an example of crown-like structure (40x magnification). C and D (hematoxylin and eosin staining): fat infiltration within the *erector spinae* muscle of an older adult; adipocytes infiltration indicated in the squared area in C (10x magnification); D (40x magnification) shows adipocytes infiltration within atrophic fibers (arrowhead) in the same subject.

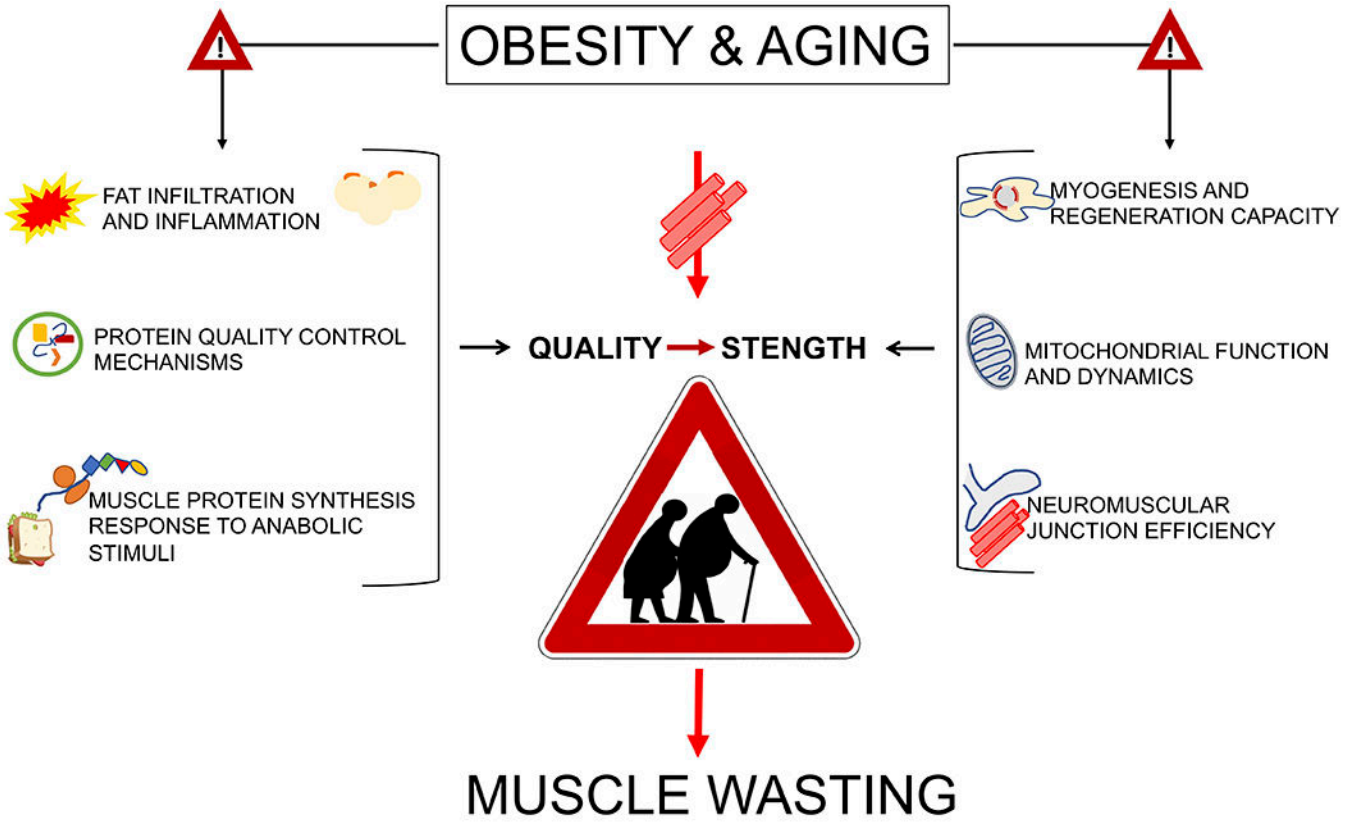

Figure 3: Schematic representation of skeletal muscle alterations occurring with obesity and aging.

Fat infiltration and inflammation; anomalies in protein quality control mechanisms (e.g., autophagy and ubiquitin proteosome system function); reduced muscle protein synthesis in response to anabolic stimuli (i.e., exercise, food ingestion); reduced myogenesis and muscle regeneration capacity; alterations in mitochondrial function and dynamics (e.g., mitophagy, fission and fusion) and in neuromuscular junction efficiency. All these processes are strictly associated with reduced muscle quality and strength, ultimately resulting in muscle wasting, disability and impaired physical function (frailty).

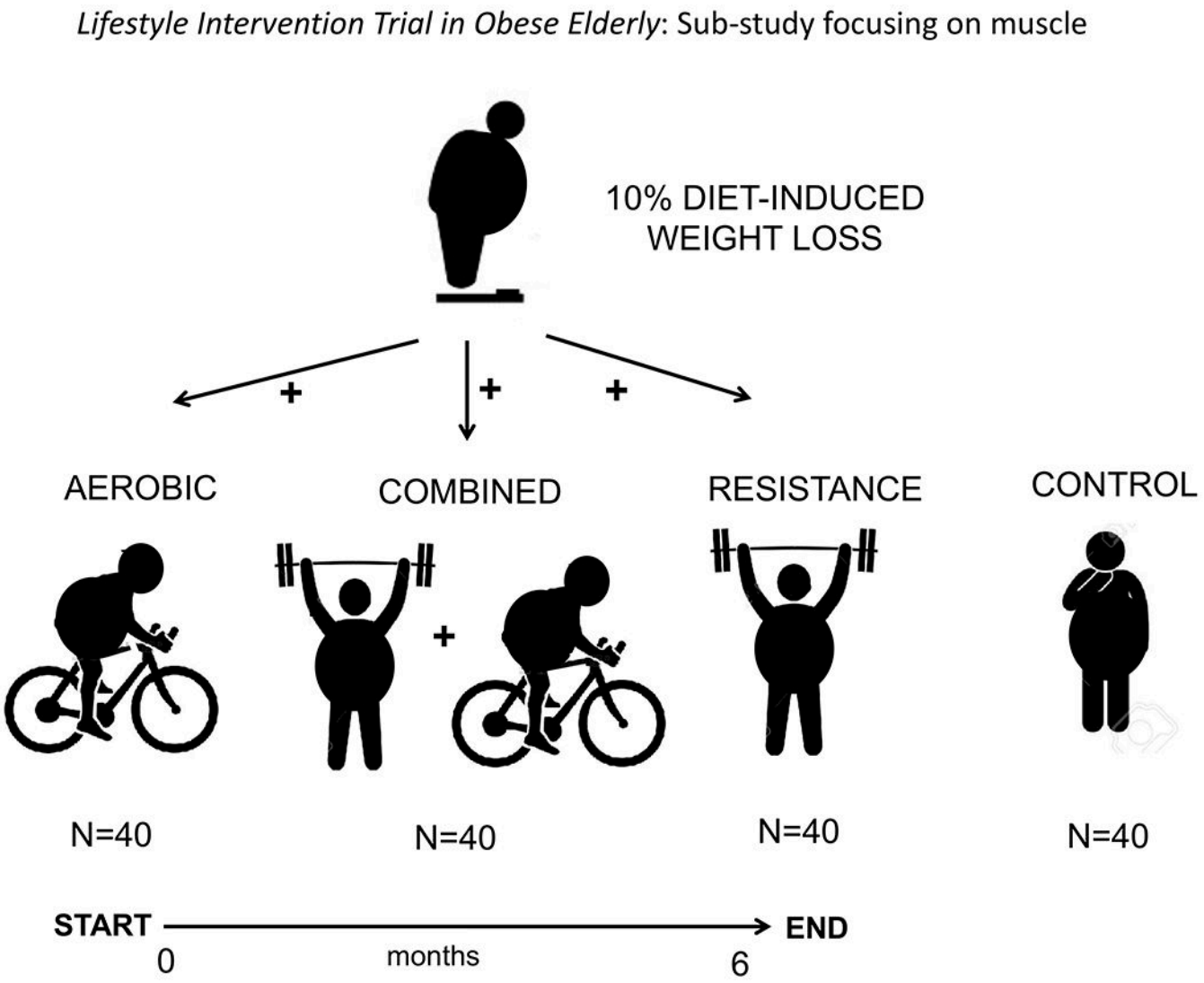

Figure 4: Schematic representation of the Lifestyle Intervention Trial in Elderly Obese (LITOE).
A total of 160 of older men and women (≥65 years of age) with obesity (BMI≥30 kg/m^2) and frailty were randomized to diet-induced weight loss plus either aerobic, resistance or the combination of both exercise modalities for 6 months. A fourth set of subjects was included in the control group who did not undergo diet or exercise intervention but received educational classes on a healthy lifestyle. Forty-seven subjects from the LITOE trial participated in the muscle sub-study and underwent *vastus lateralis* biopsies to investigate muscle protein synthesis response to anabolic stimuli (meal ingestion) and myocellular quality. The study was completed at the end of 2018 (LITOE ClinicalTrials.gov number, NCT01065636).

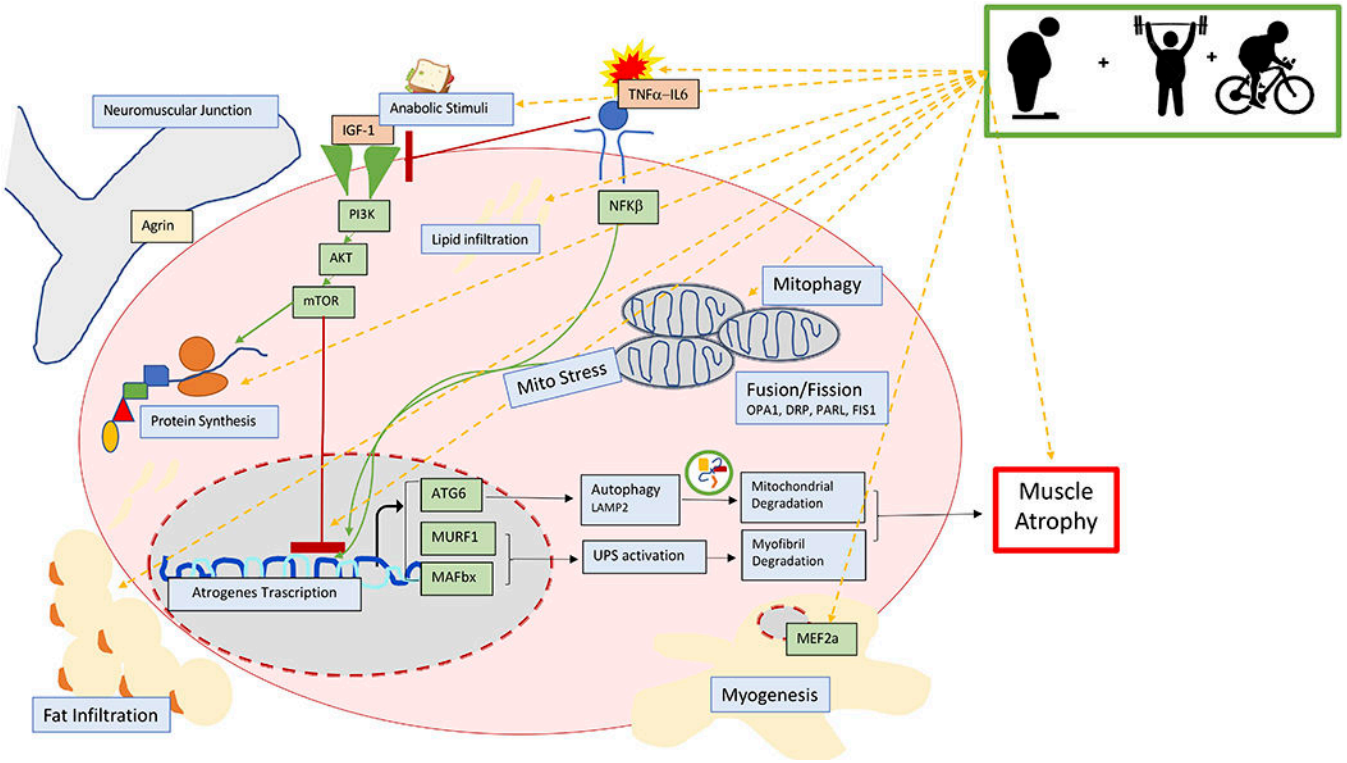

Figure 5: Pathways involved in the age- and obesity- related muscle dysfunction, affected by weight loss plus aerobic and resistance exercise.

Aging and obesity are characterized by muscle lipids infiltration and a state of chronic, low-grade inflammation, e.g., higher circulating IL-6 and TNF-α. Inflammation contributes to muscle wasting impairing i) the anabolic action of the IGF1-mTOR pathway and muscle protein synthesis response to anabolic stimuli (already lower in older adults) and ii) promoting the expression of *atrogenes* such as regulators of autophagy and ubiquitin proteosome system (Napoli et al.). On the other side, mitochondrial stress, reflected by mitophagy and mitochondrial fission hyperactivation, also contributes to *atrogenes* transcription and muscle wasting. The age-related muscle atrophy is also due to an impairment in neuromuscular junction efficiency and reduced myogenesis capacity. Based on the *LITOE* sub-study, diet-induced weight loss plus resistance and aerobic exercise training reduces myocellular stress affecting all those pathways (except for neuromuscular junction efficiency assessed measuring circulating C-terminal Agrin fragment) and results in improvement in muscle protein synthesis in response to feeding, muscle strength, physical function and attenuated muscle wasting. Red lines indicate inhibition, green arrows activation, black arrows major pathways activation, while yellow dotted arrows refer to pathways on which diet plus resistance and aerobic exercise have a positive effect.