

Sex hormones could be key to treating long COVID

March 11 2024, by Lisa Jarvis, Bloomberg Opinion



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Among the many mysteries about long COVID, one of the most vexing has been why women seem to experience the condition more often and more severely than men. Now, scientists are starting to think hormones—and the different ways they affect women and men—could be part of the puzzle.

A new study by a prominent team of researchers from the Yale School of Medicine and the Icahn School of Medicine at Mount Sinai has found that women with long COVID had significantly lower levels of testosterone compared to those who had recovered from their infection. That difference seems to be driving certain symptoms female patients experience more often and more severely than [male patients](#), such as headaches, hair loss, muscle pain and memory issues.

Low testosterone in women was also associated with elevated levels of distinct immune cells, as well as signs that dormant viruses had been reactivated. While the researchers found that men with long COVID had lower levels of estradiol (indicative of low testosterone), their symptoms were less burdensome and different immune cells were activated.

The findings make clear that hormones deserve much more attention as scientists search for answers to why and how this often-debilitating condition manifests.

The work has yet to undergo [peer review](#), the typical process by which scientific studies are vetted, but I'm highlighting it now given the enormity of need in long COVID—recent data from the Centers for Disease Control and Prevention showed some 8.8 million people in the US were living with the condition in 2022—and this team's track record in conducting high quality research.

What's most exciting about this finding is that it could directly translate into [treatment options](#). People already take hormone replacement therapies for other conditions, making it easy to test whether testosterone could help long COVID patients. Even if hormones can't fix the underlying cause of the disease, significantly alleviating symptoms would be a huge advance. Best of all, this research could have broader implications about how hormones affect other chronic conditions.

This group of researchers has been methodically studying the differences between people with long COVID and those who easily recover from their infection. Last year, they identified a collection of biomarkers, or indicators of disease that can be measured in, say, blood or saliva, that are distinct in people with the condition. All of those signals pointed to an immune system constantly operating in overdrive, a finding supported by other recent developments in long COVID.

Testosterone is believed to act as a brake on an overactive immune system, so it shouldn't be a complete surprise that levels of the hormone would be depleted in people with long COVID. But because men make so much more testosterone than women, the difference in the hormonal makeup of long COVID sufferers is easily buried in population-level data.

Indeed, the team previously identified low levels of a different hormone, cortisol, as one of the most prominent characteristics of the condition. But, after separating out the sexes, testosterone emerged as an even better predictor, says Akiko Iwasaki, the Yale immunobiologist who co-led the work.

One caveat: the researchers don't have data on people's hormone levels before they contracted COVID. But while they can't say for sure that the long COVID patients didn't start out with low levels of testosterone, their strong suspicion is that those would already have been picked up by a

doctor since they would cause other health problems.

The team is now trying to get more granular detail about how testosterone and cortisol levels fluctuate throughout the day. When we're healthy, these hormones rise and fall on a carefully-timed schedule. If they turn out to be permanently lowered in people with long COVID, it could mean something has going wrong with the organs that make them; if they've simply lost their rhythm, maybe all that's needed is to restore the correct cadence.

Hopefully, we'll have an answer soon. The team is now busy analyzing the hormone levels in saliva samples collected multiple times a day from both healthy people and long COVID patients.

Once that's sorted, the next stepâ€"one that, given the urgency of long COVID, must happen as soon as possibleâ€"would be to test whether hormone replacement therapy could alleviate symptoms.

Such a trial should be designed with care. If done right, it could not only lead to a treatment for long COVID, but also teach us more about the complex interplay between hormones and our immune system. Teasing apart those interactions could help explain why treatment is (or isn't) helping these patients, while potentially offering insights on other chronic conditions.

We can't let the opportunity go to waste. For too long, sex hormone differences have been seen as an inconvenient liability in clinical trials rather than a variable worth considering. Until recently, many drugs were only studied in male mice (lest the results be muddied by fluctuating female hormones), and even human tests skewed toward men.

Meanwhile, [chronic conditions](#) like ME/CFS (commonly known as chronic fatigue syndrome), Lyme disease, and now long COVID, tend to

be more common or more severe in women. Time and again, those women's symptoms are dismissed as psychological rather than physical.

This latest study illuminates our limited knowledge about the role of hormones in chronic disease and should be a clarion call for more work in long COVID and beyond. That can help "start to right the wrongs of this sort of sexism and ableism in women's health," says David Putrino, director of rehabilitation innovation for the Mount Sinai Health System, who helped lead the study.

Iwasaki says the team's decision to study sex [hormone](#) differences was inspired by a story she heard from the mother of a trans child whose long COVID profoundly improved after he started taking [testosterone](#) as gender-affirming therapy. That single anecdote added to other stories trickling in from people whose symptoms improved when they took hormones for other reasons.

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Citation: Sex hormones could be key to treating long COVID (2024, March 11) retrieved 28 April 2024 from <https://medicalxpress.com/news/2024-03-sex-hormones-key-covid.html>

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