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The Underrecognized Role of Impaired Muscle Function in Cancer-Related Fatigue

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By Alexander V. Ng

This timely article by Drs. Davis and Walsh provides a succinct overview of the task-dependent mechanisms that could limit neuromuscular function to result in increased muscle fatigue or decreased muscle endurance. This work has particular importance to cancer survivorship, because such mechanisms could possibly explain part (or all) of the phenomenon of cancer-related fatigue (CRF). Anemia, cachexia, and malnutrition are well-understood consequences of cancer or its treatment that can contribute to CRF, but impaired neuromuscular or muscle function resulting in muscle fatigue has attracted comparatively little attention. This finding is somewhat surprising given that the process (decreased maximal force generation) or consequences (eg, decreased endurance) are readily quantifiable using the standard techniques highlighted by Drs. Davis and Walsh.

From a broad perspective, an understanding of muscle or neuromuscular fatigue could provide a mechanistic link that is somewhat lacking in some current models of CRF. For example, it is becoming increasingly accepted that exercise is one of the few effective tools for managing unexplained CRF in the absence of anemia or cachexia. The mechanism of action of exercise could be through preserving muscle strength or endurance by preventing deterioration of function or by enhancing it.[1] This process could be particularly important in the case of peripheral fatigue secondary to disuse, whereby exercise could be thought of as a countermeasure to disuse. Of course, exercise could also exert a beneficial central effect on altered mood such as depression, which is a common correlate to fatigue.

Another possible mechanistic role for muscle in CRF that has not been fully explored centers on the relationship between proinflammatory cytokines and fatigue not explained by cachexia or anemia. In some cancers and treatments, proinflammatory cytokines are clearly becoming players, although the mechanisms have not been fully elucidated.[2] In the case of cytokine-mediated fatigue, inflammatory cytokines could have an end-tissue result that could reside in the mitochondria of muscle and manifest as a decrease in muscle endurance, or an increase in fatigability. Production of proinflammatory cytokines could occur from cancer or its treatment and exert a systemic effect some distance from the site of origin. Certainly, any role for impaired oxidative mitochondrial processes could be elucidated with ^{31}P magnetic resonance spectroscopy, as suggested by Drs. Davis and Walsh.

The authors make a case for CNS involvement in the fatigue of various chronic diseases including cancer. The implications for CNS impairment are far-reaching in cancer survivorship. For example, in many patients with breast cancer undergoing chemotherapy, the so-called chemobrain phenomena can be manifest as impaired cognition. This implies a chemotherapy-induced central alteration, which might be paralleled by impaired central activation to muscle contraction. Drs. Davis and Walsh emphasize the utility of transcranial magnetic stimulation (TMS), which, along with other electromyographic techniques, could help elucidate whether central motor impairment occurs in this population as well as test other intriguing and clinically relevant questions. Indeed, our own initial observations using TMS suggest a supraspinal role for decreased muscle endurance, albeit in a single survivor of breast cancer.[3]

Although the authors present a strong and valid argument for centrally mediated fatigue in cancer survivors, including their own excellent work, a potential contribution from peripheral factors should not be neglected. Bruera and colleagues showed evidence for peripherally mediated muscle fatigue during electrically stimulated contractions in women with advanced breast cancer.[4] In our own preliminary work with survivors of prostate cancer undergoing radiotherapy, we observed decreased endurance consistent with mitochondrial oxidative impairment with no central impairment.[5] However, a possibly centrally mediated decrease in neuromuscular efficiency has also been reported in this population.[6] Interestingly, despite this decreased neuromuscular efficiency, at rest and during exercise, the rate of muscle fatigue per se was not affected.[6]

The Clinical Relevance of Both Muscle Fatigue and CRF

Fatigue has different meanings to different people and disciplines. As we begin to understand more about fatigue, it becomes important to differentiate, to the best of our abilities, exactly what domain of fatigue we refer to. The protean nature of the fatigue construct was acknowledged by the authors, yet the current review presents a clear overview primarily of muscle or neuromuscular fatigue. The overriding question then becomes to what extent can muscle or neuromuscular fatigue explain the symptoms of cancer-related fatigue. In the case of multiple sclerosis, an autoimmune disease, symptomatic fatigue and muscle fatigue can be independent.[7,8] This last point suggests that although an understanding of neuromuscular processes may be critical to comprehending CRF, muscle fatigue and CRF may also be two independent entities. However, even if this is the case, it would not by any means imply that muscle, or physiologic, fatigue is unimportant to oncologists, because both CRF and muscle

fatigue are both clinically relevant in their own right. Finally, because CRF is most often reported as subjective fatigue (quantified by survey or questionnaire), use of a multidimensional survey instrument, with a subscale that might be sensitive to muscle or neuromuscular fatigue, could help to promote a greater understanding between muscle fatigue and CRF.

Drs. Davis and Walsh have presented a clear overview of muscle fatigue and the techniques to study it in health and disease. Their work will help to promote a greater appreciation of the role that muscle fatigue may play in the sometimes debilitating CRF so often experienced by cancer survivors before, during, or after treatment. In addition, their overview should stimulate research in an area that, despite recent attention, remains in its infancy. Only when there exists a clear understanding of CRF, including muscle fatigue, can optimal therapeutic interventions be developed.

Conflicts of interest: None to disclose

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