

In men, high testosterone can mean weakened immune response to flu vaccine

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Scientists at the Stanford University School of Medicine have linked high testosterone levels in men to a poor immune response to an influenza vaccine.

In a study to be published online Dec. 23 in the *Proceedings of the National Academy of Sciences*, the investigators show that [men](#) with relatively high amounts of circulating testosterone benefit less, as measured by a boost in protective antibodies after vaccination against influenza, than do men with lower [testosterone levels](#) and women.

In the study, women had a generally stronger antibody response to the vaccine than men. But the average response mounted by men with relatively [low testosterone levels](#) was more or less equivalent to that of women.

It has long been known that, for reasons that are not clear, men are more susceptible to bacterial, viral, fungal and parasitic infection than women are, and that men's immune systems don't respond as strongly as women's to vaccinations against influenza, yellow fever, measles, hepatitis and many other diseases. The new study may explain why this is the case.

Women are known to have, on average, higher blood levels of signaling proteins that immune cells pass back and forth to jump-start inflammation, a key component of immune-system activation. Furthermore, previous research in animals and in cell-culture

experiments has established that testosterone has anti-inflammatory properties, suggesting a possible interaction between the male sex hormone and immune response.

However, the new study found no connection between circulating levels of pro-inflammatory proteins and responsiveness to the flu vaccine. Nor does testosterone appear to directly chill immune response; rather, it seems to interact with a set of genes in a way that damps that response, said the study's senior author, Mark Davis, PhD, professor of microbiology and immunology and director of Stanford's Institute for Immunity, Transplantation and Infection.

"This is the first study to show an explicit correlation between testosterone levels, gene expression and immune responsiveness in humans," said Davis, who is also the Burt and Marion Avery Family Professor of Immunology. "It could be food for thought to all the testosterone-supplement takers out there."

The scientists took advantage of ongoing longitudinal research at Stanford. Since 2008, the research participants, who span a broad range of ages, have been getting blood drawn before and after receiving annual influenza vaccines. Many have returned year after year for their annual flu shots and associated blood draws. The participants' samples are analyzed at Stanford's Human Immune Monitoring Core, a distributed center deploying state-of-the-art instrumentation and expertise, for tens of thousands of variables, including circulating levels of numerous immune-signaling proteins; counts of various blood-cell subtypes; and the degree to which each of the roughly 22,000 genes in a participant's circulating [immune cells](#) is active or inactive.

"Most studies don't report on sex differences, a major determinant of variation in immune response," said the study's lead author, David Furman, PhD, a research associate in Davis' group. The Stanford team,

in collaboration with researchers at the French governmental research organization INSERM, aimed at probing those differences.

Analysis of samples from 53 women and 34 men showed that, on average, women had significantly stronger antibody responses to the influenza vaccine, consistent with other studies. "This was not surprising," Furman said. The women also showed higher average pre-vaccination blood levels of pro-inflammatory immune-signaling proteins, as earlier studies have found. But pre-vaccination levels of those proteins in a particular woman's blood didn't significantly predict the degree of her post-vaccination antibody response.

The analysis also showed that, in men, elevated activity of a particular set of genes that tend to turn on and off at the same time was associated with a weakened antibody response to the vaccine. The same gene cluster's activity levels didn't track closely with antibody response in women.

This piqued the interest of Furman. Previous studies have shown that some of the constituent genes of this multi-gene cluster (known as Module 52) are involved in immune regulation—and that activation of the module is somehow boosted by testosterone.

So he, Davis and their colleagues looked directly at testosterone levels in their male subjects. They separated the 34 men into two groups—those whose circulating levels of testosterone in its bioactive form were above the median level, and those with below-median levels of the hormone. They found that, in the high-testosterone men, high-activation levels of Module 52 genes correlated with reduced post-vaccination antibody levels. In the low-testosterone men—as in women—activation levels of Module 52 genes bore no significant relationship to the amount of antibodies produced as a result of the [influenza vaccine](#).

Additional analyses showed that testosterone reduces levels of certain transcription factors (regulatory proteins) that ordinarily prevent Module 52 genes from "turning on." In other words, higher testosterone levels result in more Module 52 expression. Several Module 52 genes have known immune-system connections; activation of one of these genes, for example, results in the accelerated differentiation of cells whose job it is to suppress, rather than foster, immune response. These connections make the interactions of the genes with testosterone an intriguing target of further exploration by immunologists, physiologists and drug researchers, Davis said.

But perhaps more intriguing, to many, is this: Why would evolution have designed a hormone that on the one hand enhances classic male secondary sexual characteristics, such as muscle strength, beard growth and risk-taking propensity, and on the other hand wussifies men's immune systems?

The evolutionary selection pressure for male characteristics ranging from peacocks' plumage to deer's antlers to fighter pilots' heroism is pretty obvious: Females, especially at mating-cycle peaks, prefer males with prodigious testosterone-driven traits.

Davis speculates that high testosterone may provide another, less obvious evolutionary advantage. "Ask yourself which sex is more likely to clash violently with, and do grievous bodily harm to, others of their own sex," he said. Men are prone to suffer wounds from their competitive encounters, not to mention from their traditional roles in hunting, defending kin and hauling things around, increasing their infection risk.

While it's good to have a decent [immune response](#) to pathogens, an overreaction to them—as occurs in highly virulent influenza strains, SARS, dengue and many other diseases—can be more damaging than the pathogen itself. Women, with their robust immune responses, are

twice as susceptible as men to death from the systemic inflammatory overdrive called sepsis. So perhaps, Davis suggests, having a somewhat weakened (but not too weak) immune system can prove more lifesaving than life-threatening for a dominant male in the prime of life.

More information: "Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination," by David Furman et al.

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