Study gives insight into post-exertional malaise in Long COVID patients

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A new study on Long COVID provides insights into one of its most common and debilitating symptoms, post-exertional malaise (PEM), which occurs when patients experience a worsening of many or all their other Long COVID symptoms after even minor physical or mental activity. Specifically, the study provides evidence for some hypotheses for how SARS-CoV-2 infection causes the disorder, and evidence against other hypotheses.

Most commonly, fatigue is worsened by PEM, often becoming incapacitating to the point that patients can barely function in their daily activities. Many hypotheses have been put forward for how SARS-CoV-2 infection results in PEM. They include persistence of the virus in the body, dysfunction of mitochondria, systemic inflammation, immune-system abnormalities, hormonal imbalances, and low blood flow to muscles with subsequent hypoxia.

With respect to the hypoxia hypothesis, the concern is that amyloid proteins get deposited in blood vessels. This buildup would then obstruct blood flow to the muscles.

Amyloid proteins are long fibers formed from normal cellular proteins, and often form when cells produce an unusually large quantity of a particular protein. They are most commonly associated with Alzheimer's disease, but amyloid can accumulate in any organ and cause disease.

The researchers designed the study to address all the aforementioned hypotheses of PEM. They recruited 25 patients with Long COVID and 21 healthy controls, all of whom followed the same study protocol. The researchers conducted interviews, physical examinations, exercise testing, muscle biopsies and blood tests. They also had participants complete surveys and wear an accelerometer to measure daily physical activity level.

The study had strict inclusion criteria for patients with Long COVID. Each patient was diagnosed by two expert physicians using World Health Organization (WHO) criteria for the disorder. The physicians also ruled out other causes of their symptoms and ensured the patients did not have symptoms prior to COVID. Furthermore, their post-exertional malaise was confirmed by their responses to the DePaul Symptom Questionnaire for Post-Exertional Malaise (DSQ-PEM).

Notably, PEM is a symptom of other disorders beyond Long COVID, especially myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Researchers studying these disorders developed and validated the DSQ-PEM prior to the COVID-19 pandemic. Thus the DSQ-PEM has a history of accurately differentiating patients with and without PEM regardless of cause. Prior Long COVID studies have used it as well.

The study found that Long COVID patients had substantially lower power output and VO2max on exercise testing. VO2max is a measurement of the amount of oxygen an individual's body can utilize during maximal levels of exercise. It is considered the best indicator of endurance. The lower VO2max in patients was not explained by failure to reach maximal effort as indicated by multiple physiological and biological parameters measured during the exercise test.

The researchers ruled out cardiovascular and pulmonary disease as an explanation for the reduced performance as well. Additionally, accelerometer data, muscle biopsy and study of muscle metabolism all ruled out muscle atrophy due to inactivity in Long COVID patients relative to controls.

On muscle biopsy, Long COVID patients had a higher proportion of so-called "fast twitch" muscle fibers relative to controls. This finding is significant because these muscle fibers undergo rapid fatigue. They output short bursts of high power and then take long periods of time to recover before they can generate power again.

Robert Wüst, one of the co-authors of study, noted: "We know that it is difficult to change fiber types in people, and that it doesn't happen with inactivity. Something else is changing the fiber types."

Furthermore, when the researchers accounted for size of muscles in patients and controls, patients had lower levels of skeletal muscle force. This indicates that the fiber composition of muscles was significant regardless of levels of fitness.

The researchers also found reduced mitochondrial function in Long COVID patients vs. controls through various metabolic tests. Significantly, it was not a reduction in mitochondrial numbers or activity, but a qualitative reduction in the ability of the mitochondria present to produce cellular energy through a process called "oxidative phosphorylation." Long COVID patients had reduced oxidative phosphorylation activity relative to controls both pre- and post-exercise, demonstrated via study

of their muscle biopsies.

This finding is consistent with a prior study covered by the *World Socialist Web Site*, which found persistent reductions in the production of certain key mitochondrial enzymes required for oxidative phosphorylation post-SARS-CoV-2 infection. That study, however, did not look at skeletal muscle but instead visceral organs, including the lungs and heart.

The net effect of these two findings on muscle fibers and mitochondria is that they explained the lower exercise capacity of Long COVID patients. As noted, the researchers were careful to select patients to exclude other explanations like prior heart or lung disease.

Another significant finding was that every Long COVID patient in the study experienced PEM after their exercise test. This confirms the appropriateness of the strict inclusion criteria and the validity of the DSQ-PEM survey. After the exercise test, the Long COVID patients experienced a variety of symptoms, including worsened fatigue, muscle pain and cognitive symptoms for up to seven days.

Wüst commented, "Their mitochondrial function is impaired rapidly upon exercise. This can make them go into a vicious cycle, because every time they overexert themselves, they get a crash in their mitochondrial function and their metabolism."

The researchers were nevertheless cautious in interpreting the reduced exercise capacity in Long COVID and its causes. They noted that the findings do not readily explain PEM in Long COVID patients. First, shifts in muscle fiber composition take place over long time periods, whereas the patients experienced PEM the day after exercise. The researchers also could not rule out that patients had lower exercise capacity and mitochondrial function prior to contracting COVID-19.

On muscle biopsy, the researchers did find increased amyloid deposition in Long COVID patients relative to controls. Both groups had increased post-exertional amyloid deposition in muscle. However, the amyloid deposits were not in blood vessels and did not cause hypoxia. The ultimate significance of the amyloid is unknown and a topic for future research.

The muscle biopsies of Long COVID patients also showed greater degrees of tissue damage, both pre- and post-exercise. These areas of damage in patients were associated with greater signs of tissue regeneration in response to the damage. The researchers concluded that these findings are a possible explanation for symptoms of fatigue and muscle pain and weakness in patients' post-exertional malaise.

The analysis of immune disturbances did show that Long COVID patients differed significantly in the numbers and types of immune cells present in the muscle, and the changes in these numbers with exercise was also different. The findings were suggestive that Long COVID patients' immune response to muscle tissue damage was suppressed relative to controls.

Finally, the two groups did not differ in the presence and levels of SARS-CoV-2 nucleocapsid protein or the levels of immune B cells. Thus ongoing viral replication as a cause of PEM was not a factor in this study.

The researchers summarize that PEM in Long COVID is characterized by local and systematic reductions in mitochondrial metabolism, severe exercise-induced myopathy, infiltration of muscle by amyloid-containing deposits, and significant variations in the numbers and types of immune cells present in muscle. Understanding the molecular pathways that result in these findings and their relative contribution to PEM remain topics for future study.

The study is limited, as the researchers note, by the relatively small numbers of participants. Also, given that it was an observational study, no conclusions about causality may be drawn. The patients included in the study all had severe Long COVID, so the results do not necessarily generalize to all patients with Long COVID.

Nevertheless, the study fills several gaps in our knowledge and helps improve our understanding of PEM in Long COVID. In particular, it confirms that patients with PEM get worse, not better, with exercise.

"Normally we know from all the other chronic diseases that exercise is good for you, that exercise is medicine," says Wüst. "However, these patients do get worse."

The ongoing affliction with Long COVID of tens of millions of people worldwide, a number that is growing daily due to the mass infection and reinfection of the global population enabled by the criminal policies of the ruling class, will continue to require the best efforts of scientists around the globe to understand and develop treatments for the disorder and its worst effects, including PEM. As insights are gained into the disorder, the impetus for a global elimination strategy for SARS-CoV-2 grows ever stronger.

However, such a global public health strategy remains impossible under the current capitalist system that prioritizes profits over human health and well being. The lesson for the international working class is that replacing capitalism with a world socialist economy is an urgent priority to address the pandemic and its dire consequences.