

Hypothesis summary:

Acidosis may underpin Long Covid's many symptoms

Long Covid, formally known as PASC, affects the daily lives and livelihood of millions of sufferers worldwide. The Research-Aid Networks team has come up with a new hypothesis that could potentially explain many of Long Covid's widely varying symptoms. The scientific paper describing this hypothesis was published in the journal *Frontiers in Immunology* in April 2023. The article you are reading now is the explanation for those without a medical or related scientific background.

Long Covid, or PASC

A couple of months into the current SARS-CoV-2 pandemic it became clear that some people never seem to recover after catching COVID-19. This includes many people with a mild initial infection. The WHO estimates that about ten to twenty per cent of the people who are infected with COVID-19 develop what is officially called Post-Acute Sequela of COVID-19, or PASC. The condition is also known by the patient-coined term Long Covid, with patients calling themselves Long Haulers.

The symptoms vary widely from person to person, both in terms of which organs are affected and severity. It can be so severe people become bedridden for months, years or indefinitely. Common symptoms include brain fog, memory problems, heart rate dysregulation, shortness of breath, chest pain, headaches, muscle pains, exercise intolerance and ongoing exhaustion.

There are a lot of ideas about what could underpin these symptoms. But before we go into that, let's take a small step back and see what happens when you get infected with SARS-CoV-2, the virus that causes COVID-19.

How it starts: the infection

The virus enters your body through your nose or mouth. The first thing it does is infect your airways and/or lungs. Here, it causes inflammation and tissue damage. At first doctors and scientists believed that was the main problem and that COVID-19 is mainly a respiratory disease. But it has since become clear that the virus is also especially good at damaging the cells that make up the lining of blood vessels, called endothelial cells. This causes the blood vessels to become 'leaky'. The virus can take advantage of that and enter the bloodstream. Once it's in your blood, it can spread from the lungs throughout your entire body.

This doesn't just happen in people with severe COVID-19. It can also happen in people with a mild initial infection, and it's probably what happened in patients with Long covid. Scientific research into what happens next, and what exactly causes Long covid, has thus far led to several hypotheses. There is proof for each of them. Like the symptoms, the underlying cause or causes may vary somewhat from person to person.

Current Long Covid hypotheses

One of the current Long Covid hypotheses is that its symptoms are caused by residual damage to organs and other tissues. Once the virus is in your bloodstream, it can cause inflammation and damage throughout your body. If your body isn't able to repair this damage, this can lead to all kinds of symptoms, depending on which organs and tissues are affected exactly.

There is also some proof that viral persistence could be the cause of Long Covid. It is possible that the virus is still present in the body of long haulers, hiding out in organs like the gut, or perhaps even

the brain. There is even some proof that the virus can reprogram cells of the immune system, making it extra hard to get rid of. Traces of the virus have been found in long haulers many months after their initial infection.

Then there's the idea that the immune system of Long Covid patients has become stuck in a pro-inflammatory state. Either because the virus is still present somewhere, or because of newly developed auto-immunity. Evidence for this is the presence of pro-inflammatory compounds and auto-antibodies in the blood of Long Haulers.

Finally, there is also evidence of the persistent presence of tiny blood clots. These micro-clots are probably formed by the ongoing inflammation and damage to the lining of the blood vessels. They can block small blood vessels, preventing organs and tissues from getting enough oxygen and nutrients.

A unifying principle: acidosis

All in all, enough ideas to go on. But one thing that still lacks is a unifying hypothesis about what could underpin Long Covid's many symptoms. In a new scientific paper, the Research-Aid Networks team proposes such a unifying idea. Simply put, they believe the problem may be ongoing acidosis.

Our human bodies function best when the acidity, or pH, of our blood and tissues is about 7.4. If the acidity is too high (and pH too low), your cells and organs can't function properly. The reverse is also true: if the environment of your cells and organs becomes too alkaline (and the pH too high), problems arise. So your body works hard to constantly try and maintain a steady pH level. There are multiple ways in which it can do this, such as eliminating acidic compounds through your urine or producing more alkaline molecules (bases). But some diseases can throw this delicate system out of balance.

COVID-19 is one of them. As many as 73% of the COVID-19 patients who are admitted to the hospital have an abnormal blood pH. In some patients it is too acidic; in others too alkaline. This results in what's medically known as acidosis and alkalosis. Both are well known and serious medical afflictions. In patients admitted with COVID-19, the more abnormal their blood pH value is, the sicker they are and the worse their disease outcome is.

Acidosis in Long Covid

In their scientific paper Research-Aid Network's Vicky van der Togt and Jeremy Rossman describe why they believe ongoing acidosis also occurs in Long Covid. As mentioned before, the ongoing inflammation and/or micro-clots in the bodies of Long Covid patients prevent oxygen from reaching organs, muscles, and other tissues. But our cells need oxygen to produce energy and to function. You may remember from biology class that in the absence of oxygen, cells switch to a different way of producing energy, with lactic acid as a by-product. Lactic acid is what makes your muscles feel sore and tired after vigorous exercise. And since it's an acid, production of an abnormally large amount of it may throw your body's pH-value off balance.

There may even be an additional mechanism at hand. Again, as mentioned, the SARS-CoV-2 virus seems to be able to reprogram other cells. There is evidence that it can make cells change their metabolism, increasing the likelihood that cells will use the energy-producing method that causes a build-up of lactic acid, hereby further disrupting the acid-base balance.

Also, acidosis itself promotes inflammation. So, adding everything up and combining it with what's already known about Long Covid, it is possible that Long Covid patients have become stuck in an ongoing cycle of inflammation and acidosis.

How it explains the symptoms

Acidosis can manifest itself in many ways, and there is a lot of overlap with the symptoms of Long Covid. Some of the links are obvious, like muscle fatigue, muscle pains and general exhaustion. But acidosis can also cause gastrointestinal problems, high heart rate and arrhythmia. And it could even be the cause of brain fog and other cognitive symptoms. Under normal circumstances, our brains are well protected from what's going on in the rest of our bodies by the blood-brain barrier. But the SARS-CoV-2 virus has been shown to increase the permeability of the blood-brain barrier, so it may very well be possible that the acid-base balance in the brain of COVID-19 patients is also affected.

Though it may seem contradictory, it could also explain why the blood of some patients is too alkaline instead of acidic. One of the counter-mechanisms our bodies employ when our pH becomes too acidic is hyperventilation. Indeed: the abnormal breathing pattern seen in some Long covid sufferers. When you hyperventilate, you lower the level of CO₂ (which forms an acid) in your blood, making it more alkaline. If the level of compensation is too strong, it can even turn your formerly too acidic blood too alkaline, resulting in symptoms of alkalosis.

Next steps

The beauty of the hypothesis the team has put forward is that it isn't too hard to put to the test. In their research paper they sketch an outline of how this could be approached. Blood pH, arterial blood gases and lactate levels can quite easily be measured. According to the team it would be ideal to do this before and after light exercise and to compare the results of different groups of Long Covid patients with non-patients. It would also be interesting to track some of these parameters continuously in patients over a longer period and compare the results with the patient's own notes about symptoms and their severity. The team hopes that a research group that reads about their ideas is willing to pick up the challenge.

If the hypothesis about acidosis turns out to be true, this could open the way for new Long Covid treatments, as well as treatments for potentially related diseases like ME. Acidosis is well-studied and there are treatments available.