Immune system and COVID-19 by sex differences and age

Tiziana Ciarambino1, Ombretta Para2 and Mauro Giordano3

Abstract
In COVID-19 disease, are reported gender differences in relation to severity and death. The aim of this review is to highlight gender differences in the immune response to COVID-19. The included studies were identified using PubMed, until 30 October 2020. The search included the following keywords: SARS-CoV-2, COVID-19, gender, age, sex, and immune system. Literature described that females compared to males have greater inflammatory, antiviral, and humoral immune responses. In female, estrogen is a potential ally to alleviate SARS-COV-2 disease. In male, testosterone reduces vaccination response and depresses the cytokine response. In the older patients, and in particular, in female older patients, it has been reported a progressive functional decline in the immune systems. Differences by gender were reported in infection diseases, including SARS-CoV-2. These data should be confirmed by the other epidemiological studies.

Keywords
age, aging, COVID-19, gender, immune system, SARS-CoV-2, sex, vaccine

Date received: 12 January 2021; revised: 19 March 2021; accepted: 6 May 2021

Introduction
The novel coronavirus COVID-19 was reported, as a pandemic, by the World Health Organization (WHO), on 11 March 2020. The ages of infected people range from a 4-week-old to >90 years and very few cases are observed in children and infants. Male patients represent 59%–68% of all reported cases with higher mortality rates. In over 75-year subjects, this population, in fact, represent a poor immune function, and they are most susceptible to infection and to complications. In particular, the death rate in COVID-19 patients is 2.8% for female and 4.7% for male. In Italy, male patients represent 65% of all deaths with death ratio male/female: 1.79. For each female died for COVID-19, 1.5 to 2 males died for this virus. The quality and magnitude of immune response may, therefore, vary between men and women, pre- and post-menopausal women, or adults compared to children. Pre-menopausal adult women generally have stronger immune responses than children, men, or women during the post-menopause. Different are the factor for gender differences in COVID-19 infection. In particular, there are multifactorial reasons (such as genetics, lifestyle differences, comorbidities, hormones, immune system, and aging) for these differences. The aim of this review is to highlight gender differences in the immune response to COVID-19.

Methods
The included studies were identified using PubMed, until 30 October 2020. The search included the following keywords: SARS-CoV-2, COVID-19, gender, age, sex, immune system, and aging. Clinical trials, and
Immune response differences by gender

Sex hormones, for example, testosterone and estrogen, play diverse roles in immune responses. Estrogen receptors (ERα and ERβ) are expressed in a diverse array of immune cells (T, B, natural killer cells, macrophages, DCs, and neutrophils). It is well known that estrogen suppresses T and B cell lymphopoesis, activates B cell function, and influences T cell development. Moreover, estrogen regulates a number of cytokines (such as interleukin (IL)-1, IL-10, and interferon γ (INFγ)) that modulate the immune response. While estrogen has immune-stimulatory roles, progesterone and androgens are immune-suppressive and counteract the pathways affected by estrogen. In particular, progesterone increases IL-4, reduces IFN-γ T helper cell type 1 (Th1) responses, and reduces T cell proliferation and T cell dependent antibody responses. However, in CD8 T cells, progesterone reduces IFN-γ and cytotoxicity. The androgens also have immune-suppressive effects on the immune response. Testosterone in comparison to estrogen may predispose men to a widespread COVID-19 infection. Low serum levels of T, which should be supposed to characterize the hormonal milieu in seriously ill individuals, may predispose men, especially elderly men, to poor prognosis or death. Furthermore, the effect of sex hormones on immune cell functions are proposed to be dose-dependent. However, it has been reported that immune profiles by gender diverge as age increases, even though the hormone levels decrease with age.

Immune response differences by age

The age is factor that induces the modification of immune response. One of the crucial attributes of an aging immune system is a chronic low-grade pro-inflammatory state. This state is greater in female than in male subjects. To this regard, Ilardi et al. have reported that gender and aging are a risk factor for COVID-19 infection. In particular, it has been reported that immune-aging is an important factor in the increased susceptibility of older adults to infection as well as their poor vaccination responses. Immune-aging is strongly linked with a suboptimal innate immune response to viral pathogens. Physiological aging is accompanied, in fact, by a sub-clinical chronic low-grade state of systemic inflammation, inflamm-aging, characterized by elevated serum levels of acute phase proteins (e.g. C-reactive protein) and pro-inflammatory cytokines (e.g. TNF-α, IL-6, and IL-8). It has been reported that inflamm-aging predisposes older adults to severe COVID-19 by suppressing the immune response to SARS-CoV-2.

However, with aging, we observe both changes in cellular composition and in function. In particular, in older patients (>65 years old), females have increased frequency of T and B cells, while blood B cells (numbers and percentages) were lower in older male. To this regard, aging is accompanied by a reduction in the size of the peripheral B cell pool, with CD19+ B cells significantly lower in older adults. Some authors have reported an age-related increase in the percentage or number of circulating CD27+ memory B cells. Other study reported that the frequency of immunoglobulin M (IgM) memory B cells is decreased or unchanged with age, but aging is associated with secretion of antibodies that are weaker and of lower affinity. In addition, CD8+ T cells are particularly efficient in clearing virus-infected cells and promote the production of virus-specific antibodies that block the entrance of extracellular virus.

However, naïve T cell frequencies decreased with age, particularly in CD8+ T cells in both male and female subjects. This is associated with gradual replacement of functional epithelial cells with fat and fibrous tissue, thymic involution, and T cell immune-senescence. In female subjects are reported elevated thymic function compared to male at all ages. Another important factor of immune-aging is reduced natural killer cell cytotoxicity (NKCC), decline in lytic activity, and reduction in cytokine and chemokine production. Beyer et al. reported that female (18–64 years of age) generate a more robust protective antibody response and that the response of female to a half dose of the influenza vaccine is equivalent to the antibody response of male to the full dose. Moreover, Wang et al. evidenced that in older female, influenza vaccination has been associated with lower hospitalization and mortality rates compared to male. However, the progressive reduction in testosterone levels observed in males, with aging can promote cell damage and inflammation. Therefore, aging has been linked with such chronic activation of innate immunity, with low-grade inflammation.

Immune system in COVID-19 infection

The deleterious clinical manifestation of COVID-19 could be from a combination of exuberant innate immune responses and virus-induced direct cytopathic effects when the adaptive immune response fails to eliminate the virus. Severe COVID-19 patients exhibit significantly higher plasma levels of pro-inflammatory cytokine/chemokine, accompanied by impaired T cell and antibody response. The elevation of these cytokines, including IL-6, has led to the hypothesis that an innate “cytokine storm” is the main cause for the toxicity, respiratory depression, and end-organ damage, seen in the severe COVID-19 cases. However, it has been reported...
that dysregulated immune response was associated with the severity of COVID-19. In particular, disease severity was associated with reduced numbers of T cells in the blood and male subjects experience a stronger “inflamm-aging” syndrome than female. It has been suggested that an accumulation of senescent cells may be responsible for this increase in lung inflammation with aging.

The COVID-19 contributes to the damage to various organs, and it can infect endothelial cells and circulate through the body. In fact, severe endothelial injury has been found in the lungs from COVID-19 patients. Probably, the reduced susceptibility of females to viral infections could be attributed to the protection from X chromosome and sex hormones. It has been reported that dysregulated immune response was associated with the severity of COVID-19.

Females and viral infections

Female are disproportionately affected by autoimmune disorders, whereas male is more susceptible to infectious diseases. These differences are observed, both in terms of their intensity and prevalence. Probably, the reduced susceptibility of females to viral infections could be attributed to the protection from X chromosome and sex hormones. To this regard, it has been reported that the response to viruses differs between females and males. Several studies have described that, during viral infections, females have greater inflammatory, antiviral, and humoral immune responses compare to males. Sex steroids can have a crucial role on the function of inflammatory cells and regulation of the immune response. In fact, it has been reported that they exert the following actions:

- Suppressive role in immune functions, acting on the androgen receptors.
- Suppresses immune cell activity by reducing inflammatory and promoting anti-inflammatory mediators.

These responses contribute to better clearance of viruses, including SARS-CoV-2 in female subjects. These data are in agreement with other studies that described higher antibody levels in adult females compared to males. However, testosterone reduces vaccination response, while estrogen is a potential ally to alleviate SARS-COV-2 infection.

ACE-2 and gender differences

Angiotensin-converting enzyme 2 (ACE-2) represents the primary route of infection of COVID-19. It is located on X chromosome, and female may have higher levels of this enzyme. It is expressed in lungs, kidneys, myocardium, gastrointestinal system, and reproductive organs. Although it remains unclear how a greater expression of ACE-2 in female patients seems not linked to worst rates of infection and worst outcomes in COVID-19 pandemic, it is clear that ACE-2, that represents the route of infection, also exerts several immunomodulating effects that may explain less severe clinical outcomes. Actions exerted by this enzyme consist not only in the conversion of angiotensin I, but also in immunomodulation and prevention of lung injury, with a protective effect in female subjects.

What is known for Vaccine?

An effective vaccine is the best long-term therapy to the COVID-19 pandemic. The two most primary endpoints for defining the effectiveness of a COVID vaccine are as follows:

- Protection from infection as defined by seroconversion.
- Prevention of clinically symptomatic disease.

Effective vaccines are essential for interrupting the chain of transmission from animal reservoirs and infected humans to susceptible hosts. They are often complementary to antiviral treatment in the control of epidemics caused by emerging viruses. For rational COVID-19 vaccine, it is critical to understand the fundamental host–coronavirus interaction and protective immune mechanism. The benefit of a cocktail vaccine strategy could induce immunity that can protect the host against not only the S-ACE2 interaction and viral entry to the host cells, but also protect against the accessory non-structural adhesin proteins (e.g. nsp3), which might also be vital to the viral entry and replication. However, in relation to vaccine response by gender, a study of 331 Chinese patients, with confirmed SARS-CoV-2 infection, reported that the anti-SARS-CoV-2 immunoglobulin G (IgG) responses were related to the severity of the disease. The sex distribution of recovering cases was 36% and 65% for male and female, respectively. Interestingly, the anti-SARS-CoV-2 IgG titers were similar by gender in patients with mild COVID-19 disease. In patients with severe disease, the female subjects exhibited a higher antibody response than male, with the production of antibodies at earlier phases of the disease. These results were also consistent with other studies describing higher antibody levels (including more functional antibodies) in adult females compared to adult males. The more intense immune responses in female predispose these subjects to autoimmune diseases, and to experience more adverse reactions to the vaccine.
Conclusion

It has been reported that an age-related increase in viral-induced inflammation has associated with exaggerated response with significant lung damage, leading to the increased morbidity and mortality rates in older adults. The current literature about COVID-19 indicates that the immune system plays a crucial role in setting the severity of the disease. To prevent progression of the severe forms of the disease, the immune system needs to be targeted. Moreover, higher titers of anti-S and anti-N IgG and IgM correlate with worse clinical readouts and older age, suggesting potentially detrimental effects of antibodies in some patients. Even if they are not adopted in the current race for safe and effective COVID-19 vaccines, it is not too early for governmental agencies and not-for-profit organizations around the world to support the commercialization of these technologies to prepare for the need of rapid mass vaccination for the whole world in the next pandemic.

Key messages

- Females have increased resistance to viral, bacterial, fungal, and parasitic organisms than males.
- Females are less susceptible to microbial infections.
- Females have a higher innate immune response than males.
- Females produce lower levels of inflammatory mediators and increase the production of immunosuppressive molecules to reduce systemic inflammation.
- The protection of females to microbial and viral affections is attributed to the protection provided by the X chromosome and sex hormones, which modulate the innate and adaptive immunity.
- Elevated estrogen levels in female COVID-19 patients may reduce the severity and mortality of COVID-19 deaths through an elevation in the innate and humoral response.
- Men tend to have a higher risk of severe infection and mortality related to COVID-19.
- The severity of COVID-19 is related to the level of the pro-inflammatory cytokines and subsets of immune cells.

Acknowledgements

The authors thank the Doctor Cecilia Politi (Internal Medicine Department, Hospital of Veneziale Isernia, ASREM, Italy), and the authors also thank the doctor Laura Leoncini (Direttore Sanitario P.O. Marcianise, ASL Caserta, Italy).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Tiziana Ciarambino https://orcid.org/0000-0002-3917-1478

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