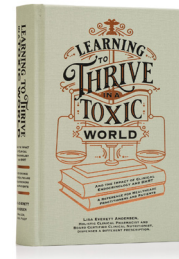


Hormones and the Immune System

Lisa Everett Andersen, B.S.C. Pharm, CCN, FIACP, FACA
Author, Holistic Clinical Pharmacist and Board Certified Clinical Nutritionist



If you have read Section III of *Learning to Thrive in a Toxic World*, then you have an idea of the varied roles sex hormones play in our bodies' daily functions. But do you know your immune system is dependent on hormones to properly respond to any acute invasion?

As with everything else they affect, steroid hormones have their own individual jobs and work synergistically to support a healthy immune system. Endocrine disruptors like synthetic hormones, as well as pesticides, herbicides, plastics, and other chemicals, create a deficit in endogenous hormones and upsets their balance subsequently diminishing the power of your immune system. This deficit is becoming a bigger and bigger hindrance to our overall health and well-being. For example, when any form of estrogen is swallowed and made to run in an abnormal fashion through the liver, it increases D-dimer. Studies in both China and the U.S. note elevated biomarkers D-dimer, as well as IL-6, CRP, LDH, and ferritin in those sick with COVID-19. Extreme amounts of LDH and D-dimer elevation in these patients were found to equal a higher chance of death. It becomes clear that improper hormone replacement and xenoestrogens actually can destroy the complex and amazing immune system we were designed to have.

HORMONES AND VIRUSES

In 2020, as intensive care unit physician, Sara Ghandehari, MD, treated an increasing number of COVID-19 patients, she noticed the majority of people with symptoms and the most severe cases in her ICU were male. She also noticed most of the women were of postmenopausal age, and they rarely treated pregnant women. In doing some research, she realized her hospital was not the only one seeing this phenomenon. Could it be women were protected by estrogen and progesterone? It is known that children and young adults, regardless of sex, typically fair well against the virus - so is another key factor testosterone?

Opposite of what has been witnessed for COVID-19, there is a higher percentage of reproductive aged females versus males who fall ill or die due to influenza, such as with the 2009 H1N1, avian H7N9 or H5N1 viruses. In 2009 a study was done on mice injected with the 2009 H1N1 influenza virus. Of the female mice, 75% of the placebo group died. However, 92% of a group treated with testosterone recovered. Of the male mice, they found that although testosterone levels were high pre-infection, all groups displayed significantly reduced levels on the 3rd day of infection and without testosterone supplementation. What we have found is testosterone treatment can be used to reduce pro-inflammatory IL-1 β cytokine levels in the lungs.

So what does it all mean? Keep in mind both men and women make progesterone, estrogen, and testosterone; women simply make much more progesterone and estrogen and men more testosterone. The rub is having and maintaining physiologic levels. When any of the sex hormones fall in men or women, whether due to aging or endocrine disruption, we become symptomatic and comorbidities creep in. These are the same comorbidities that make people the most susceptible to any virus, including COVID-19 and SARS. For example, low hormone production can lead to diabetes, insulin resistance, obesity, cardiovascular issues, increased inflammatory biomarkers, etc. Worst case COVID-19 outcomes are found among those who are diabetic, obese, have cardiovascular issues, elderly, and whose immune systems are otherwise compromised.

Hypogonadism, or low levels of sex hormones, increases pro-inflammatory cytokines. Cytokines are dispersed by the body as a reaction to virus invasion. Too many cytokines, however, create a cytokine storm in which the immune system attacks invader and healthy cells, causing great amounts of inflammation along the way. Hypogonadism also lowers nitric oxide activity. Nitric oxide exists in the body for a number of reasons, including to support a healthy cardiovascular system and as an antiviral agent. You can already see the importance of balanced hormones and how not having enough can make anyone sick. However, there is much more to the story.

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PROGESTERONE

Amphiregulin (AREG) is made by the body in response to many acute attacks, such as allergens, venoms, toxins, injury, infection, and viruses. It acts as both a resistor of such attacks as well as a mediator - in other words, AREG controls the body from reacting with an exaggerated immune response. It does this by managing inflammation and repairing tissues. But what does AREG have to do with hormones? Well, without progesterone, we have no AREG.

Progesterone is absolutely crucial to keeping our bodies functioning properly. It is protective against diabetes. It is an antioxidant, and helps in the regulation of Vitamin C and other antioxidants. It has been shown to pull excess fluids off the lungs in respiratory illnesses. Progesterone inhibits inflammation by decreasing cytokine release. It is protective of our cardiovascular system. It has been shown to improve the outcome of pulmonary disease when administered to menopausal women and is a major part of any pulmonary tissue repair following infection.

In a study, doses of both lethal and sublethal influenza A virus were injected into mice, some of which were then given progesterone therapy. Those treated with progesterone had a “faster recovery due to increased TGF- β , IL-6, IL-22, numbers of regulatory Th17 cells expressing CD39, and cellular proliferation, reducing protein leakage into the airway, improving pulmonary function, and upregulating the epidermal growth factor amphiregulin (AREG) in the lungs.” In other words, in the midst of a terrible and potentially deadly viral exposure, progesterone stimulated the immune system, protected the heart and lungs, and increased production of our friend, AREG, and in doing so, increased the chances of survival.

ESTROGEN

Because immune regulatory genes are encoded by X chromosomes, women genetically have a more stellar immune response than men, probably due to the need for procreation and gestation. Part of this immune protection is provided by estrogen.

When looking for clues as to who was getting sick with COVID-19 and who was not, researchers realized ACE2 proteins were acting as an open door for the virus into lung cells. The two most commonly used drug classes for hypertension are ACE II inhibitors (Angiotensin-converting-enzyme II inhibitors) and ARBs (Angiotensin II receptor blockers); medications that raise levels of ACE II proteins in the lungs. (While ACE II inhibitors reduce ACE II in the blood vessels, it raises the levels in the lungs.) ARB's raise levels as much as 500 times in the lungs. ACE is what corona viruses use to enter the lung cells. ACE2 is regulated differently in men versus women, which is thought to be because of estrogen. Studies show estrogen can reduce ACE2 protein in the kidneys, lungs, blood vessels, and perhaps other tissues as well.

Much like progesterone, estrogen protects against many of the same illnesses and disease states that make people susceptible to COVID-19, such as diabetes, cardiovascular issues, aging, etc. Estrogen modulates the function of beta cells, keeping insulin levels maintained and a comorbidity avoided. Estrogen encourages a healthy immune system by decreasing stress, increasing REM sleep, and acting as an antidepressant.

Most have heard of T helper cells, the immune response cells that produce interleukin and interferon - major fighters in any viral or bacterial attack. Balanced production of these immune responses is crucial - too little will not kill the virus and too much leads to attacking healthy cells. Estrogen improves T-helper-2 cell activity.

One of the more interesting activities of estrogen in immune response involves our nasal mucus. As one of the first filters of any air-borne substance, the cilia of the nasal lining blocks allergens or pathogens. Estrogen maintains the nasal mucus. When a foreign substance attempts to break through, estrogen determines the amount of nasal passage swelling due to turbinate hypertrophy and increases the production of mucus to trap and extract the invader substance. This nasal mucus contains mucins, electrolytes, IgA and IgG lysozyme, lactoferrin, and oligosaccharides, all of which have antiviral and antibacterial properties. Many times, this

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action prevents viral penetration deeper into the body. But if the invading substance makes its way past this first defense, estrogen increases phagocyte activity and natural killer cells in order to destroy the virus and create immunity.

Another way viruses and allergens are introduced into our bodies is by mouth. Estrogen stimulates hyaluronic acid production, IgG, IgA, etc., again, making it possible to neutralize the virus or allergen before it has a chance to take hold. Estrogen also improves function of the lower respiratory tract by acting directly on the bronchial epithelial cells to produce similar antiviral agents. Nitric oxide, with its anti-viral properties, is increased in production as well as activity due to estrogen signaling.

Perhaps one of the most important tasks of estrogen is quelling inflammation. In the most severe reactions to COVID-19 and SARS, inflammation has been shown to be a crucial deterrent of poor outcome and is the undying instigator of other severe health problems, including cancers.

TESTOSTERONE

Again, the comorbidities prevalent in COVID-19 patients are the same ones that occur with low testosterone production - obesity, diabetes, cardiovascular issues, increased inflammatory biomarkers, etc. Many who have suffered from COVID-19 infections had trouble breathing, and some had damage to their lungs. It is important to note that a 2020 study found “normal circulating testosterone levels show a protective effect on several respiratory outcomes,” while low testosterone is associated with a decrease in respiratory muscle activity. In fact, testosterone strengthens all tissues, including the muscles of the respiratory system (pharynx, lungs, diaphragm) and heart. Testosterone replacement improves peak oxygen consumption, and is shown to have a protective effect on several respiratory outcomes including forced expiratory volume (FEV1) and forced vital capacity (FVC). Testosterone also modulates the ACE II/interferon interaction in lung cells, allowing the body to essentially stop COVID-19 from affecting the lungs.

According to a recent study, “the hypothesis arises that (low) testosterone may have a role in the cascade of events leading to progression of COVID-19 infection due to the cytokine storm.” The authors of the study go on to say that testosterone has been shown to reduce pro-inflammatory cytokines. “Pro-inflammatory cytokines have a central role in the progression of COVID-19 infection. Reduction of cytokine activity and/or their receptors (anti-cytokine therapy), can be useful for treatment. In this context testosterone may downregulate inflammation. As a matter of fact, several studies carried out both in animals and humans showed that hypogonadism is associated with increased pro-inflammatory cytokines and that testosterone treatment reduces IL-1 β , IL-6, and TNF- α . Furthermore, the association between an increase of pro-inflammatory state and decline in testosterone is often observed in aging men and in men with stable coronary artery disease.”

Unfortunately, many people, perhaps more than those infected with COVID-19, have suffered mentally through the pandemic. Studies are slow on this front, but surveys have shown an increase in substance abuse, depression, anxiety, and possibly suicides. Low hormones can be the cause or add to the effects of any mental health issue. Testosterone is the hormone of comradery, giving us the desire to have connections with and empathy for others. It provides us with a sense of well-being and energy. So whether a person is sick with a pandemic virus themselves or concerned for others, it is testosterone that gives us the desire to compete in life and stay alive!

DHEA

Much like testosterone, DHEA strengthens all the muscles including skeletal, heart, and respiratory muscles (pharynx, lungs, diaphragm). When your muscles are strong, it is more difficult for viruses to affect them. DHEA is another hormone that directly affects the immune system by promoting T cell function in lymphocytes, increasing monocyte immune cell titers, IL-2, and natural killer cell numbers and activity. DHEA is vital for helping to increase the titers of beta immune cells and beta cell activity as well as increasing IgFI and protecting the body from insulin resistance, optimizing metabolism and keeping diabetes in check.

PREGNENOLONE

We have discussed inflammation's role in viruses. Many scientists believe controlling the inflammation of COVID-19 may be just as important as providing antivirals. To combat the inflammation, a large amount of doctors turned to synthetic corticosteroids. In a case study, 2104 patients on ventilators or oxygen therapy were given 6mg of dexamethasone for 10 days. It did reduce deaths within that population by 1/3, however the therapy showed no benefit for any COVID-19 patients who were not on ventilators. How could this be? If it decreases inflammation, why did it only work in the worst cases and with somewhat minimal results?

For starters, it is well known that synthetic steroids weaken the immune system. This, of course, goes against all efforts to help someone get well from a virus. This is also why WHO and the U.S. National Institutes of Health are not recommending these steroids. If dexamethasone was our only option, then risks could be weighed, but it is not.

In addition to the administered synthetic steroids, an observational study of hospitalized COVID-19 patients found excessive amounts of cortisol. Stress creates many hormonal reactions, including the production of cortisol, as it is our "fight or flight" hormone. It is what keeps us alive in dire, acute situations, but prolonged production results in decreased testosterone and pregnenolone, both of which reduce excessive inflammation. Many of the COVID-19 patients they tested had cortisol levels higher than patients that had just had major surgery. So again, what we have are steroids that are either foreign substances (synthetic steroids) or are excessive to the point of being destructive. And like what we would expect with synthetic steroids, the doctors found that the higher the level of cortisol, the faster the patient deteriorated.

Pregnenolone is a steroid hormone that is safe, effective, and complimentary to the body's biochemistry in reducing inflammation, so much so it can be administered as a substitute for a synthetic steroid, but not so much as to cause damage. It is anabolic in its activity rather than catabolic. Quieting autoimmune diseases and restoring normal immune function is one of its rock star qualities. It can be used in combination with DHEA to augment these effects. It is potent when administered with DHEA or alone in patients experiencing failure to thrive, cachexia, or general muscle-wasting. By inhibiting this deterioration, it keeps people from becoming too weak to fight off pathogens.

Those who are healthy do not tend to fall or to fall as hard from viruses as those who are not. There is no doubt that therapeutic supplements, exercise, clean water, restful sleep, and good hygiene are all part of what dictates your health. But as patients and practitioners, we need to remember the vital role our endocrine system plays in immune response.

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