

In response to the article, "Interrelationship of Sarcopenia and Cardiovascular Diseases: A Review of Potential Mechanisms and Management," by Rivera, et al., published in JAFES Vol. 39 No. 1.

Sarcopenia Can Be Physiological or Pathological, Primary or Secondary

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We read with interest the review article by Rivera et al., on the relationship between sarcopenia and cardiovascular diseases such as atherosclerosis, hypertension, coronary heart disease, and heart failure.¹ Cardiovascular diseases have been found to trigger sarcopenia through processes such as inflammation, oxidative stress, endothelial dysfunction, neuronal and hormonal changes, malnutrition, and reduced physical activity.¹ It was concluded that cardiovascular drugs, hormone replacement, changes in diet and nutritional intake, and physical activity can attenuate sarcopenia.¹ The study is noteworthy, but some points warrant discussion.

The first point is that we disagree with the view mentioned in the introduction that sarcopenia is a disease.¹ Sarcopenia can be both a disease and a physiological condition, which is why it should be classified as either physiological or pathological sarcopenia. Physiological sarcopenia is an age-related regression of skeletal muscles without the presence of a disease that could explain the muscle atrophy. It is characterized by the fact that regular muscle training no longer leads to an increase in muscle volume or leads to only a marginal increase. Pathological sarcopenia is characterized by the fact that, in addition to physiological sarcopenia, muscle atrophy is caused by an underlying disease. Diseases associated with muscle wasting include neuropathies, myopathies, central nervous system diseases that cause muscle weakness, previous surgery, rheumatologic and orthopaedic diseases, decreased blood supply, endocrinologic diseases, and malignancies.² Since physiological and pathological sarcopenia can coexist, it is not always easy to distinguish the extent to which one or the other contributes to the loss of muscle mass.

The second point is that sarcopenia can also be classified as primary or secondary. Primary sarcopenia is due to genetic causes or has no identifiable cause, while secondary

sarcopenia is due to comorbidities that manifest with muscle wasting. The distinction between the two is crucial, as secondary sarcopenia may be amenable to treatment if the underlying cause is treatable.

The third point is that factors other than comorbidities also contribute to muscle wasting in older people. These include diet, level of physical activity, whether or not someone uses whole-body electrical stimulation (WB-EMS), lifestyle, and current medications. In particular, people on a low-protein diet are at risk of losing muscle mass because essential amino acids are not sufficient to meet the protein requirements needed to produce adequate amounts of muscle proteins, especially those of the contractile apparatus and those involved in signaling, pore functions, and energy production. Although regular physical activity does not guarantee that muscle mass will be preserved, it helps maintain muscle volume in physiological sarcopenia. WB-EMS is known to be clinically effective in influencing sarcopenia and is well accepted by older people.³ For older people who are unable or unwilling to perform dynamic strength exercises, WB-EMS may be a less daunting alternative to maintain muscle mass and strength.³ In order to assess whether sarcopenia is physiological/pathological or primary/secondary, it is crucial to know the current medications and dietary habits of the person affected. Substances that can cause muscle wasting include statins, fibrates, alcohol, amiodarone, procainamide, glucocorticoids, beta-blockers, furosemide, chlorthalidone, propofol, antiepileptic drugs (e.g., lamotrigine, phenytoin), omeprazole, colchicine, D-penicillamine, immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab), antiretroviral drugs (e.g., zidovudine), immunosuppressants (e.g., cyclosporine), and tumor necrosis factor inhibitors (e.g., etanercept, adalimumab).⁴

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The fourth point is that factors such as autonomic innervation, viral reservoirs, copy number variants, reduction in the number of satellite cells, inability of muscle cells to divide or replicate, ethnicity, haplotype, mitochondrial DNA (mtDNA) copy number, oxidative stress, and mtDNA polymorphisms should also be considered in the assessment of sarcopenia.

In summary, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. In people with sarcopenia, it must be clarified whether it is physiological or pathological and whether it is primary or secondary before an intervention can be recommended. Secondary sarcopenia is multicausal and not only due to cardiovascular disease.

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RESPONSE OF THE AUTHORS

We thank the authors for their thoughtful comments regarding our published article, "Interrelationship of Sarcopenia and Cardiovascular Diseases: A Review of Potential Mechanisms and Management." We appreciate the opportunity to clarify several aspects of our manuscript.

First, the authors raise an important consideration regarding the distinction between physiological and pathological sarcopenia. We agree that it is essential to recognize the different categories of sarcopenia for appropriate clinical assessment and management. However, we would like to clarify that, for the purposes of our review, we characterized sarcopenia as a disease in accordance with the definition established by the European Working Group on Sarcopenia in Older People (EWGSOP2). In line with its aim to increase awareness and improve detection and treatment of sarcopenia in clinical practice, EWGSOP2 defines sarcopenia as a muscle disease characterized by low muscle quantity and quality.¹ Thus, our characterization of sarcopenia as a disease reflects the EWGSOP2 consensus definition rather than suggesting that all age-associated muscle loss is pathological.

Second, we agree that distinguishing between primary and secondary sarcopenia is important, especially because addressing underlying causes may benefit patients with secondary sarcopenia. Our review acknowledges this while specifically focusing on cardiovascular disease as one of several potential contributors to secondary sarcopenia, with emphasis on their reciprocal relationship. Recognizing this relationship may help inform therapeutic strategies that address both cardiovascular disease and associated skeletal muscle dysfunction.

Third, we appreciate the authors' discussion of the multifactorial nature of sarcopenia. Consistent with this perspective, our review discusses the role of malnutrition, physical inactivity, neurohormonal modification, inflammation, oxidative stress, and endothelial dysfunction in contributing to the interrelationship between sarcopenia and cardiovascular disease.² We also welcome the authors' discussion of whole-body electrical stimulation as an additional potential intervention, especially for older people who are unable or unwilling to perform dynamic strength exercises. Furthermore, we appreciate the authors' emphasis on medications that can cause muscle wasting. As discussed in our review, although statins and beta-blockers play crucial roles in treating cardiovascular disease, further investigation is required to better understand their potential effects on skeletal muscle. For example, statins may exacerbate muscle loss in patients, while beta-blockers may be associated with increased total body fat mass without improvement in lean body mass.² Thus, these considerations outlined in our review are in line with the authors' point that the effects of cardiovascular medications on skeletal muscle may vary, and they emphasize the need for an individualized management strategy.

Lastly, we recognize that additional genetic and cellular mechanisms may contribute to sarcopenia. However, a comprehensive discussion of these pathways was beyond the scope of our review, which focused specifically on the interrelationship between cardiovascular disease and sarcopenia.

We thank the authors for their engagement with our work and for highlighting additional considerations in the evaluation and management of sarcopenia. We hope that this exchange further emphasizes the importance of recognizing sarcopenia as a multifactorial condition while advancing our understanding of its reciprocal relationship with cardiovascular diseases.

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