Literature Review: The Role of Testosterone in Modulating Immune Responses to Vaccination Across Molecular and Systemic Levels

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Abstract

Vaccination remains one of the most effective strategies for preventing infectious disease, yet responses to vaccines vary significantly across individuals. Emerging evidence highlights biological sex—and specifically testosterone—as an important factor influencing immune function and vaccine efficacy. Testosterone, widely recognized as an immunosuppressive hormone, alters cytokine production and immune cell activity, leading to weaker antibody responses in males compared to females. This literature review synthesizes findings from both animal and human studies, including work by Posma, Wunderlich, and Furman, to evaluate testosterone's role at molecular and systemic levels. Results consistently demonstrate that elevated testosterone levels correlate with reduced vaccine efficacy, impaired protective immunity, and altered inflammatory pathways such as arachidonic acid metabolism. These findings challenge the "one-size-fits-all" model of vaccine administration and raise the possibility of developing sex-specific or personalized vaccine strategies. Understanding the immunomodulatory role of testosterone not only informs future vaccine development but also holds implications for improving public health outcomes through more tailored vaccination approaches.

Introduction

Vaccination has long been recognized as one of the most effective preventive measures against infectious disease. Vaccines target and stimulate the immune system to trigger a response and provide antibodies against potentially dangerous infectious disease. This stimulation allows the immune system to recognize and remove pathogens, thereby reducing morbidity and mortality rates. As the process of developing and administering vaccines evolve, there is a growing awareness of the consideration of who the recipients are of the vaccines. For example, there has been more attention drawn to the biological sex of the recipients of vaccines.

New research into this topic has revealed that the biological sex of the person receiving the vaccine has an impact on how they respond to it. Males and females have different levels of hormone levels such as testosterone that affect their biological processes. This blatant difference can induce different responses to vaccine administration. This newfound data has raised some questions regarding the current “one size fits all” approach to vaccine administration.

The objective of this literature review is to analyze the role of testosterone levels in vaccine responses among biological humans and to evaluate the possible need for personalizing vaccines based on sex. By analyzing the existing scholarly research, this review will address the pressing question: "What is the effect of testosterone levels on vaccine administration in humans: Should personalized vaccines be introduced based on sex?

Search Methods

To obtain a sufficient review of the scholarly literature on the topic of hormone effects in the immune system and its relation to vaccines, numerous databases were used. These included scholarly information domains such as EBSCO, Google Scholar, and the University of South Florida Library. The terms searched in databases that refined the research were as such: Immune

System, Cytokines, Lymph nodes, T-Cells, Testosterone in Immune system, Vaccines in Immune system. The literature was restricted to sources presented between 1990 and Present (2024).

The Immune Response

The immune system is a vital part of the human body for overall health. An immune response is triggered when a vaccine is introduced to the body. This immune response can be affected by a multitude of factors, including age, preexisting medical conditions, and even sex. When a vaccine is given, there is often early inflammatory events that follow (Siegrist 2016). The immune system uses two different types of responses to combat invading pathogens. One response is Innate, which occur to the same extent no matter how many times the infectious agent interferes with the body (Delves 2000). The other response is the adaptive or acquired response, which improves the responses as the immune system encounters the given infection repeatedly (Delves 2000)

The immune system uses Innate and acquired responses which often work together to eliminate pathogens (Delves 2000). In the adaptive (also referred to as acquired) response, the body acquires new types of immune cells to fight pathogens, known as B and T lymphocytes, often called B and T cells (Yatim 2015). The initial detection of pathogenic agents is typically done by the innate immune system; although, B-cells may also complete this task (Clem 2011). Specifically, the immune system detects epitopes on antigens, which are small subregions on the antigens that trigger recognition, and consequently an immune response. The Innate response will use antigen-presenting cells such as macrophages or monocytes to attach and bind to the infectious agents (Clem 2011). The macrophages or monocytes will then insert the processed antigen along with the MHC protein onto the surface of the antigen-presenting cell (Clem 2011).

The way that the vaccine induces immunity can be even further delved into. The response to a bacterial infection is different than one of a viral infection. The viral antigen will be connected to the MHC I protein and presented by the antigen-presenting cell to a CD8 cell which will likely trigger cell-mediated immunity. On the other hand, if it is a bacterial or parasitic antigen, the antigen will be bound with MHC II protein and presented by the antigen-presenting cell to a CD4 cell which will likely trigger antibody-mediated immunity (Clem 2011).

In the immune system, white blood cells play an important role in its immune function. Lymphocytes and Monocytes are two types of white blood cells. Monocytes are a part of the body's first line of defense and are especially important in innate immunity and Lymphocytes are specifically vital in the adaptive response of the immune system. Both types produce cytokines, which aid in the (re)modeling of tissues, whether it is developmentally programmed, constitutive, or unscheduled (Nathan 1991). As we delve into the molecular processes of the immune system, it is important to know the types of cytokines that originate from these Monocytes and Lymphocytes. Specifically, Lymphocytes produce IL-2 cytokines as well as others. The T cells and clones allow production of IL-2, IFNr, and TNF8, or IL-4, IL-5, IL-6, IL lo, and IL-13 as their unique products (Paul 1994). These are interleukins and interferons that coordinate immune responses. Monocytes release cytokines like tumor necrosis factor (TNF) and interleukin-1 (IL-1).

Cell membranes also play an important role in the immune system. Arachidonic acid is a crucial part of these cell membranes and has specific properties that can affect the immune system. Arachidonic acid is a polysaturated fatty acid, its chemical formula is C20H32O2 20:4 (ω-6), which characterizes many of its properties. 20:4 refers to the 20-carbon atom chain along with four double bonds (Hanna 2018). (ω-6) refers to "the position of the first double bond from the last, omega carbon atom" (Hanna 2018).

Arachidonic acid has four double bonds in the cis position which allows interaction with proteins and consequently providing fluidity, even at low temperatures (Hanna 2018). Furthermore, the four double bonds also enable interaction with oxygen which leas to bioactive oxygenated molecules through enzymatic and non-enzymatic mechanisms (Hanna 2018). When arachidonic acid is released, it is metabolized by key enzymes and leads to the formation of different eicosanoids. These include the Cyclooxygenase Pathway, which converts into prostaglandins and thromboxanes; and the Lipoxygenase Pathway, which converts into leukotrienes and lipoxins (Samuelsson 1987). Prostaglandins, thromboxanes, and leukotrienes all play a role in promoting inflammation. This allows for an effective immune response by allowing T and B cells to access and target pathogens or damaged tissues. Lipoxins, on the other hand, help resolve inflammation, promoting a shift from an active immune response to tissue healing and recovery.

Testosterone and the Immune System

It has long been known that testosterone is regarded as an immune suppressor. Consequently, this brings credence to the hypothesis of vaccine administration being affected by testosterone. The hormone testosterone can affect the cytokine production, so therefore, this can induce a difference in the immune responses of people of the opposite sex. A study done in 2004 by Elske Posma, Henk Moes, Maas Jan Heineman, and Marijke M. Faas explores this. They observed how there was a difference in specific cytokines production such as a decreased percentage of interleukin (IL)-2-producing lymphocytes, increased percentage of IL-12, IL-1*β,* and increased percentage of tumor necrosis factor (TNF)-*α*-producing monocytes in males compared with females (Posma 2004). The researchers investigated whether testosterone is a key player in this difference.

The results showed interesting findings that led to the team's conclusion. The key results were that a substantial decrease in the percentage of IL-2 cytokines producing lymphocytes after stimulation of the male lymphocytes in comparison to the female lymphocytes. Nevertheless, there was a difference in the percentage of IL-4 and IL-10 lymphocytes, as well as IFN- *γ* producing lymphocytes in males and females. Furthermore, there was an increase in the forementioned IL-12, IL-1β, and TNF-α cytokines producing monocytes in males rather than females. This led the researchers to look at how testosterone played a role in this cytokines production from both monocytes and lymphocytes. They found no effect of testosterone in the production of IL-2 cytokines or the IFN-γ cytokines. Moreover, they found that testosterone does play a significant role in the production of IL-12 and IL-1β by monocytes and increases the number of cells producing the cytokines.

Testosterone and Vaccine Efficacy – Study Analysis

Wunderlich and colleagues

The effect of Testosterone on Vaccines is an interesting topic, especially due to Testosterone being widely known as an immunosuppressive agent. A plethora of studies have been reviewed with a relation to varying types of vaccines to showcase the best discussion of this topic. Wunderlich; F. Thomas explains that testosterone was found to suppress the development of protective immunity in mice against infections with malaria parasites (Wunderlich 1993).

Consequently, a study was done on mice to showcase the specific effects of testosterone on the vaccine. The experiment used a s Plasmodium Chabaudi model, which assisted in providing insight into the relationship between hormone levels and vaccine administration. The mice experimented on in this study were from the inbred strain B 10.A and were given an anti disease vaccine which composed of surface membranes of P. chabaudi-infected erythrocytes (Wunderlich 1993). The surface membranes are referred to as ghosts because they are infected cells, rid of their internal components, but still retaining the infected “neo-proteins" (Wunderlich 1993). These ghosts acted as antigens to stimulate an immune response due to their infectious properties. As mentioned previously, the vaccine is anti-disease, which targets the disease to improve symptoms.

A group of the mice were selected, after the vaccine was administered, to receive periodic doses of testosterone. The testosterone was administered subcutaneously, twice a week for four weeks (Wunderlich 1993), which allowed for slower absorption into the bloodstream. The goal was to observe if testosterone affects the immune system’s response to a vaccine and also the “challenge” with infected erythrocytes (Winderlich 1993). This model clearly shows the effect of testosterone at both a molecular and macroscopic level and examines how hormonal modulation may affect the efficacy of the vaccine by suppressing the immune system.

Therefore, with the experiment being done with a control group and an experimental group, the researchers assessed whether the mice with testosterone treatment showed a reduced immune response compared to the untreated population. The studies findings showed that male mice exhibited reduced survival rates and impaired vaccine-induced immunity compared to their female counterparts. The experiment showed that only 55% of the mice population treated with testosterone were converted to self-healers, but in fact, a substantial 84% of the female population converted to self-healers. This indicated a difference in response due to sex, specifically there was a difference is immune response modulation. The data gives credence to the hypothesis that since testosterone suppresses the immune system, it impairs the efficacy of vaccines by reducing the immune system's ability to give a sufficient response.

The effect of testosterone treatment on vaccine efficacy is further proved in the dosage of the hormone. There were multiple doses administered to the experimental group and each dosage produced findings that overall coincided with the study's conclusion. Even at the lowest dose of 30 micrograms (0.03 mg), there was a notable decline in survival rates compared to the control. And then at the highest dose of 0.9 mg, the percentage of mice that converted to self-healers dropped to 34%. Moreover, testosterone had long lasting experimental effects. The obvious impairment lasted for weeks following the treatment's end. Even 10 weeks after the testosterone treatment was discontinued, only about 60% of the testosterone-treated mice could be converted to self-healers, which differs from the 100% of control mice. This shows the level of suppression of immune system functionality due to testosterone.

Furman and colleagues

Another comprehensive analysis done by David Furman and colleagues also provides insight into the effects of testosterone on vaccines in the immune system. This study analyzes the trivalent inactivated influenza vaccine (TIV) and testosterone's effect on it in the immune system. The study used participants that were either male or female to analyze the neutralizing antibody response to the TIV. The researchers investigated this using numerous immune system components such as serum cytokines, chemokines, blood cell subset frequencies, genome wide genome expressions, and different responses to vitro stimuli. The study was done on close to 100 total participants, with 53 females and 34 males (Furman 2014).

The study used baseline data from a previously published viable source where 91 healthy donors, in 2008 and 2009, participated in an influenza vaccine study at the Stanford-Lucile Packard Children's Hospital Vaccine Program.This was the case apart from the neutralizing antibody response to the vaccine and the "determination of testosterone measurements from the serum" (Furman 2014). The participants were separated based on the measurement taken, these separations were made based on age, sex, BMI range and more.

The blood was taken pre-vaccination and 21-35 days after the TIV administration. The blood was used for gene expression analysis. The peripheral blood mononuclear cells were then obtained through a process called density gradient centrifugation and kept at – 80 degrees Celsius and transferred to liquid nitrogen for preservation. To process the serum, before use, the serum was separated by centrifugation of clotted blood and stored at – 80 degrees. Peripheral blood mononuclear cells, also called PBMCs, along with whole blood, and serum were used for a variety of purposes, including levels of cytokines and chemokines, gene expression analysis, leukocyte subset frequency, testosterone levels, and CMV and EBV serostatus (Furman 2014). Samples of the serum from both day 0 and the last day were used for virus microneutralization titer determination (Furman 2014).

The results of the study showed an inverse correlation between the antibody responses and testosterone levels. As noted previously, testosterone is an immune suppressor, but the data in this study that focuses on the antibodies, further refines and supports this generalization. The study, using the contrast between men and women, found that women had a better and more robust antibody response than the male counterparts. This could be attributed to the higher levels of pro-inflammatory cytokines (Furman 2014). Moreover, this could be linked to the fact that testosterone inhibits antibody responses. The study narrowed further to include molecular mechanisms present in testosterone and vaccine efficacy. Furman and colleagues discussed the pathway of arachidonic acid. arachidonic acid is a polysaturated fat that plays a pivotal role in the inflammatory response and the immune response. When a vaccine is administered, cells are stimulated and enzymes release arachidonic acid from cell membranes, but testosterone can influence the expression of the genes in the arachidonic acid. Testosterone has been found to shift these toward a more anti-inflammatory phenotype, which is shown by reduced production of pro-inflammatory mediators. Furthermore, mechanisms have been found in the study, such as testosterone being able to bind to androgen receptors in immune cells. This leads to the upregulation or downregulation of genes involved in arachidonic acid metabolism. At a macroscopic level, this provides relevant information to support the assumption that testosterone, as an "immune suppressor", can weaken the immune response to a vaccine administered in the body (Furman 2014).

Discussion

By analyzing different arguments, assumptions, and conclusions in the scholarly conversation surrounding how testosterone plays a role in a vaccine's effect on the immune system, common themes can be analyzed to effectively review the literature. Many studies assumed and concluded that testosterone is an immune suppressor. With the given notion that men have an unsatisfactory immune response in comparison to women, studies such as one done by Furman and colleagues, one by Wunderlich and colleagues, along with a study by Elske Posma and colleagues have concluded that this is highly correlated to vaccine efficacy.

Another common theme is the molecular mechanisms that underlie tesosterones suppresion of the immune system. One key mechanism involves the influence of testosterone on arachidonic acid metabolism. As discussed earlier, arachidonic acid is a polyunsaturated fatty acid that plays a crucial role in inflammation and immune cell activation (Furman 2014). Ultimately the expression of genes involved in arachidonic acid metabolism can be changed by testosterone and effectively make the response to vaccines weaker.

The findings of these studies and scholarly journals have a significant impact on public health. Understanding the impact of testosterone on the effects of vaccines can lead to further research and academic discussion, which could then be applied to inform the development of personalized vaccines or vaccination strategies based on sex. Moreover, this research can have a profound impact on vaccination strategies for those with high testosterone levels and therefore improve vaccine efficacy. Future research could provide insight into the molecular mechanisms through experimental data collection and analysis. This could involve investigating the specific genes and pathways involved in the regulation of the immune response by testosterone. Additionally, studies could be done to experimentally determine if personalized vaccines are a viable option to improve vaccine efficacy and improve public health.

Conclusion

In conclusion, the research presented shows how testosterone significantly affects vaccine efficacy. With the conclusion that, because of testosterone's effect on the immune system, men often have a weaker immune response to vaccines than women. The scholarly conversation suggests that biological differences, particularly hormone levels, play a significant role in vaccine response. The implications for personalized vaccine strategies based on sex should be carefully considered, especially when aiming to optimize public health outcomes. Future research should focus on developing and testing sex-specific vaccine protocols to ensure equitable and effective protection for all recipients.

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