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REVIEW

Sarcopenia: describing rather than defining a condition

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Abstract
Background Traditional definitions of sarcopenia have described an aging-associated disorder roughly defined as muscle mass two standard deviations below the young adult demographic. In an effort to clear the ambiguity pertaining to such descriptions, two international bodies have put forth working definitions of sarcopenia, namely The Society of Sarcopenia, Cachexia and Wasting Disorders in 2011, and The European Working Group on Sarcopenia in Older People in 2009.
Review This paper will look at the current zeitgeist of sarcopenia through a range of studies and will argue that what we have is an amalgamated and often conflicted description, rather than a definition, of the sarcopenic condition. Herein, we will consider whether such descriptions of sarcopenia should center on the consideration of the neuromuscular junction (NMJ) rather than describing the condition more in terms of muscular pathology.
Conclusion Consideration was given to studies of the NMJ to advance the idea that present notions of the sarcopenic condition are incomplete and that at its' core, sarcopenia is an age-related disorder of the NMJ.

Keywords Sarcopenia · Myofiber · Motor unit · Neuromuscular junction · NMJ · Muscle · Aging

The age-associated loss of musculature form and functionality is somewhat loosely termed sarcopenia. Clinically, the term "sarcopenia with impaired mobility" is more applicable. The Society of Sarcopenia, Cachexia and Wasting Disorders coined this term [1] which is defined as "*a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group*." This definition goes further, making the important point that "*the limitation in mobility should not be clearly attributable to the direct effect of specific disease*." In other words, sarcopenia and the pathophysiological processes underlying is an independent disease entity. Despite having such a definition, efforts to further clarify sarcopenia continue, with Anker et al. [2] classifying it as a muscle wasting disease that is chronic in nature and due to aging/senescence. Pathophysiologically, this condition is known to represent a physical degradation of muscle fibers; however, a strong neurological component has been inferred. The nervous involvement is less well characterized and is often given less weighting than it deserves. Further, there is a lack of consensus regarding many aspects of sarcopenia [3].

Another current working definition of sarcopenia has been put forth by the European Working Group on Sarcopenia in Older People (EWGSOP). This body attempted to reach a consensus, defining sarcopenia as '*a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death*' [4]. In providing this definition, the EWGSOP is quick to acknowledge however that it is inappropriate to define sarcopenia solely in terms of muscle mass as the causes and effects are many and varied. Age-associated changes in the motor unit (MU) are often described [5] and are thought to contribute to the sarcopenic process, perhaps more so than changes to musculature. With aging, MUs undergo successive reduction in numbers with limited adaptation, ultimately leading to a decline in motor control [6]. When innervation of a myofiber is lost, neighboring MUs will expand to reinnervate the myofiber in question, leading to an enlargement of MU area [7]. Significant fiber type switching is also seen, whereby mainly type II myofibers are reinnervated by slower type I motor neurons, forcing a

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switch in myofiber phenotype [8]. This adaptive process is referred to as MU remodeling; however, again there is conjecture as to whether MU remodeling plays a causal or compensatory role in sarcopenia. The evidence and debate in this area is wide ranging. In a review by Edström et al. [9], it is argued that impediments to myofiber repair are the sole driving force behind sarcopenia, whereas in another review, Figueiredo et al. [10] defines sarcopenia as a secondary effect of impaired neuronal function. Ultimately, we have varying and often conflicting descriptions of sarcopenia, meaning that at present a definition remains beyond reach.

In a study by Ling et al. [6], MU characteristics with aging were measured, taking surface representations of human quadricep MUs electromyographically under various effort levels. This study found an increase in the size of the MU and a decline in the MU firing rate with age at contractions relevant to general mobility. However, these changes were slight until the age of 75, beyond which the effects were substantially greater. On this basis, Ling et al. put forth the idea that these MU alterations occur later than the age of sarcopenic onset, thus indirectly referring to the condition as a muscular pathology. This idea of MU enlargement, which is preceded by a level of denervation, occurring after myofiber degradation stands apart from many of the other investigations. A simple example of such is given with a study by Deschenes et al. [11]. Herein, the NMJ of early aged rats was observed through cytofluorescent staining to determine whether denervation is precipitous of sarcopenic myofiber alterations. Myofiber size and composition in both the plantaris and soleus muscles were assessed using histochemical procedures. Significant signs of denervation were observed with little change in myofiber phenotype, indicating that denervation, and by extension MU enlargement, occurs before myofiber degradation. Thus, the existence of a precipitating presynaptic or postsynaptic factor remains an area of debate. These two studies give a context of the conflicting descriptions pertaining to the sarcopenic process. While both delineate neuronal and muscle pathology as two somewhat distinct processes, it may be more appropriate to envisage a more singular process, with the two pathological states comprising a single degenerative condition.

The contribution of the NMJ to this process is not well characterized. Sarcopenia is most likely produced by interplay of neuronal and muscle factors; such an interaction would logically occur at the NMJ. Balice-Gordon [12] confirms that there is a reciprocal exchange of trophic factors occurring between nerve and muscle fibers at the NMJ. A complex milieu of interactions continues throughout life [13] and is important for maintaining structural integrity of the NMJ, which plays a key role in overall neuromuscular integrity. Apel et al. [14] tested the hypothesis that aging would impair the response of the NMJ following transection and repair of the tibial nerve of the rat. Both young and old rats underwent transection, then after various time intervals, the gastrocnemius was examined for signatures of NMJ recovery. This study cites that denervation is known to evoke increased turnover of nicotinic acetylcholine receptors (nAChRs) in the postsynaptic NMJ, but that a steady-state concentration of nAChR is believed to be crucial to maintaining NMJ stability following denervation. Similarly, myogenic regulatory factors (MRFs) were cited as central to regenerative muscle processes. The results of this study showed impaired upregulation of both nAChR and MRF in the mRNA profiles of old rats. Histological examination of the aged NMJ following transection observed consequent degradation and loss of endplate area. Observed concentrations of the α-subunit of nAChR and MRF4 were elevated in both young and old rats following transection, but substantially more in the former, suggesting a link between decline of these factors and impaired NMJ stabilization. Apel et al. [14] conclude that the aging of muscle impairs its molecular response to nerve injury. The impairment was ultimately deemed to be postsynaptic, describing sarcopenic pathology as one of the musculature.

In a review of sarcopenia studies by Vandervoort [7], a trend towards exercise-mediated partial recovery of function was elucidated. Resistance training especially was observed to modulate a significant increase in muscle performance in aged subjects. However, only moderate increases in muscle mass were observed, leading to the idea that a large basis of the functional regain lies in neuronal adaptation. A contemporary study by Valdez et al. [15] considered the effects on the NMJ in this context, examining the effects of both exercise and caloric restriction. The key findings of this investigation were that both activities reconcile the age-related alterations of the NMJ. As a reference, the NMJ of aged control rats was first characterized. Antibody stain of the NMJ allowed for time-lapse imaging comparisons of the same subjects before and after engagement of the regimes. Caloric restriction was used on rats from 4 to 24 months of age. Relative to controls, the calorically restricted NMJ was remarkably preserved, with damage to postsynaptic NMJ and axonal degeneration observed less frequently. Caloric restriction was seen to attenuate loss of motor neurons and myofiber turnover. Rats at 22 months of age were subjected to exercise programs for 1 month. This led to the observation of reduced postsynaptic NMJ degradation; however, similar changes in the axon were marginal. Overall, age-related alterations in the NMJ actually decreased following exercise, although this was in the absence of any notable changes to the motor neuron or myofiber numbers. The beneficial effects of exercise were specific to the working muscles, suggesting they stem from local interactions at the NMJ. In contrast, the effects of caloric restriction were unilaterally evident. Caloric restriction impeded loss of motor neurons and myofibers, indicating the effects of exercise are intrinsic to the NMJ. This study by Valdez et al. [15] highlights the importance of the NMJ to the sarcopenic

process. As the NMJ underpins muscle physiology, it likely underpins muscle pathology. Thus, it may be more appropriate to form descriptions of sarcopenia in terms of the NMJ.

These strategies of endurance exercise and caloric restriction result in increased mitochondrial capacity in the muscle [16], suggesting that mitochondrial dysfunction plays a critical role in the sarcopenic process. In a study by Dupuis et al. [17], transgenic mSOD1 mice were found to display hypermetabolism in the skeletal muscle. mSOD1 mice are utilized as a model for amyotrophic lateral sclerosis, a degenerative motor neuron disease, and it was found that feeding these mice a high fat diet delayed muscle denervation. On this basis, Dupuis et al. [17] examined whether muscle hypermetabolism is a causal factor of neuronal degeneration. To observe hypermetabolism, transgenic mice overexpressing uncoupling protein 1 (UCP1) were used. UCP1 is a thermogenic mitochondrial protein that uncouples electron transport from ATP synthesis, instead producing heat. In these mice, serum concentrations of proteins indicative of muscular dystrophy were not observed, and microscopic examination of myofibers confirmed the absence of muscle degeneration. NMJ deterioration with age was observed exacerbated by mitochondrial uncoupling. Labeling of axonal structure further indicated a progression of deterioration from the NMJ culminating in a loss of motor neurons. The findings of this study ultimately do indicate that muscle mitochondria are heavily involved in the maintenance of the NMJ. Dupuis et al. [17] postulated an alteration of muscle-borne retrograde signals; however, such mechanisms have not been elucidated. This hypothesis is based on the findings indicating NMJ degeneration being due to neuronal instability rather than any postsynaptic deficit. Specifically, the assembly of AChR clusters in response to neural agrin was found to be normal, indicating that postsynaptic machinery remained intact at the NMJ. Axonal regeneration after injury was also impeded. So although in this case the alteration derives from muscle mitochondria, the degenerative process is believed to be borne out by the neuron. Overall, these are essentially similar findings to that of Apel et al. [14], but their subsequent postulations differ somewhat. Whereas Apel et al. deems aged muscle to progress towards an impaired maintenance of the postsynaptic NMJ following nerve injury, Dupuis et al. [17] puts forth the notion of an unstable presynaptic motor neuron that falters with an alteration in muscle retrograde signals. Such confounding descriptions effectively highlight how the sarcopenic process is yet to be defined.

Mitochondria play a regulatory role in apoptosis, which Wenz et al. [16] cites among mechanisms behind the sarcopenic process. To this end, Wenz et al. investigated the role of PGC-1α, a key regulator of mitochondrial synthesis. PGC-1α was upregulated in rodent muscle under the promoter muscle creatine kinase and the effects measured using various techniques. Increased PGC-1α was observed to reduce muscle apoptosis, autophagy, and proteolysis as well as increasing mitochondrial metabolic function in muscle fibers. Wenz et al. [16] cite previous findings indicating PGC-1α plays a role in NMJ remodeling. In this context, they investigated whether its upregulation in the muscle had an effect on NMJ organization and acetylcholinesterase (AChE) expression during aging. AChR at the NMJ were elevated, and distributions of AChE were altered, more closely resembling a younger wild-type NMJ. Wenz et al. [16] conclude an upregulation of PGC-1α contributes to keeping NMJ proteins in a "younger state," which by extension would reduce impairment of function with age. Overall, an upregulation of PGC-1α and thus muscle mitochondria was found to preserve structural integrity of both myofibers and, more specifically, the NMJ. Further, functionality of mitochondrial oxidative enzymes was preserved. These findings were linked to an observed increase in metabolic and exercise capacity in the aged rodents, with a preservation of muscle physiology. Similarly, they give some indication of the physiology of the beneficial effects of exercise in staving off sarcopenia, in that exercise is known to increase mitochondrial proliferation in the musculature [18]. Further, mitochondria undergo progressive degeneration with aging [19]. So from studies such as this, we find indications of what may very well lead to defining the mechanisms behind the sarcopenic process.

From a consideration of current sarcopenic research, the definition put forth by the EWGSOP does seem quite incomplete. In fact, much of the current working hypotheses on sarcopenia are open to questioning. If the work discussed in this review is any indication, the characterization of sarcopenia will need to be extended to encompass more relevant factors. Unfortunately, what these studies also bear out is that the sarcopenic condition is manifested by an intensely complex interplay of factors that contribute to the degenerative process. This continues to make defining sarcopenia a somewhat elusive task. At first glance, sarcopenia could be considered a muscular disorder, but this is too simple. Sarcopenia should be considered a disorder of the neuromuscular junction.

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Conflict of interest David Rhys Alchin declares that he has no conflict of interest.

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