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Models of Accelerated Sarcopenia: Critical Pieces for Solving the Puzzle of Age-Related Muscle Atrophy

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Abstract

Sarcopenia, the age-related loss of skeletal muscle mass, is a significant public health concern that continues to grow in relevance as the population ages. Certain conditions have the strong potential to coincide with sarcopenia to accelerate the progression of muscle atrophy in older adults. Among these conditions are co-morbid diseases common to older individuals such as cancer, kidney disease, diabetes, and peripheral artery disease. Furthermore, behaviors such as poor nutrition and physical inactivity are well-known to contribute to sarcopenia development. However, we argue that these behaviors are not inherent to the development of sarcopenia but rather accelerate its progression. In the present review, we discuss how these factors affect systemic and cellular mechanisms that contribute to skeletal muscle atrophy. In addition, we describe gaps in the literature concerning the role of these factors in accelerating sarcopenia progression. Elucidating biochemical pathways related to accelerated muscle atrophy may allow for improved discovery of therapeutic treatments related to sarcopenia.

Keywords

Aging; Proteolysis; Satellite Cells; HIV; COPD; Disability

1. Introduction

Sarcopenia, the age-related loss of muscle mass and quality, is a major healthcare concern for older adults (Figure 1). The condition is associated with the development of functional disability (Janssen et al., 2004; Visser et al., 2005) and may lead to the loss of independence for afflicted individuals. Because of the costs associated with caring for an individual with compromised function, sarcopenia has been linked to elevated healthcare costs (Janssen et al., 2004). Moreover, the absolute costs associated with sarcopenia are likely to rise sharply in the coming decades considering that the total number of persons over 65 yr is expected to double over the next 25 years (Federal Interagency Forum on Aging-Related Statistics, 2009). Hence, additional knowledge of mechanisms underlying sarcopenia development is necessary to advance prevention and treatment efforts that will improve the quality of life for millions of older adults.

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1.2 Need for a Standardized Definition

Currently, clinical awareness of the signs and consequences of sarcopenia is lacking. This problem stems, at least partially, from the absence of an established clinical definition of sarcopenia (Visser, 2009) which precludes medical diagnosis of the condition. Without a definition, the ability of physicians to recognize and appropriately treat sarcopenia will remain poor. Previously, this same challenge faced clinicians treating patients with cachexia (Evans et al., 2008). In addition to these clinical difficulties, the absence of a universally-accepted definition of sarcopenia creates challenges for investigators studying the underlying causes of the condition. Presently, scientists disagree on whether sarcopenia refers only to age-related muscle atrophy as it was originally proposed (Roubenoff and Hughes, 2000), or whether muscle function-i.e. strength and endurance-should be included as part of the definition (Clark and Manini, 2008; Visser, 2009). Muscle function is clearly the critical step that links sarcopenia to functional disability (Clark and Manini, 2010), but the degree to which remains unclear. Not intending to disregard the importance of muscle function, the aim of the current article is to describe age-related changes in skeletal muscle size and the role of co-morbid conditions.

1.3 Consequences of Sarcopenia

Individuals tend to lose muscle mass at a rate of 1-2% per year after the age of 50 years (Lauretani et al., 2003)(Hiona and Leeuwenburgh, 2008; Marcell, 2003). This decline is primarily due to the progressive atrophy and loss of type II muscle fibers and motor neurons (Larsson et al., 1978; Tomlinson et al., 1973). However, other morphological changes occur during the atrophy process including increased variability in fiber size, accumulation of non-grouping, scattered and angulated fibers, expansion of extracellular space, and deposition of protein aggregates within the interstitial matrix (Kim et al., 2008). These morphological changes occur in conjunction with increased infiltration of non-contractile material such as adipose and connective tissues (Brooks and Faulkner, 1994; Goldspink et al., 1994; Goodpaster et al., 2008; McNeil et al., 2005; Petersen et al., 2003). These changes contribute to declines in functional capacity of the muscle that contribute to functional disability (Evans, 1997; Janssen et al., 2002; Muhlberg and Sieber, 2004; Rolland et al., 2008; Visser et al., 2005).

While impaired locomotion is certainly the hallmark concern of sarcopenia, muscle atrophy may impair other physiological functions including glucose regulation, hormone production, and cellular communication. Moreover, muscle tissue provides the body's only major “reserve” of readily available amino acids. Thus, inadequate muscle mass prior to the onset of a disease condition may be dangerous in patients who need a large protein reservoir to recover. As a result, patients with sarcopenia prior to disease diagnosis may face impaired recovery from surgery (Rutan and Herndon, 1990; Watters et al., 1993) or increased risk of mortality (Prado et al., 2009). Still, while contributions of sarcopenia to functional impairments are well-documented, data regarding the importance of skeletal muscle in the recovery from life-threatening situations, such as severe burns or traumatic surgeries, are few. Like a standardized definition, further study of the clinical impact of sarcopenia in these stressful situations could improve physician awareness of the problem.

2. Potential Mechanistic Triggers of Sarcopenia

Developing treatments for sarcopenia is also complicated by the large number of contributing mechanistic factors. Age-related changes in both systemic and cellular properties contribute to loss of organelles, cytoplasmic contents, and protein from skeletal muscle. The loss of these critical myocyte components results in either atrophy or complete fiber loss. Age-related changes in these contributing factors are numerous and include,

among others, increases in oxidative stress and pro-inflammatory cytokine production and decreases in production of anabolic hormones such as testosterone. These changes ultimately trigger cellular changes to the myocyte. Among the cellular mechanisms commonly proposed to be involved in the onset and progression of sarcopenia are myocyte apoptotic signaling (Marzetti et al., 2008b), altered protein synthesis and/or turnover (Combaret et al., 2009), and impaired satellite cell (SC) function (Hepple, 2006) Further complexity is added to this discussion by the number of upstream factors that may affect each of these specific mechanisms. For example, proteolytic signaling may be stimulated by a number of factors including catabolic hormones (Ma et al., 2003), pro-inflammatory cytokines (Li and Reid, 2000; Tsujinaka et al., 1996), or denervation (Sacheck et al., 2007). Moreover, ubiquitin-proteasome system (UPS) upstream factors can modulate multiple regulatory pathways. For example, tumor necrosis factor alpha (TNFα) can either stimulate proteolysis through the UPS or induce apoptosis via the death-receptor pathway. A comprehensive review of all of these systemic factors is beyond the scope of the present review. Here we briefly describe three cellular mechanisms commonly implicated in the development of sarcopenia.

2.1 Myonuclear apoptosis

Several reports indicate that enhanced activation of apoptosis takes place in aged skeletal muscle, likely contributing to the development of sarcopenia (reviewed in Marzetti and Leeuwenburgh, 2006). Apoptosis is an evolutionary conserved process of programmed cell death, which is performed via a systematic set of morphological and biochemical events, resulting in cellular self-destruction without inflammation or damage to the surrounding tissue (Kerr et al., 1972). Execution of apoptosis in skeletal muscle displays unique features due to the multinucleated nature of myofibers. Therefore, apoptosis in myocytes may result in the elimination of individual myonuclei and the surrounding portion of sarcoplasm, without the dismantling of the entire fiber (reviewed in Dupont-Versteegden, 2005). Thus apoptosis is a necessary process for eliminating non-viable muscle tissue, however the process may be damaging if unregulated.

The mitochondrion is considered the main site for the integration of apoptotic signaling and can induce apoptosis via multiple pathways (Wenz et al., 2009). Therefore, an intimate link exists between mitochondrial damage and apoptotic cell death, which may be particularly relevant at old age (Marzetti et al., 2009b). In fact, when an event occurs that compromises the integrity and proper functioning of mitochondria, several apoptogenic factors stored in the mitochondrial intermembrane space are released and initiate the series of events that culminate in cell destruction.

Aside from mitochondria-mediated apoptosis, other pathways of myonuclear apoptosis may be involved at advanced age. In particular, the death receptor-mediated pathway, triggered by TNFα, appears to be upregulated in aged rodent muscles (Marzetti et al., 2008a; Marzetti et al., 2009a; Phillips and Leeuwenburgh, 2005; Pistilli et al., 2006). Furthermore, TNFα signaling can induce protein breakdown in skeletal myocytes (Li et al., 1998), via activation of the ubiquitin-proteasome pathway (Llovera et al., 1997). The temporal relation between the initiation of apoptosis and the induction of proteolysis as well as the relative magnitude of the two processes during age-related muscle wasting is still unclear. However, recent data suggest that apoptotic signaling is required for and precedes protein degradation during muscle atrophy (Argiles et al., 2008).

Although a definite mechanistic link between myonuclear apoptosis and sarcopenia is un-established, data from animal models suggest this link exists (Baker and Hepple, 2006; Marzetti et al., 2008c). Moreover, other rodent studies report an association between myocyte apoptosis and declines in muscle mass and strength (reviewed in Marzetti et al.,

2008b). Despite the fact that most studies in animal models appear to support a key role for apoptosis in age-related muscle atrophy, evidence in humans is still scarce. As a result, to date only three reports have been published examining the occurrence and severity of myocyte apoptosis in healthy elderly humans (Malmgren et al., 2001; Park et al., 2009b; Whitman et al., 2005). In fact, a recent report indicated increases in the expression of the mitochondrial caspase-independent mediator apoptosis inducing factor (AIF) in semitendinosus muscle of middle-aged men relative to younger controls (Park et al., 2009b). This finding is consistent with previously described data from animal experiments and supports the involvement of mitochondria-driven apoptosis in sarcopenia development. However, continued study in this area is needed before a definitive role for nuclear apoptosis can be declared in the development of human sarcopenia.

2.2 Alterations in muscle protein turnover

Loss of muscle proteins, resulting from an imbalance between protein synthesis and breakdown, appears to be a contributing factor to sarcopenia (Combaret et al., 2009). While muscular protein synthesis may not be impaired at old age in the basal state (Volpi et al., 2001), the postprandial response to anabolic stimuli, including insulin, is blunted in muscles of elderly persons (Cuthbertson et al., 2005; Fujita et al., 2009; Guillet et al., 2004). Researchers have attributed this defect to an age-related state of insulin resistance (Guillet et al., 2004), independent of diabetes mellitus (DM), and to reduced or slowed responsiveness of the aged muscle to the stimulatory effect of amino acids (Drummond et al., 2008; Wolfe, 2006). Additionally, low-grade chronic inflammation, which is highly prevalent among older persons, may also directly impair protein synthesis (Balage et al., 2009). This hypothesis is substantiated by the restoration of postprandial muscle anabolism in old rats treated with the non steroidal anti-inflammatory drug ibuprofen (Rieu et al., 2009). In fact, in the ibuprofen treated group, significant decreases in circulating levels of fibrinogen, IL6, and IL1β were accompanied by a 24.8% increase in muscle protein synthesis (Rieu et al., 2009).

Notably, pro-inflammatory cytokines, in particular TNFα, are potent stimulators of muscle proteolysis via activation of the UPS (Llovera et al., 1997). This pathway is responsible for the bulk of muscle proteolysis and is initiated by the repeated covalent binding of 76-amino acid ubiquitin monomers to proteins targeted for degradation. Ubiquinated proteins are subsequently transferred into a large proteolytic complex, the proteasome, where hydrolysis takes place. Existing data are unclear whether proteasome activity and function are decreased or increased in aged muscle. Nonetheless, evidence suggests that the activation and regulation of the ubiquitin-proteasome pathway may be altered with age (Combaret et al., 2005). Clavel and colleagues (2006) reported that expression of muscle-specific ubiquitin ligases atrogin1/MAFbx and MuRF-1 is upregulated in the tibialis anterior muscle of old rats, concomitant with increased TNFα mRNA abundance. Similarly, protein levels of MuRF1 and atrogin1/MAFbx as well as the proteasome chymotrypsin-like activity are reportedly increased with aging (Hepple et al., 2008).

In addition to pro-inflammatory cytokines, glucocorticoids (GCs) are potent triggers of muscular protein catabolism. For example, cortisol antagonizes the IGF1/insulin-stimulated pathways, blocks production of IGF1, and upregulates proteolysis via the ubiquitin-proteolytic, lysosomal, and calpain systems (Schakman et al., 2008). Although a comprehensive understanding of how GCs upregulate proteolysis is undetermined, researchers have shown that GCs are capable of inducing atrogin1/MAFbx and MURF1 expression via increases in FoxO transcription factors (Imae et al., 2003; Sacheck et al., 2004; Sandri et al., 2004). In addition, GCs appear to inhibit synthesis of myofibrillar proteins (Sacheck et al., 2004). In support of the involvement of GCs in sarcopenia, recent

data indicate that sarcopenic individuals have elevated cortisol levels compared to healthy adults (Waters et al., 2008).

While the UPS is responsible for the degradation of the majority of denatured proteins, another cellular quality control mechanism, autophagy, exists that may contribute to sarcopenia in aged muscle. Autophagy, or cellular "self-eating", is responsible for the degradation of surface membrane proteins and endocytosed, extracellular proteins in skeletal muscle (Lecker et al., 1999). Importantly, autophagy is the only mechanism so far described capable of degrading cellular organelles such as damaged mitochondria (Lemasters, 2005). In addition, protein aggregates are removed by autophagic pathways when the UPS fails. Autophagic function declines during normal aging (Cuervo and Dice, 2000; Cuervo et al., 2005; Donati et al., 2001), which may result in accumulation of lipofuscin, protein aggregates and damaged mitochondria (Terman and Brunk, 2006). In contrast, two recent studies revealed a mechanistic link between skeletal muscle atrophy and increased autophagy through the activation of the transcription factor FoxO3 and its downstream targets (Mammucari et al., 2007; Zhao et al., 2007). Hence, further research is needed to understand how changes in autophagic function intervene in the pathogenesis of sarcopenia.

2.3 Impaired SC function and regeneration

Muscle's ability to repair and regenerate itself, through SC commitment to myogenic lineage, is another critical component in the maintenance of mass and function. Adult myofibers are terminally differentiated, post-mitotic cells partially maintained by resident SCs that fuse with damaged muscle fibers to regenerate myonuclei. These cells are located between the basal lamina and the sarcolemma and are required for the regeneration and hypertrophy of myocytes. In response to physiological or pathological stimuli, SCs are activated, proliferate and subsequently fuse to existing muscle fibers and/or to one another, forming myotubes and eventually mature myocytes (Schultz and McCormick, 1994). Studies in experimental animals showed age-dependent decreases in SC number and proliferative capacity (Gibson and Schultz, 1983; Schultz and Lipton, 1982). Similarly, researchers reported reduced SC number in older persons compared to younger individuals (Kadi et al., 2004). Interestingly, this reduction appears to preferentially affect type II fibers (Verdijk et al., 2007), thus providing a further explanation for the higher degree of age-related atrophy suffered by fast-twitch muscles.

The mechanisms underlying the age-dependent decline in SC number and proliferative capacity are incompletely understood. One hypothesis is that impaired proliferative potential of SCs is largely due to replicative senescence (Jejurikar and Kuzon, 2003). However, this mechanism may not be relevant to human sarcopenia, since the proliferative potential of SCs remains substantially stable over time after childhood (Renault et al., 2000). Alternatively, SCs isolated from skeletal muscle of old rats exhibited decreased differentiation as well as reduced expression of myosin heavy chain and creatine kinase compared to SCs from young animals (Lees et al., 2006). Moreover, cultured aged SCs give rise to less organized and more fragile myotubes (Renault et al., 2000). In addition, SCs from old rats display a greater susceptibility to apoptosis than those from young rodents (Jejurikar et al., 2006). As a whole, these data suggest that defects intrinsic to aged SCs may contribute to their reduced functionality at old age.

However, results from muscle cross-transplantation between young and old rats suggest that factors related to the host environment may also influence SC function (Carlson and Faulkner, 1989). Indeed, the regenerative capacity of old hind limb muscles transplanted into young recipients was not different from that of young muscles grafted into same-age hosts. In contrast, young muscles transplanted into old hosts failed to display greater regenerative capacity than old muscles grafted into same-age recipients. Additional support

for the importance of the external SC environment is provided by data from models of heterochronic parabiosis, the joining of two animals of differing ages to share a single circulatory system (Brack et al., 2007; Conboy et al., 2003). These studies demonstrated that satellite cells from old animals tend to convert from a myogenic to a fibrogenic lineage as they begin to proliferate. More importantly, these changes were mediated by changes in systemic factors, including decreased activation of Notch signaling (Conboy et al., 2005) and excessive WNT signaling (Brack et al., 2007). Upon exposure of older muscle to a young circulatory system, the fibrogenic fate of old SCs was reversed (Brack et al., 2007; Conboy et al., 2005). Thus, the external cellular environment appears to play an important role in age-related changes to SC regenerative capacity. Although the entire milieu of systemic changes affecting satellite cell function is not completely delineated, the reduced production of anabolic hormones such as IGF1 and testosterone is known to be a key factor (Musaro et al., 2007; Nnodim, 2001; Severgnini et al., 1999; Sinha-Hikim et al., 2003). Recent work in this area has suggested that a spliced variant of IGF1, known as mechano-growth factor, may also play a critical role in satellite cell proliferation (Hill and Goldspink, 2003; Hill et al., 2003). However, many questions remain in regard to this hypothesis (Matheny et al., 2010). Continued research concerning these systemic changes is critical to developing therapeutic treatments for sarcopenia that target satellite cells.

3. A Changing Paradigm

To date, research regarding sarcopenia has largely focused on investigating biological changes that are directly attributable to chronological aging without completely considering the co-occurrence of lifestyle and disease conditions that are also likely to affect the progression of sarcopenia. Previous sarcopenia-related research has predominantly involved otherwise healthy older adults, likely to ensure tight research designs. Meanwhile, sarcopenia also occurs in the large number of older adults afflicted with co-morbid conditions. In fact, these individuals will likely suffer most from the detrimental effects of sarcopenia. Therefore, the primary aim of the present review is to provide a framework that defines the etiology of sarcopenia while taking into account factors other than chronological age.

We review here extensive evidence demonstrating that unhealthy lifestyle and/or the presence of chronic diseases are capable of accelerating muscle loss in middle-aged and older adults. Because elevated risk of co-morbid diseases and behavioral factors such as sedentary lifestyle are established phenomena in older individuals, we suggest that these factors should be increasingly recognized and independently accounted for in the study of sarcopenia. Within this review, we will discuss a number of diseases and behavioral conditions that can theoretically accelerate the progression of sarcopenia (Figure 2). The secondary purpose of such discussion is to highlight specific areas where further research is needed to enhance understanding of the interactions between age and factors that may accelerate sarcopenia. A review of such topics does not exist, however such an approach is necessary to develop working models of accelerated sarcopenia that may enhance study and treatment of the condition. As such, we believe that these models of accelerated models are critical to solving the puzzle that currently faces investigators researching sarcopenia.

4. Behavior-mediated pathways

Chronological aging and genetics, significant contributors to the onset and progression of sarcopenia, are beyond human control and are therefore considered non-modifiable risk factors for sarcopenia. However, humans often contribute to sarcopenia progression and/or disease development through lifestyle choices. A wealth of data exist which demonstrate beneficial effects of exercise or nutritional interventions to functioning of older individuals

(Goodpaster et al., 2008; Kalapotharakos et al., 2007; Manini and Pahor, 2009; Sugawara et al., 2002). Yet many older adults make poor dietary choices and engage in inadequate amounts of physical activity. In the U.S., approximately 80% of individuals over the age of 65 years do not engage in regular physical activity (Federal Interagency Forum on Aging-Related Statistics, 2009). Furthermore, 88% do not perform muscle strengthening exercises, known to provide many beneficial effects to skeletal muscle. Meanwhile, the US Department of Agriculture's Healthy Eating Index indicates that approximately 80% of older individuals could benefit from improvements in their diet including increased protein and fiber intake and decreased consumption of saturated fats (Federal Interagency Forum on Aging-Related Statistics, 2009). Although some degree of sarcopenia is unavoidable in all older adults, poor dietary and physical activity choices might compound the problem (Buford et al., 2010).

4.1 Physical inactivity

Exercise training is one of the simplest, most feasible, and inexpensive strategies available to combat the onset of sarcopenia and reduce the rate of functional decline. Although protein degradation is often accelerated in sedentary older adults, the neuromuscular system of these individuals retains a tremendous ability to adapt in response to heavy loading (reviewed in Narici et al., 2004). Experimentally-based studies support a dose-dependent increase in lean mass and physical function as a result of acute resistance exercise (He and Baker, 2004; Hillsdon et al., 2005; Leveille et al., 1999; Manini and Pahor, 2009). Resistance exercise provides a host of physiological benefits to muscle including, but not limited to, reduced inflammation (Greiwe et al., 2001), increased mitochondrial function (Melov et al., 2007), improved myogenic signaling (Kosek et al., 2006), and SC activity (Mackey et al., 2007). Even adults who are sedentary into their 80's demonstrate a sharp increase in muscle mass and strength following short-term resistance training (Fiatarone et al., 1994). Incredibly, these results occur with nominal time commitment as data indicate maintenance of muscle strength with one day of strength-building per week (Trappe et al., 2002). Recent studies have also indicated that aerobically-focused training programs are capable of preserving muscle mass in older adults (Chomentowski et al., 2009; Goodpaster et al., 2008). Aerobic exercise provides physiological benefits that conserve muscle mass through improved muscle blood flow (Currie et al., 2009), decreased oxidative stress (Bloomer et al., 2005), and decreased GC sensitivity (Duclos et al., 2001). These studies indicate that short-term exercise training can either increase muscle mass or delay its decline in older adults.

The extent to which chronic training contributes to the prevention of sarcopenia is not clearly delineated. To date no conclusive data are available to determine if chronic training attenuates the progression of sarcopenia or simply provides an upward shift in the amount and quality of muscle with a similar rate of decline over time (Figure 3). The best attempts to understand the effects of chronic training on muscle changes have studied master athletes. These athletes are the most physically-active older adults and provide a unique opportunity to study the potential benefits of regular exercise on the prevention of sarcopenia (Hawkins et al., 2003). Master athletes appear to have greater muscle strength and power than their sedentary peers (Pearson et al., 2002). However, despite regular and typically life-long training, these athletes experienced age-related declines similar to sedentary controls for both peak power (1.3% vs. 1.2%) and force (0.6% vs. 0.5%) (Pearson et al., 2002). These data suggest that training may not be sufficient to alter the trajectory of skeletal muscle loss in older adults. Unfortunately, no longitudinal data exist to directly compare age-related changes in muscle mass or myofiber number between sedentary individuals and master athletes. This information is critical to determining if chronic training can alter the rate of muscle loss in older adults or simply adjust the starting point.

In addition to questions concerning the effectiveness of exercise in combating sarcopenia, a pertinent question in the context of the present review is if sedentary lifestyle accelerates the loss of skeletal muscle mass in older adults. For over a quarter century, experts have differed in opinions regarding the contribution of a sedentary lifestyle age-related muscle loss (reviewed in Faulkner et al., 2007). These differences in opinion are not surprising given inherent difficulties understanding the heterogeneity of physical activity patterns across the lifespan as well as challenges in measuring free-living activity. These challenges can be addressed through the development and standardization of assessment techniques for physical activity and the energy expended during such activity. Recently, Manini and colleagues (Manini et al., 2009) utilized the doubly-labeled water technique to measure energy expenditure during free-living activity in older adults. Participants were placed into equal thirds based on energy expended due to physical activity, and individuals in the highest third of daily activity energy expenditure had the greatest amount of lean mass. However, the rate of muscle loss in these individuals over five years was very similar to those in the lowest third of free-living activity. These data suggest that physical inactivity may not *directly* accelerate the trajectory of sarcopenia. However, a sedentary lifestyle certainly adds to the risk of numerous pathological conditions (Arsenault et al., 2009; Venables and Jeukendrup, 2009; White et al., 2009), many of which do appear to accelerate sarcopenia progression (discussed below).

4.2 Under-nutrition and Obesity

A proper diet is critically important to slowing sarcopenia progression, as well as in maintaining overall healthy aging (Houston et al., 2008; Paddon-Jones and Rasmussen, 2009). Traditional discussions of dietary importance in sarcopenia focused on inadequate intake and the frail phenotype. Insufficient caloric intake, also known as the anorexia of aging (Morley et al., 2005), may lead to the development of sarcopenia through a lack of amino acid availability and subsequent decreases in muscle protein synthesis (Friedman et al., 1985; Waters et al., 2003). In addition, older individuals suffering from protein energy malnutrition (PEM) are unlikely to gain muscle mass and strength while engaging in resistance training (Rolland et al., 2008). PEM may also severely compromise quality of life and the ability to thrive, especially when combined with co-morbid diseases (Vetta et al., 1999).

As a result, insufficient protein intake appears to be a critical factor for sarcopenia development in older adults. Recent data indicate that lean mass in older adults is significantly and positively associated with dietary protein intake (Houston et al., 2008). Over the course of three years, the individuals who consumed more than the recommended dietary allowance (RDA) for protein of 0.8 g/kg/day experienced the smallest losses of lean mass (Houston et al., 2008). In contrast, persons who experienced the most significant muscle atrophy consumed protein in quantities either at or below the RDA. This study is significant because it adds to a growing body of literature suggesting that the current RDA for protein intake may not be adequate to maintain optimal skeletal muscle health in older adults (Evans et al., 2008; Look AHEAD Research Group et al., 2007; Morais et al., 2006; Sood et al., 2008).

The timing and type of protein intake by older adults may be critical to maintenance of muscle mass. Reports indicate that ageing does not reduce muscle protein synthesis in response to a high-protein (25-30 g) meal (Paddon-Jones and Rasmussen, 2009; Volpi et al., 2001). However, protein synthesis declines in the elderly when meals contain less protein or are ingested in conjunction with carbohydrates (reviewed in Paddon-Jones and Rasmussen, 2009). Subsequently, Paddon-Jones and Rasmussen (2009) suggested that sufficient protein with each meal should be encouraged more so than simply an overall increase in daily

protein intake. Despite sound rationale, further clinical evidence is needed to confirm the validity of this approach.

These authors suggest that protein synthesis may be maximized in older adults by supplementing meals with essential amino acids. Indeed, essential amino acids-i.e. leucine, isoleucine, and valine-may be the most critical for stimulation of protein synthesis in older adults (Dillon et al., 2009; Henderson et al., 2009). Most notably, a number of studies suggest that leucine may be the most critical amino acid for stimulation of muscle protein synthesis (Anthony et al., 2002; Combaret et al., 2005; Holecek et al., 2001; Katsanos et al., 2006). Despite these data, further investigation is needed to determine optimal protein intake measures-both during meals and through supplementation-to combat sarcopenia. Regardless, these measures will likely need to be combined with exercise to be effective (Verhoeven et al., 2009).

In addition to PEM, caloric insufficiency (CI) in older adults can accelerate the progression of sarcopenia. This CI often stems from the anorexia of aging, a common phenomenon in older individuals (Visvanathan and Chapman, 2009). Many factors contribute to decreased food intake in the elderly, including loss of appetite, gastrointestinal changes, altered taste and smell, social changes, and economic limitations (reviewed in Bales and Ritchie, 2002). CI often results in unintentional weight loss that includes the loss of lean mass. Significant increases in circulating pro-inflammatory cytokines and cortisol due to CI are among the mechanistic triggers thought to contribute to this loss of lean mass (Bales and Ritchie, 2002; Douyon and Schteingart, 2002; Bouchard et al., 2009).

Like CI, excess caloric intake that results in obesity may also accelerate sarcopenia (Bouchard et al., 2009; Jarosz and Bellar, 2009). This concept may seem counter-intuitive as obese older adults clearly have higher amounts of muscle than their non-obese counterparts (Villareal et al., 2004). However, muscle quality in obese individuals is poor due to increases in intramuscular adipose tissue (Villareal et al., 2004) which may contribute to muscle weakness, frailty and disability (Blaum et al., 2005). As a result, a new concept was created highlighting sarcopenic obesity that was initially defined as appendicular skeletal muscle mass/height^2 of two standard deviations below a young reference group (Baumgartner et al., 2004).

Sarcopenic obesity is associated with increases in both cortisol and pro-inflammatory cytokines, factors which promote muscle catabolism, abdominal fat accumulation, and the development of insulin resistance (Epel, 2009). Fat accumulation in the muscle has been linked with decreased muscle function and muscle quality (Goodpaster et al., 2001; Manini et al., 2007; Visser et al., 1998), although no causal link has been established (Manini et al., 2007). Theoretically, excess adipose tissue would disturb the surrounding tissues through an increased inflammatory load (DiStefano et al., 2007). While once thought to be metabolically inert, adipose tissue is now known to secrete more than 50 different protein molecules, many of which are related to inflammation (Jarosz and Bellar, 2009). These inflammatory signals may contribute to accelerating muscle atrophy in elderly obese individuals by excessively stimulating proteolysis and perhaps myonuclear apoptosis. However more data are needed to confirm this hypothesis.

Obesity may also contribute to accelerated muscle loss through high levels of oxidative stress (Furukawa et al., 2004). High-calorie meals, particularly those consisting of quickly absorbable foods and drinks, have been found to produce abnormally large elevations in blood glucose and triglycerides (O'Keefe and Bell, 2007). Monnier and colleagues (2006) demonstrated that these elevations are directly linked to increased generation of reactive oxygen species (ROS). Thus, repeated consumption of high calorie, energy dense meals may

not only promote weight gain but also increase oxidative damage to tissues (O'Keefe and Bell, 2007). Although data in support of this hypothesis are scarce, oxidative stress derived from caloric excess may contribute to the obese sarcopenic etiology. Over the course of the aging process, an accumulation of DNA alterations and mutations from ROS accumulation can lead to impairments in protein synthesis and ATP generation, and thus compromise cell viability (Hiona and Leeuwenburgh, 2008). Furthermore, ROS accumulations may contribute to telomere shortening (von Zglinicki et al., 1995), dysregulation of Ca^{++} release from the sarcoplasmic reticulum, apoptosis (Adhihetty et al., 2007), NF-κB activation (Gloire et al., 2006), and UPS upregulation (Li et al., 2003). Despite these suggestive data, further study of the impact of oxidative stress on the development and acceleration of sarcopenia due to obesity is necessary to establish a causal relationship.

Collectively, studies to date suggest that both under-nutrition and obesity can contribute to the sarcopenic process. Thus, a critical window of optimal caloric intake exists for maintaining the health of skeletal muscle. Therefore, older adults should consume calories in balance with caloric expenditure to maintain weight and to ensure adequate protein intake. Moreover, the current RDA for protein of 0.8 g/kg/day may not be adequate for the elderly. Older individuals may also derive enhanced benefit from consuming supplemental leucine, but future randomized controlled trials are needed to confirm this hypothesis.

5. Disease-mediated pathways

Although chronic disease conditions are common in elderly patients, gerontologists and geriatricians have yet to fully understand the role that specific diseases may have on the development and trajectory of sarcopenia. Traditionally, scientists have studied sarcopenia primarily in healthy older adults to isolate the effects of aging per se on skeletal muscle. However, these studies exclude a significant portion of older adults who are afflicted with a co-morbid disease. Here, we discuss-both mechanistically and morphologically, how several of these diseases might contribute to accelerating the progression of sarcopenia. Notably, these disease-mediated models are congruent with the established definition of cachexia (Evans et al., 2008). Indeed, cachexia represents a primary accelerating model of sarcopenia. On the other hand, cachexia can occur in individuals of all ages-distinguishing it from sarcopenia. Furthermore cachexia is associated primarily with the effects of the disease much like sarcopenia research has focused on the effects of aging *per se*. We argue that future sarcopenia research should investigate the interaction between disease and aging processes.

5.1 Cancer

Cancer is perhaps the most well-known pathological condition which induces muscle atrophy (Tisdale, 2003). Cancer incidence and survivorship are highest in adults over the age of 60 years (Jemal et al., 2007; Wingo et al., 1998). Moreover, the likelihood of developing breast, colon, leukemia, lung, melanoma and non-Hodgkin lymphoma, prostate, and uterine cancers is higher with increasing age (Brenner, 2002). Many, but not all cancers are associated with some form of muscle atrophy (Tisdale, 2003) and this atrophy is associated with an elevated risk of death (Dewys et al., 1980; Mantovani et al., 2001). Therefore, older persons with sarcopenia are likely to experience a severe drop in body mass prior to and following cancer diagnosis (Lundholm et al., 1976). In children, cancer often leads to long-term muscle deficits that manifest in adulthood (Ness et al., 2007; Oeffinger et al., 2006; Warner, 2008). A similar pattern of muscle loss in older adults could drastically accelerate the progression of sarcopenia compared to age-matched, cancer-free counterparts. Cancer-related muscle atrophy is typically associated with the development of cachexia, a serious condition during which patients rapidly lose large amounts of body mass with proportional decreases in muscle and adipose tissue (Tisdale, 2009). As such, the onset of cancer in late

adulthood has important implications for the development and progression of sarcopenia. Here we briefly describe the most common mechanisms underlying cancer-related muscle atrophy and call for future research into the progression of sarcopenia in older cancer survivors.

The presence of a tumor initiates a cascade of events leading to muscle wasting often labeled as the cancer cachexia syndrome. In response to the tumor, the acute phase response is responsible for the production of mediators such as serum amyloid A, C-reactive proteins, fibrinogen, and other proteins that are rapidly synthesized in the liver for the purpose of limiting tumor injury. The liver uses endogenous amino acids to produce these proteins, and skeletal muscle provides the largest and most accessible depot in the body. However the process is quite inefficient. For example, 2.6 g of muscle protein are required to synthesize 1 g of fibrinogen (Preston et al., 1998; Reeds et al., 1994). Subsequently, muscle atrophy develops very rapidly during cachexia.

Pro-inflammatory cytokines are among the most potent catabolic triggers regulating cancer-cachexia (Deans et al., 2006; Mantovani et al., 2000). While cytokines are released systemically, their local actions on specific tissues are unique. Cancer cachexia seems to specifically target skeletal muscle since the visceral protein compartment is preserved even when weight loss reaches 30% (Fearon, 1992; Preston et al., 1987). A recent study indicated that TNFα is highly selective in targeting myosin heavy chains for breakdown in both cell culture and tumor models of wasting (Acharyya et al., 2004).

In addition to direct effects on muscle, cytokines are also capable of crossing the blood brain barrier and altering the function of hunger regulatory systems (Gutierrez et al., 1993). Subsequently, cancer patients with cachexia develop anorexia at an incidence rate of 15-40%. This anorexia is a major contributor to muscle wasting and is thought to originate from elevated levels and sensitivity to cytokines (Rubin, 2003). Data indicate that food intake is suppressed when TNFα and IL1 are administered either centrally or peripherally (Ramos et al., 2004). These cytokines appear to act on the ventromedial nucleus, a critical brain structure critical for the regulation of body mass, to stimulate early development of satiety. This early satiety may result from cytokine-mediated alterations in production of satiety-related hormones neuropeptide-Y (NPY, appetite stimulant) and pro-opiomelanocortin (POMC, appetite suppressant). Additionally, ciliary neurotrophic factor (CNF, a a neuronally-derived cytokine), is increased in the hypothalamus of tumor-carrying animals and subsequently causes anorexia by inhibiting gene expression of NPY and its receptors as well as NPY release. Excess CNF thereby inhibits production of NPY and NPY receptors (Xu et al., 1998a; Xu et al., 1998b). Meanwhile, POMC-derived appetite changes in cancer patients originate from elevations of hypothalamic serotonin and its precursor amino acid tryptophan (Blaha et al., 1998; Cangiano et al., 1990; Cangiano et al., 1994; Rossi Fanelli et al., 1986). These data suggest that not only do cytokines directly interact to promote muscle protein breakdown, but they dysregulate appetite control centers and lead to anorexia.

In addition to changes in caloric intake, elevations in resting energy expenditure may contribute to cancer-related muscle atrophy. The presence of hypermetabolism may be cancer-type specific with high prevalence found in lung and pancreatic cancer (Fredrix et al., 1991a; Fredrix et al., 1991b). In contrast, no substantial changes in metabolism are typically observed in gastric or colorectal cancer (Fredrix et al., 1991a; Fredrix et al., 1991b). Cancer-induced hypermetabolism may be linked to elevated thermogenesis through mitochondrial uncoupling, in which the proton gradient across the inner membrane is dissipated without ATP synthesis. In animal models of cachexia, gene expression of uncoupling protein (UCP)-2 and UCP-3 in skeletal muscle is reportedly upregulated (Bing et al., 2000).

Increases in UCPs may stem from tumor-related increases in TNFα, as intra-venous injections of the cytokine appear to increase both UCP-2 and UCP-3 in skeletal muscle (Sanchis et al., 1998). Thus, hypermetabolism may be involved in cachexia through high energy demand for mitochondrial respiration that leads to an inefficient synthesis of ATP.

Over the past few decades, the early detection of cancer, improved surgical techniques, the development of more effective antineoplastics and improvements in radiochemotherapy protocols have substantially increased chances of tumor eradication. Such advances have increased patient survival and clinicians are now faced with increased focus on management of post-care quality of life. Older cancer survivors are faced with major challenges in overcoming the loss in muscle caused by the disease and the battles against sarcopenia, both of which have no known cures. Additional work is needed on the effects of cancer on the aging process that includes understanding how mechanisms of cachexia differ in aged persons, determining recovery patterns in aged muscle, and developing interventions aimed at preserving muscle tissue following cancer diagnosis.

5.2 Hypoxia-related Diseases

Although cardiovascular and respiratory diseases, such as chronic heart failure (HF), peripheral arterial disease (PAD), and chronic obstructive pulmonary disease (COPD) may begin to develop during middle age, the highest burden of symptoms is suffered by elderly patients (Ito and Barnes, 2009). Importantly, older patients with any of these conditions typically experience muscle wasting in magnitude of 10-40% greater than healthy age-matched controls (Anker et al., 1999; Clyne et al., 1985; Gosselink et al., 1996; Hambrecht et al., 2005; Marquis et al., 2002; McDermott et al., 2007; Regensteiner et al., 1993). Furthermore, hypoxic disease-related atrophy is associated with reduced strength, culminating in impaired muscle function (Schulze et al., 2004). Thus, interventions for these patients are needed to slow or reverse the expansion of the sarcopenic population.

One of the most likely triggers of muscle atrophy common to HF, PAD and COPD patients is chronic and/or intermittent hypoxia. This degree of hypoxia exposure is sufficient to cause muscle fiber atrophy, partially via suppression of mRNA translation and subsequent protein synthesis (Bigard et al., 1991; Hoppeler et al., 1990; Wust et al., 2009). In fact, hypoxia causes hypophosphorylation of mammalian target of rapamycin (mTOR) and its downstream effectors eukaryotic translation initiation factor 4E binding protein 1 (4EBP1), the 70-kDa ribosomal protein S6 kinase (p70S6K), ribosomal protein S6 (RPS6), and eukaryotic translation initiation factor 4G (eIF4G) (Arsham et al., 2003). Research is mixed regarding age-related changes in protein synthesis with studies showing both a decrease (Balagopal et al., 1997; Welle et al., 1993; Welle et al., 1994; Welle et al., 1995; Yarasheski et al., 1993) or no change (Volpi et al., 1999; Volpi et al., 2000; Yarasheski et al., 1999). In either case, hypoxia in combination with advanced age may significantly suppress protein synthesis and could explain the accelerated atrophy in HF, PAD and COPD patients.

Another potential causal mechanism of hypoxia-related atrophy receiving significant attention is the chronic overproduction of pro-inflammatory cytokines. An array of evidence indicates that levels of these cytokines are elevated, and related to muscle atrophy in HF, PAD and COPD patients (Anker et al., 1999; Di Francia et al., 1994; Signorelli et al., 2003; Signorelli et al., 2007; Van Helvoort et al., 2006). At present, adequate evidence is not available to determine differences in cytokine levels, and relationship to muscle mass, between healthy and diseased older individuals. However, accelerated muscle loss in hypoxia-diseased patients through even greater concentrations of pro-inflammatory cytokines is plausible.

While PAD-mediated sarcopenia shares the mechanistic bases of chronic HF and COPD, PAD patients also experience impaired muscle mitochondrial function. Interestingly, PAD patients show accelerated mitochondrial dysfunction through downregulation of electron transport chain complexes I, III and IV in skeletal muscle compared to age matched controls (Pipinos et al., 2006). Moreover, markers of oxidative damage (Pipinos et al., 2006)and frequency of the mitochondrial DNA 4977 bp deletion (Bhat et al., 1999) are reportedly increased in the skeletal muscle of PAD patients. Despite this evidence, mitochondrial dysfunction may simply be a consequence of the pathology and thus additional research is needed to establish a causal link.

5.3 Kidney disease and liver failure

Older persons are especially susceptible to renal failure due to the high prevalence of arteriosclerosis, hypertension, and diabetes mellitus. Patients with chronic kidney disease (CKD) typically present with reduced exercise tolerance, due to the concurrence of muscle atrophy, anemia, cardiac dysfunction, inadequate nutrition, inactivity, and psychological factors such as negative mood states (Adams and Vaziri, 2006). Importantly, low exercise capacity is also a powerful, independent predictor of mortality in patients with end-stage renal disease (Sietsema et al., 2004). Similar to sarcopenia, the loss of muscle mass in CKD patients appears to be primarily due to type II fiber atrophy. In middle-aged predialytic patients, type IIa and IIx fiber cross-sectional area was 25-30% smaller than in healthy controls (Sakkas et al., 2003). This CKD-related atrophy appears to be largely influenced by altered protein turnover rates as the synthetic rate of muscle contractile and mitochondrial proteins was reduced in middle-aged CKD patients compared to healthy controls (Adey et al., 2000). Furthermore, rates of muscle protein degradation are significantly accelerated in the presence of CKD, mainly due to enhanced activation of the UPS (Du et al., 2005). Systemic levels of pro-inflammatory cytokines are elevated in uremic subjects, negatively affecting insulin and IGF1 signaling and promoting UPS activation (Zanetti et al., 2008). Similarly, metabolic acidosis, which is highly prevalent among CKD patients, can induce UPS upregulation and increased branch amino acid oxidation in skeletal muscle (Bailey et al., 1996; Holecek et al., 2001).

Similar to chronic renal insufficiency, liver failure is also associated with significant loss of muscle mass (Tessari, 2003). Protein-calorie malnutrition is thought to be a major determinant of cirrhosis-related muscle wasting (Muller, 2007), however altered protein metabolism also contributes to muscle atrophy in liver failure patients (Tessari, 2003). In fact, investigators using a rat model of biliary cirrhosis reported 10-15% muscle mass loss and increased myofibril degradation despite normal food intake (Lin et al., 2005). A previous review of protein metabolism in liver cirrhosis (Tessari, 2003) suggested that accelerated muscle proteolysis in liver failure may be due to the catabolic action of pro-inflammatory cytokines, whose circulatory levels are usually increased in cirrhotic patients. Muscle protein synthesis is also reduced in liver failure patients, possibly resulting from decreases in systemic production of anabolic factors such as growth hormone and IGF1 (Moller and Becker, 1992).

As described above, the bulk of research concerning regulation of muscle mass in CKD and liver failure patients has focused on alterations in protein metabolism. However, many other important questions remain unexplored, including the roles of myonuclear apoptosis, myogenic signaling, and muscle regeneration in muscle atrophy of individuals afflicted with these diseases. In addition, further study of muscle bioenergetics is needed in each of these disease conditions. Evidence suggests that mitochondrial DNA (mtDNA) is depleted in patients with both CKD and cirrhosis (Lim et al., 2000; Pesce et al., 2002), suggesting that impairments in muscular bioenergetic efficiency may contribute to the pathogenesis of uremic and/or hepatic myopathies.

5.4 Diabetes mellitus type 2

Over 23 million Americans, or 7.8 percent of the population, are currently afflicted with type 2 diabetes mellitus (DM). Of those with the condition, approximately 25-30% are over 60 years of age (Danaei et al., 2009). Along with the well-characterized effects of insulin resistance on muscle (DeFronzo and Tripathy, 2009), sarcopenia and type 2 DM share a common set of lifestyle factors, including physical inactivity and a poor diet that contribute to accelerated muscle atrophy. Moreover, a “vicious cycle” can ensue in which each condition accelerates the progression of the other condition.

DM may accelerate the development of age-associated changes in body composition through a number of mechanisms. For example, insulin resistance decreases the activity of anabolic hormones that activate the phosphotidyl-inositol-3-kinase (PI3K) pathway, thus reducing muscle protein synthesis (Guttridge, 2004; Morley, 2008). Moreover, changes in skeletal muscle metabolism may also lead to the greater extramyocellular lipid content in diabetic individuals and thereby influence muscle function and quality (Sakkas et al., 2006), possibly by increasing myonuclear apoptosis (Peterson et al., 2008). Various neuropathies associated with diabetes and the resultant decrease in motor end plates can cause weakness, ataxia, and poor coordination thereby playing an important role in the pathogenesis of physical function decline and sarcopenia (Morley, 2008). Lastly, diabetic patients often have accelerated progression of atherosclerosis (Morley, 2000), which can decrease peripheral blood flow, resulting in poor muscle perfusion (Morley et al., 2005). Collectively, the physiological changes associated with DM, in combination with changes from associated lifestyle behaviors, may lead to decreased muscle quality, and accelerated sarcopenia progression.

Not only does diabetes lead to muscle atrophy, but muscle atrophy also contributes to diabetes progression through a reduction in insulin sensitivity (Kolterman et al., 1980). At the cellular level, accumulating evidence suggests that impairments in mitochondrial functioning may underlie the development and progression of both sarcopenia and Type 2 diabetes (Lamson and Plaza, 2002). Sub-optimal mitochondrial function appears to impair β-cell functioning (Porte and Kahn, 1991) as well as skeletal muscle health by increasing myofiber susceptibility to apoptosis (Adhihetty et al., 2007; Koves et al., 2005). Evidence also exists to indicate that mitochondrial dysfunction may affect glucose transport throughout the body and precede the development of DM (Lee et al., 1998). Given the important role mitochondrial function appears to have in skeletal muscle quality and glucose/insulin regulation, the mitochondria may represent a key target for future interventions for both sarcopenia and DM. At present, however, additional research is needed to clearly demonstrate the role that mitochondrial dysfunction plays in the etiology of both conditions.

5.5 Human Immunodeficiency Virus

Until recently, relatively few patients infected with Human Immunodeficiency Virus (HIV) lived to older adulthood and thus few data exist regarding sarcopenia in older HIV-infected individuals. Remarkably, the development of highly active antiretroviral therapy (HAART) has extended survival of many HIV-infected individuals by managing viral loads and improving CD4 cell counts (Antiretroviral Therapy Cohort Collaboration, 2008; Moore and Chaisson, 1999; Palella et al., 1998). Subsequently, from 2001 to 2004 the estimated number of HIV-infected individuals over the age of 50 years in the U.S. increased from 65,000 to 105,000. This new total represents over one fourth of HIV-infected Americans and by 2015 over one-half of HIV infected patients are expected to be over 50 years old (Centers for Disease Control and Prevention, 1998; Kirk and Goetz, 2009). Despite the advent of HAART, the loss in lean mass remains common among HIV-infected patients. Thus sarcopenia will soon be an important issue the HIV+ population will have to face.

In the absence of HAART, HIV infection inevitably leads to Acquired Immunodeficiency Syndrome (AIDS). Patients reaching this stage of disease are often diagnosed with cachexia as they have 22% less lean mass in the lower extremities compared to healthy controls (Grinspoon et al., 1999). HIV-infected individuals also typically have elevated circulating levels of pro-inflammatory cytokines TNFα, IL1β, and IL6. These cytokines, while counteracting viral replication (Belec et al., 1994; Thea et al., 1996), are also capable of inducing cachexia as described above (Belec et al., 1994; Zoico and Roubenoff, 2002). Data from HIV-infected men indicate the production of these cytokines from peripheral mononuclear cells (PMCs) can predict losses in lean mass (Roubenoff et al., 2002). The elevated inflammatory milieu is also involved in myopathy-inducing pathways resembling polymyositis (Dalakas and Hohlfeld, 2003; Simpson and Bender, 1988). In polymyositis, muscle fiber death is mediated through $CD8^+$ cytotoxic T cells. Specifically, the major histocompatibility complex class I (MHC-1), a genomic region encoding sarcolemmal expression of antigens, binds $CD8^+$ cytotoxic T cells causing focal invasion and death of non-necrotic fibers (Nishio et al., 2001). HIV-infected muscle also may display nemaline myopathies, conditions diagnosed by the identification of granular-appearing rod material (Cabello et al., 1990; de Sanctis et al., 2008; Sheikh et al., 1999). Symptoms in HIV-infected patients are similar to the congenital form of nemaline myopathy in which patients report mild to severe muscle weakness (Feinberg et al., 1998). The condition is linked to post-translational modification of α-actinin, a protein responsible for anchoring the myofibrillar actin filaments (Schultheiss et al., 1992). These inflammatory-mediated and non-inflammatory mediated myotropic conditions may contribute to accelerated muscle loss in HIV-infected older adults.

HIV infection also induces alterations in protein balance through common catabolic and anabolic processes. HIV-related muscle atrophy is associated with increased muscle proteolytic gene expression and whole body proteolysis measured through urinary 3-methyl histidine excretion (Otis et al., 2008). Additionally, HIV-infected individuals also appear to have low production of anabolic hormones such as testosterone (Cohan, 2006; Grinspoon et al., 1996; McNurlan et al., 1997) and these declines are associated with loss of lean mass and fatigue (Barroso et al., 2010; Dolan et al., 2007; Grinspoon et al., 1996). In fact, treating HIV+ men with supra-physiological doses of testosterone resulted in an increase in lean mass (Knapp et al., 2008). However these increases did not carry over to self-reported or performance-based measures of physical function (Knapp et al., 2008). While HIV-infected individuals have blunted muscle protein synthesis in response to growth hormone administration (McNurlan et al., 1997), these patients are found to retain transcriptional responsiveness to testosterone therapy (Montano et al., 2007). Therefore, post-transcriptional mechanisms may be involved in the alterations to muscle protein balance.

Future research is also needed to determine the effect of HAART medications on muscle atrophy. To fill important gaps in knowledge, more research is required to pinpoint the independent effects of HAART on aging muscle and determine the long-term burden that these medications may have on mechanisms associated with sarcopenia. In addition, data are needed to determine if the age at seroconversion affects the degree of muscle loss in older persons with HIV. Finally, research is needed to discover the mechanistic differences in sarcopenia progression between HIV-infected and non-infected older adults.

6. Conclusions and Future Directions

Sarcopenia is a growing societal healthcare problem due to the rapid expansion of the elderly population and the limited number of therapeutic approaches to the problem. Although the biologic and epidemiologic intricacies of the condition cannot be fully covered in a single review, we have provided here a wealth of information detailing the immense

complexity of the problem. Sarcopenia is more than simply muscle atrophy attributable to the effects of chronological aging. Rather, this condition is accelerated by unhealthy lifestyle behaviors and co-morbid conditions including cancer, HIV, PAD, hypoxia-related diseases, organ failure, and DM. The complexity of sarcopenia is further complicated that each of these factors affects muscle atrophy in a slightly different manner. Due to this complexity, combating the growth of the sarcopenic population will take a substantial unified effort from experts in gerontological and skeletal muscle research, clinical prevention and rehabilitation, and drug discovery and development.

Many previous authors have provided data and interpretation critical to understanding the basic mechanisms responsible for muscle atrophy at old age. These mechanisms range from systemic changes such as reduced production of anabolic hormones to cellular mechanisms governing myofiber size and viability. These data, together with the discovery of yet unknown pathways, are critical to the creation of new therapeutic approaches. However, we argue that these approaches should be developed within the context of the paradigm proposed here.

This paradigm focuses on teasing out factors that accelerate the progression of sarcopenia. Current and past literature on sarcopenia has primarily classified factors such as sedentary lifestyle or chronic disease under a large umbrella known as “age-related factors.” However these factors are not common to all elderly and/or sarcopenic individuals. Within clinical study cohorts, a large degree of heterogeneity exists that complicates the work of clinical and translational scientists studying sarcopenia. Furthermore, variability in lifestyle and disease conditions induces different atrophy-related mechanisms and degrees of atrophy. Therefore, global therapeutic approaches are unlikely to prove equally effective in all models of sarcopenia. For example, exercise may serve as an adequate therapeutic approach for inactivity-related sarcopenia. However other interventions may be required to combat sarcopenia in individuals with co-morbid conditions. Subsequently, well-controlled investigations are needed to compare skeletal muscle atrophy in “healthy” older adults to atrophy in various patient populations. Such investigations will enable scientists to identify, develop and appropriately administer therapeutic approaches specific to each model of sarcopenia. Due to the critical need for improved study of the sarcopenic condition and the heterogeneity of sarcopenia development, this paradigm has significant potential to improve the translation of research findings into more effective preventive and/or treatment strategies. In conclusion, we believe that factors that theoretically accelerate the loss in muscle mass should be routinely considered in the design of future investigations on this subject.

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List of Definitions

4EBP1	eukaryotic translation initiation factor 4E binding protein 1
atrogin1/MAFbx	muscle atrophy F box
AIF	apoptosis inducing factor
CI	caloric insufficiency
CKD	chronic kidney disease
CNF	ciliary neurotrophic factor
COPD	chronic obstructive pulmonary disease
DM	diabetes mellitus
eIF4G	eukaryotic translation initiation factor 4G
FoxO	Forkhead Box O
GC	glucocorticoid
HAART	highly active antiretroviral therapy,
HF	heart failure
IGF1	insulin like growth factor 1
IL	interleukin
MHC	major histocompatability complex
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
MuRF1	muscle-specific RING finger 1
NFkB	nuclear factor kappa B
NPY	neuropeptide Y
p70S6K	70-kDa ribosomal protein S6 kinase
PAD	peripheral artery disease
PEM	protein energy malnutrition
PI3K	phosphotidyl-inositol-3-kinase
POMC	pro-opiomelanocortin

PMC	peripheral mononuclear cell
ROS	reactive oxygen species
RPS6	ribosomal protein S6
S6K1	ribosomal protein S6 kinase
SC	satellite cell
TNFα	tumor necrosis factor alpha
UCP	uncoupling protein
UPS	ubiquitin-proteasome system

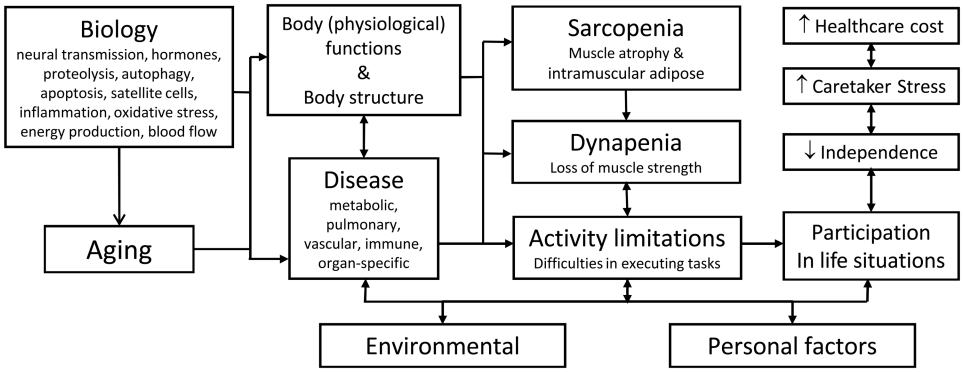

Figure 1.

Mechanisms and consequences of sarcopenia placed within the context of the International Classification of Function (ICF) model developed by the World Health Organization. Sarcopenia is influenced by a host of diseases, cell biology and aging, that manifest through direct or indirect physiological consequences. Subsequently the condition contributes to a number of personal, familial, and societal consequences. Sarcopenia mediates activity limitations (i.e. physical limitation & disability) through influences on muscle strength (dynapenia). Dynapenia: the loss in muscle strength and function that partially results from muscle atrophy (Clark and Manini, 2008). Participation in life situations is the ICF language used to describe the ability of individuals to participate in daily societal activities such as going to the grocery store, attending family events, or traveling.

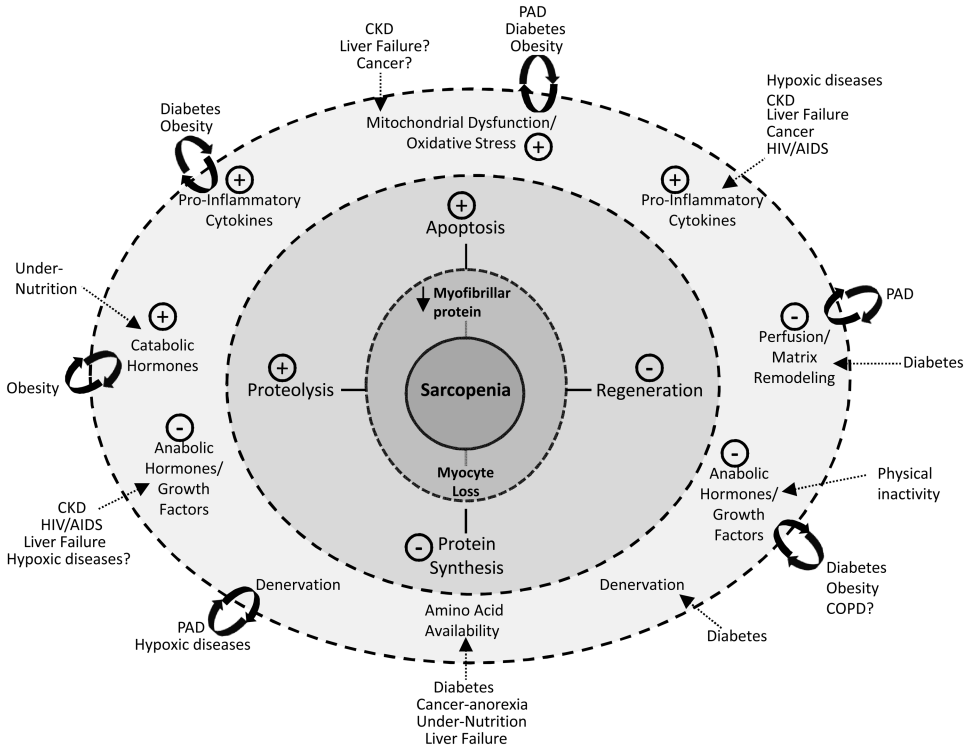

Figure 2.

Mechanisms associated with accelerated sarcopenia due to disease conditions and behaviors. Although aging contributes to the presence of these atrophy-related mechanisms, these behaviors and diseases enhance their activity. The figure is interpreted directionally from outer to inner rings (light to dark grey) ultimately leading to myocyte and myofibrillar protein loss. Plus signs (+) indicate upregulation and negative signs (-) equate to downregulation of a specific pathway. The figure represents a step-down approach to how certain disease conditions and behaviors can modulate four of the major mechanistic pathways involved in sarcopenia: apoptosis, proteolysis, regeneration and protein synthesis. This figure is not intended to be exhaustive or detailed (i.e. a signaling pathway) and thus it may be prone to misrepresentation because of the complexity of interactions involved with multidimensional conditions. However, the model is drawn to illustrate the interactions that serve to feed the major pathways that accelerate sarcopenia. These interactions include, but are not limited to changes in: pro-inflammatory cytokines, anabolic hormones, denervation, mitochondrial function and tissue blood perfusion. Some pathways have feed-forward properties where disease etiology exacerbates the condition (e.g. denervation worsens muscle perfusion in PAD). PAD: Peripheral Arterial Disease, CKD: Chronic Kidney Disease.

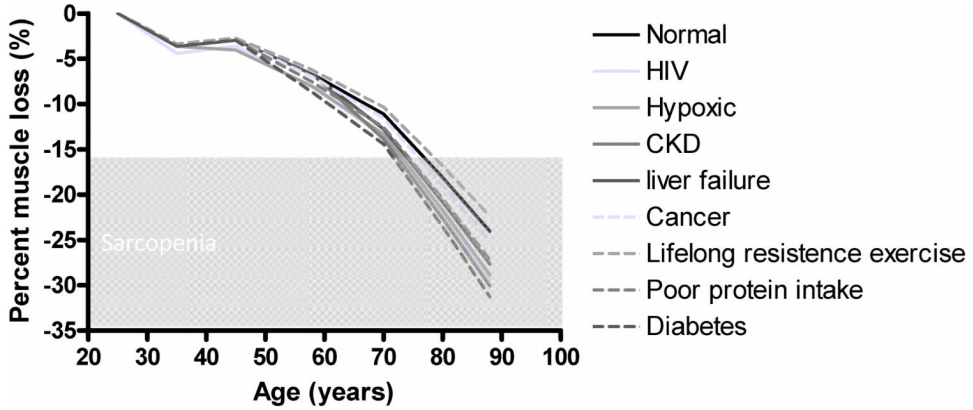

Figure 3.

The accelerated rate of sarcopenia via various behaviors and diseases depicted based on estimates from the literature. Progression of sarcopenia differs based on the age of disease/condition onset [HIV (onset ~35 years old): 22% greater (Grinspoon et al., 1999), Hypoxic conditions (onset ~60 years old): 20% greater (Anker et al., 1999; Clyne et al., 1985; Gosselink et al., 1996; Hambrecht et al., 2005; Marquis et al., 2002; McDermott et al., 2007; Regensteiner et al., 1993), Chronic Kidney Disease (onset ~70 years old): 25% greater (Sakkas et al., 2003), Liver failure (onset ~70 years old): 15% greater (Lin et al., 2005), Cancer (onset ~60 years old): 4.5% greater (Tisdale, 2003), poor protein intake (onset ~60 years old): 13% greater (Houston et al., 2008)and DM (onset ~60 years old): 30% greater (Park et al., 2009a), and Lifelong resistance exercise (onset ~25 years old): 7% less. The Figure assumes that the average decline in muscle mass is ~1.5% per year after the age of 50 years (Lauretani et al., 2003).