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Reply: Muscle abnormalities in Long COVID

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Dear Editor,

The biology of the "kickbacks" (post exertional malaise, PEM) after activity experienced by people with the post-COVID-19 condition (long COVID) is debated. Some specialists believe it is a result of a protective brain response, and others that it is the result of pathophysiology in the muscle itself. Appelman and colleagues report on muscle damage following a maximal effort physical exercise test in patients with PEM with the COVID-19 condition, and these results are interpreted as showing that exercise damages the tissues of people with PEM and should therefore be avoided. However, we believe the data reported do not support this interpretation, as the patients were substantially deconditioned; the physical activity was extreme and biological changes would be expected in anyone; and there were no control patients with a post-COVID-19 condition without PEM. The implications of erroneous interpretation of these data could result in patients fearing that PEM causes physical damage and consequently avoiding approaches to rehabilitation that could help them. Our criticisms are as follows:

The patients studied with post-COVID-19 condition were substantially less active before the experiment than the controls were: average steps per day was 4000, compared to 8000 in the controls. Noteworthy, these data only concern the previous week, although deconditioning effects carry over from longer time periods. Moreover, no data are given about other physical activity, whereas patients experiencing PEM usually reduce significantly moderate to intense exercise[1]. It is already known that changes to muscle fibers are strongly related to training over several weeks[2]. Their baseline data showed deconditioning both from the maximal exercise test, and from skeletal muscle biopsy: higher proportion of highly fatigable glycolytic fibers, trend to lower capillary-to-fiber ratio, lower mitochondrial enzyme activity and lower ratio of citric acid to lactate (shift away from oxidative metabolism)[3–5]. As observed in ordinary life, there can be severe muscle pain when returning to intense exercise after periods of a few weeks of relative rest, which gradually disappears when the interval between exercises is shortened. Indeed, the observed morphological and metabolic muscle changes after maximal exercise test could all be consequences of unusually intense exercise, especially in patients who are physically deconditioned.

The study did not include muscle data from patients without PEM, so linking PEM to these muscle changes (which could be present also in people with post-COVID-19 condition without PEM) may be misleading, and furthermore this putative link lacks clinical plausibility. No detailed clinical description of PEM symptoms is provided, but among symptoms reported by patients one and eight days after intense exercise, none indicative of muscle pathology changed. It is of note, that the usual PEM symptoms and their duration described in long COVID or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS, in which PEM is commonly reported[6]) do not correspond to the post-exercise symptoms of known inflammatory myopathies, metabolic, or mitochondrial disorders[7,8].

The authors note that all the patients experienced PEM, despite considerable variability in initial muscle characteristics, and conclude that "the pathophysiology of fatigue and a reduced exercise capacity is distinct from the rapid development of PEM in long COVID patients." An alternative interpretation is that a patient's experience of symptoms correlates poorly both to the physical effort and any pathological muscle changes seen in this population. A recent study on chronic fatigue conditions, including ME/CFS, shows an alteration of effort preference, rather than physical fatigue, due to dysfunction of integrative brain regions, with consequences on autonomic functioning

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and physical conditioning[9]. Therefore, an alternative explanation of post-exercise symptoms is that they result from the interaction between altered interoception (conscious and unconscious self-awareness of internal bodily state), allostatic load (failure of stress adaptation with perceived burden that influences how current and future energy needs are maintained) and peripheral influences (muscle fatigue).

The authors also note: "The development of post-exertional malaise could lead to a further reduction in exercise capacity in patients, as the acute reduction in mitochondrial SDH activity, occurrence of tissue necrosis, and possibly intramuscular accumulation of amyloid-containing deposits could worsen skeletal muscle metabolism and force production over time, causing a vicious downward circle." This suggestion is not supported by the observation that there were no significant differences in muscle pain, fatigue severity scale or daily step count before and after the PEM. In addition, many patients have reported complete recovery despite initially experiencing PEM[6]. Nevertheless, the fear of developing PEM has the potential to contribute to a vicious circle of an attentional focus on symptoms, leading to exercise avoidance which itself worsens the symptom experience and leads to further physical deconditioning and associated disability.

Although the authors did not provide any recommendations about physical activity for patients with long COVID, their findings have been widely interpreted in the media as indicating that exercise causes muscle damage in people with this condition, implying that exercise should be avoided. We are of the view that this interpretation is both scientifically unfounded and harmful to patients. Indeed, although we agree that intense exercise, such as the type tested, is not to be recommended, several studies have reported benefit from more gradual increases exercise both in patients with ME/CFS[10] and patients with post-COVID-19 conditions[11]. It is particularly notable that no patient in these studies of the benefits of collaboratively graduated exercise had to stop because of worsening of symptoms[1,11–15]. An interpretation of the data that exercise is always harmful must therefore be robustly corrected.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

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Author contributions

The authors confirm their contribution to the paper as follows: study conception, draft manuscript preparation: B.R., P.G., J.C.. All authors (B.R., P.G., Y.A., D.H., A.D., D.W., M.S., B.G., P.L., M.T., P.F., W.H., T.P., C.L., V.W., T.C., J.C.) contributed to the development and refining of the manuscript. All authors (B.R., P.G., Y.A., D.H., A.D., D.W., M.S., B.G., P.L., M.T., P.F., W.H., T.P., C.L., V.W., T.C., J.C.) reviewed the results and approved the final version.

Competing interests

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Additional information

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