Commentaries on Viewpoint: Muscle atrophy is not always sarcopenia

SARCOPENIA SHOULD STAY SARCOPENIA

TO THE EDITOR: Sarcopenia has been defined initially as the decrease of muscle mass and function during aging. As pointed out by Hepple et al. (2), this definition has been extended to muscle atrophy situations such as undernourishment or acute catabolic states (ACS) like sepsis and cancer. Sarcopenia is not the result of pathology and has been reported among healthy, well nourished, physically active elderly subjects (3). It is a slow process, taking place over decades, whereas muscle loss during ACS occurs in days or weeks. Sarcopenia in an individual can even result from the random succession of ACS because the capacity to recover muscle mass lost during ACS decreases with aging (1, 4). How can you explain that “sarcopenia” results from “sarcopenia” if you do not make the difference with the lifetime processes and the acute catabolic condition? One of the clearest experimental evidence that the loss of muscle mass with aging is explained by different mechanisms relatively to ACS is that in the fasting state, a clear decreased muscle protein synthesis rate has been rarely demonstrated in old individuals (5), whereas it is classically shown during ACS. The slow erosion of muscle mass during aging is partly explained by a lower sensitivity of muscle anabolism to meal intake (5). Thus the strategies to limit muscle loss during aging are probably not the same as during ACS due to the slow kinetics involved and differences in underlying mechanisms. In conclusion, we really think that the term “sarcopenia” should be limited to the age-related alteration of muscle mass and function.

REFERENCES


IS MISUSE OF THE TERM SARCOPENIA DUE TO A LACK OF BIOMARKERS?

TO THE EDITOR: We applaud Russell Hepple (3) for arguing against the increasing use of the term sarcopenia as synonymous with muscle atrophy. The lack of biomarkers that are specific for muscle aging contributes substantially to this semantic confusion. Indeed, the sarcopenic muscle displays histopathological features that justify the restriction of the term to the geriatric field. These morphological traits also allude to pathogenetic mechanisms distinct from those underlying other muscle atrophying conditions. However, reliance on histopathology to define sarcopenia generates some practical issues. Which histopathological traits are expected in sarcopenic elderly with concomitant cachexia-inducing condition(s) (e.g., cancer, chronic obstructive pulmonary disease, heart failure, renal failure, etc.)? Unfortunately, such a case is not the exception in geriatric medicine, rather the rule (2). Perhaps a histopathological spectrum exists from sarcopenia alone to sarcopenia associated with other muscle atrophying conditions and some overlap is expected. Also, different subsets of sarcopenia (e.g., obese and nonobese) may show distinct histological alterations. Finally and more importantly, histopathology may not be a realistic outcome measure in clinical trials on sarcopenia. These and other considerations highlight the need for easily accessible biomarkers of muscle aging. Circulating COOH-terminal agrin fragment (4) and heat shock protein 72 (5) have been proposed as markers of sarcopenia, whereas serum levels of procollagen-3 NH₂-terminal peptide are associated with muscle anabolic response to hormonal supplementation (1). The task we all are called to pursue is to establish whether these and other molecules truly qualify as biomarkers of muscle aging. The “copyright” on sarcopenia is worth the challenge.

REFERENCES


Emanuele Marzetti
Lecturer in Geriatrics
Thomas W. Buford
Roberto Bernabei
Catholic University of the Sacred Heart School of Medicine

Dominique Dardevet
Research Director, PhD
Isabelle Savary-Auzeloux
Didier Remond
Laurent Mosoni
Clermont Universite
Universite d’Auvergne
Unite de Nutrition Humaine
Clermont, France

Emanuele Marzetti
Lecturer in Geriatrics
Thomas W. Buford
Roberto Bernabei
Catholic University of the Sacred Heart School of Medicine

8750-7587/12 Copyright © 2012 the American Physiological Society http://www.jappl.org
SARCOPENIA IS NOT ALWAYS MUSCLE ATROPHY

TO THE EDITOR: The term sarcopenia has been misused over the past decades because of several reasons, as pointed out by Dr. Hepple (4). In addition, although first described as a loss of muscle mass and strength (3), sarcopenia has been mostly characterized using mass or strength only, although muscle mass explains only 4–60% of muscle strength in older men and women (1). Recently, the new term dynapenia (2) has been proposed to characterize the loss of muscle strength, which contributes to a clear distinction between both concepts.

However, our definition of sarcopenia, even if clearly implicating an effect of age on mass, remains shaky and hard to capture. Indeed, the term sarcopenia was initially derived from the Greek root “poverty of flesh” (Sarc, which, eventually, turned into the loss of muscle mass. But these are not synonyms and there may thus be confusion between a small muscle mass and the loss of muscle mass. Yet most studies measure muscle mass or size at one time point only, without any consideration of its evolution. Hence, even if an older person displays a small muscle mass, it cannot be ascertained that it actually results from some loss (or atrophy). No methodology can allow us to discriminate between an actual loss vs. a “lifelong” small (but functional) muscle mass. Obviously, when looking for implied mechanisms and treatment to counteract sarcopenia, our actual inability to rigorously characterize older individuals who have experienced muscle atrophy due to aging likely diminishes our ability to find clear answers.

REFERENCES

ON MUSCLE ATROPHY, AGING, AND DISEASE

TO THE EDITOR: We appreciate Hepple’s (2) article proposing distinction between sarcopenia and other forms of muscle atrophy. He stimulates an important discussion regarding differences between atrophy due to aging per se and that due to other causes. Hepple proposes that problems arise from misapplications of the term sarcopenia that make it synonymous with muscle atrophy irrespective of age as the underlying cause. To this end, he laments use of the term “where muscle atrophy is present but aging per se is not the cause.” Although we agree completely with the general premise that muscle atrophy and sarcopenia are nonsynonymous terms, we feel that further discussion is needed. Recently, we reviewed the importance of considering extra-chronological factors in the scientific and clinical evaluation of sarcopenia (1). Such an approach is critical because aging is inherently intertwined with increased risk of developing numerous chronic diseases.

Thus separating the unique contributions of aging and disease to muscle atrophy is impractical—if not impossible—in clinical research and patient care. For example, diabetes mellitus among older adults is associated with exacerbated muscle atrophy and strength loss (3, 4) and increased risk of physical disability (5). Although diabetes is common among seniors, development of the condition is certainly not inherent to the aging process. Ignoring the contribution of diabetes and other chronic diseases will limit, rather than enhance, our understanding of the biological causes of sarcopenia. Accordingly, rather than creating segregated views of aging and disease, we should seek increased understanding of these relationships to move the field forward.

REFERENCES

Tom W. Buford
Assistant Professor
Emanuele Marzetti
Todd M. Manini
Department of Aging and Geriatric Research
University of Florida

THE DILEMMA OF DEFINING SARCOPENIA

TO THE EDITOR: The Viewpoint “Muscle atrophy is not always sarcopenia” (4) emphasizes an important challenge facing health care providers interested in sarcopenia—its definition. From the perspective of clinical researchers the Viewpoint not only highlights controversy about the definition but also the need to learn from colleagues in other areas of the field. We agree with the author that muscle histopathology differs among conditions that lead to muscle function deficits. Clearly, potential sarcopenia treatment/prevention interventions will be more effective if they target the underlying cause. However, the clinical presentation and health impact for a particular individual might be very similar. Recognizing the need to bring the diagnosis of sarcopenia to clinical care, we endorse the consensus definition of the European Working Group on Sarcopenia in Older People (2). This approach combines measures of muscle mass and function while importantly separating primary sarcopenia (age related) from secondary causes, e.g., inflammatory diseases or malnutrition. Such an approach is often used clinically (e.g., secondary hypertension, vasculitis, osteoporosis) and helps identify individuals at risk for adverse health outcomes while emphasizing differences in histopathology and pathophysiology. As such, we proposed HIV as a
Potential cause of secondary sarcopenia (1) with the underlying pathophysiology of this early aging process being “inflamm-aging” (3, 5). In conclusion, we advocate for classifying adults as sarcopenic when they meet current consensus criteria regardless of their chronological age while distinguishing between primary or secondary sarcopenia based on the likely underlying cause. Hopefully, this definition will prove to be beneficial for both clinicians and scientists.

REFERENCES


Bjoern Buehring
University of Wisconsin-Madison
Osteoporosis Clinical Research Program
Elizabeth Kirchner
Leonard Calabrese
Cleveland Clinic Orthopedic and Rheumatologic Institute

COMMENTARY ON VIEWPOINT: MUSCLE ATROPHY IS NOT ALWAYS SARCOPENIA

TO THE EDITOR: We are in agreement with Dr. Hepple’s Viewpoint article “Muscle atrophy is not always sarcopenia” (2). We would like also to emphasize that not only is the original terminology of sarcopenia losing its “roots in aging,” recent literature has completely altered its originally intended meaning. Sarcopenia has been conceptually connected to the loss in muscle mass, muscle strength/power, physical performance (e.g., walking speed), and a combination of the three (3). Definitions to operationally defined sarcopenia have become synonymous with the frailty syndrome that is often characterized as unintentional weight loss, self-reported exhaustion, grip strength muscle weakness, slow walking speed, and low physical activity (1). As noted by Dr. Hepple, successful therapeutics cannot be developed unless a biological mechanism is clearly linked to the condition. Finding a biological mechanism in a myriad of phenotypes will make an already complex task almost impossible. Therefore, not only should we target muscle histological traits as recommended by Dr. Hepple, we need to simplify our clinical approaches by preserving the original definition of sarcopenia as the age-related loss in muscle mass. Focusing our efforts on biological mechanisms that are clearly connected to sarcopenia will inevitably reduce confusion in this once explicit field. On another note, it is logical to explore biological hallmarks that are specific to sarcopenia. However, easily obtainable serum biomarkers have not yielded reliable results (4) and collection of muscle tissue for histology might be impractical in clinical settings. Therefore, noninvasive techniques (e.g., NMR spectroscopy, etc.) might better serve future treatment strategies.

REFERENCES


Todd M. Manini
Assistant Professor
University of Florida
Brian C. Clark
Ohio University

VIEWPOINT—MUSCLE ATROPHY IS NOT ALWAYS SARCOPENIA

TO THE EDITOR: The initial definition of sarcopenia was specifically circumscribed to the skeletal muscle mass losses associated with aging. However, the causes of sarcopenia are highly multifactorial and involve hormonal, neurological, immunological, and lifestyle factors. Additionally, it is conceivable that the different mechanisms involved in this loss may assume distinctive preponderance in different individuals, being difficult to determine what are purely age-related muscle losses and hence circumscribed to the initial sarcopenia concept from what are not and therefore should be stowed in another drawer. In his article, Prof. Hepple (4) claims that menopause-associated skeletal muscle losses (MASML) should not be considered sarcopenia; however, the causes leading to MASML as well as its main features resemble those seen in age-related sarcopenia. In age-related sarcopenia there is a decrease in skeletal muscle fiber number and size, decreased mitochondrial oxidative capacity, increased intermyofibrillar connective tissue, and increased expression of MyHC I isoform expression (2, 5). Notoriously, these same changes have been shown to occur in skeletal muscle in response to estrogen loss (3). Causes leading to sarcopenia are various and may include degeneration of motor neurons, decreased growth hormone and sexual hormones circulating levels, increased glucocorticoid levels, oxidative stress, and physical inactivity (1, 5). Again, these have also been shown to be associated with MASML either in human or in animal studies. Unquestionably “muscle atrophy is not always sarcopenia” (4), but perhaps instead of contributing to the clarification of the sarcopenia concept, its over compartmentalization may carry more confusion than clarification.

REFERENCES

SARCOPENIA SHOULD BE DEFINED AS AN AGE-RELATED CONDITION BASED ON CLINICAL BUT NOT CELLULAR FEATURES

TO THE EDITOR: In his Viewpoint, Hepple (4) notes that the term sarcopenia is being used to describe skeletal muscle impairments caused by factors other than aging, notably cancer. Interestingly, the term most often synonymous with muscle wasting in cancer, cachexia, seems to have caused similar frustrations due to its own somewhat nebulous definition. This lead to a concerted effort to define cachexia more thoroughly (3), ironically including [one definition of (1)] sarcopenia as a possible criteria. The fact that this “official” usurpation of the term sarcopenia by cachexia researchers was published in a very prominent medical journal vindicates Hepple that there is a legitimate threat to the intended definition and usage of the term sarcopenia.

In his original conception of the term, Rosenberg (5) clearly defined sarcopenia as age-related skeletal muscle impairment, and it is therefore logical, if not also ethical, to ensure that aging remains a mandatory component of defining sarcopenia even as the official definition becomes more complex. However, the specific cellular mechanisms of sarcopenia, beyond the loss of mass and strength, appear to have been left intentionally broad, both by Rosenberg and the research community over the years. Thus it would be against the spirit of the original definition to “over-define” the term based on specific qualities such as fiber type clustering, etc. The European Working Group on Sarcopenia in Older People provide an excellent framework for defining sarcopenia (2) as an aging syndrome from a clinical perspective, while maintaining flexibility on the underlying cellular mechanisms.

REFERENCES

Osvaldo Delbono
Jackson R. Taylor
Wake Forest School of Medicine

LOST IN TRANSLATION?

TO THE EDITOR: We read with great interest the paper of Hepple (1) and, from a clinical point of view, agree with his views. Muscle wasting, in its broadest sense, is a very complex phenomenon attributable to several causes and that can result in varied consequences. Sarcopenia is only one aspect of this issue. Although seemingly similar, and hardly distinguishable from sarcopenia in clinical practice, cachexia also has specific characteristics (inflammation and weight loss) and thus may be considered as a separate entity (3). The very recent review of Jeejeebhoy (2) well illustrates the overlap of these clinical features and the difficulty of establishing clear separations between these syndromes because they may have common symptoms and could be the cause or the consequence of one another. Not surprisingly, the treatments associated with each of these conditions also differ (5). For instance, resistance training is the treatment that seems most appropriate in sarcopenic individuals, whereas in cachectic patients, although there are few studies and certainties, therapeutic agents are preferred. Beyond this debate concerning the need and the difficulties to clearly define and characterize each condition, this article reflects the considerable advances that have been made in the understanding of the muscle and its functioning using both animal and human models. On this point, attention should be paid to the ability to transfer findings from the animal to the human model. Recent works from Stimpson et al. (4) demonstrate the desire to develop biomarkers in animals that would be applicable in a clinical routine in human.

REFERENCES

Mylène Aubertin-Leheudre
Professor
Sébastien Barbat-Artigas
Charlotte H. Pion
Université du Québec A Montréal

“SARCOPENIA” HAS EARNED ITS LIVING

TO THE EDITOR: Originally the concept of sarcopenia was mainly targeted against health professionals to draw attention to the loss of muscle mass and function during normal aging. To select a descriptive name remains reasonable considering the
yet unresolved controversy about the origin of the condition. However, in clinical practice it is in fact rare to find old people with no other reason than aging itself for their muscle wasting. Therefore, we believe that sarcopenia is a concept that should not be reserved exclusively to denote muscle wasting occurring in otherwise healthy aging (1). Nevertheless, it is of major importance to understand the underlying mechanism(s) in each single case to tailor the most effective therapy. A plethora of possible causes of explaining the mechanisms underlying muscle loss and strength in aging has been presented. However, with the diagnostic procedures at hand in clinical practice, i.e., body imaging and performance tests; we cannot yet distinguish the mechanisms in operation.

We agree with Dr. Hepple that the morphological appearance of muscle wasting in otherwise healthy aging is distinct from many other conditions with muscle loss. It should, however, be noted that the histopathology found in studies of human muscles reflects the mixed effect of the aging processes and other processes affecting muscle mass and function, e.g., reduced physical activity, altered nutritional status, and systemic disease(s). What’s more, each human muscle is unique, composed of muscle fibers with characteristics and size suited for its genetically determined structure and function (8). Studies on rodents have dominated the scene trying to identify the mechanisms behind aging-associated muscle wasting. Dr. Hepple argues that rodent models are feasible to study processes in human muscle aging. Although some studies on aging-related muscle wasting in rodents have shown that there is a concordance with (corresponding) studies on aging humans (3, 6), extrapolation between species must be done cautiously. From numerous animal models it has been claimed that mechanical loading that includes lengthening contractions induce extensive myofiber degeneration and a robust inflammatory response followed by repair from activated satellite cells and or other stem cells (7). As this type of damage is not known to occur in humans, such studies do not help to elucidate the cause of decreased muscle mass and strength in humans. Active, nonobese rodents (calorie restricted) live longer as do humans and show less wasting of skeletal muscle at corresponding chronological age and, furthermore, necrosis is not a part of the histopathology of muscles from these rodents (2, 9). Still, we do agree with Dr. Hepple that several lines of evidence suggest that denervation is a significant component of muscle loss and reduced muscle strength in normal aging. Nonetheless, more research is needed to settle the contribution by “myogenic” vs. “neurogenic” factors, but utilization of rodent experimental models encompassing usage-induced muscle damage and necrosis will not be a successful route in this attempt.

REFERENCES