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Men and COVID-19: A Pathophysiologic Review

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Abstract

Coronaviruses are single-stranded ribonucleic acid viruses that can cause illnesses in humans ranging from the common cold to severe respiratory disease and even death. In March 2020, the World Health Organization declared the 2019 novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the first pandemic. Compared to women, most countries with available data report that men with COVID-19 have greater disease severity and higher mortality. Lab and animal data indicate that men respond differently to the SARS-CoV-2 infection, offering possible explanations for the epidemiologic observations. The plausible theories underlying these observations include sex-related differences in angiotensin-converting enzyme 2 receptors, immune function, hormones, habits, and coinfection rates. In this review we examine these factors and explore the rationale as to how each may impact COVID-19. Understanding why men are more likely to experience severe disease can help in developing effective treatments, public health policies, and targeted strategies such as early recognition and aggressive testing in subgroups.

Keywords

Men, COVID-19, SAR-CoV-2, coronavirus, pandemic, crisis, pathology, public health

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Coronaviruses, a large group of single-stranded ribonucleic acid (RNA) viruses, cause illnesses in humans ranging from the common cold to severe disease including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In December 2019 in Wuhan, China, a new coronavirus appeared that virologists believe originated in bats and transferred to humans via an intermediary animal host (Andersen et al., 2020). The new virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes the disease recognized by the World Health Organization (WHO) as 2019 new coronavirus disease or COVID-19 (MayoClinic, 2020). As a novel virus with little or no preexisting immunity to it, the SARS-CoV-2 spread through China and many countries. Recognizing its worldwide spread, in March 2020 the WHO declared COVID-19 as the first pandemic caused by a new coronavirus (WHO, 2020c).

COVID-19 infection can be asymptomatic or cause symptoms such as cough, fever, and shortness of breath that usually appear within 5 to 6 days of infection. While

the disease appears to produce mild to moderate illness in most people, in others the infection can cause life-threatening pneumonia and death. While each day scientists learn more about the disease, the current consensus is that transmission occurs primarily from droplets transmitted by person-to-person contact as well as when a person touches a virally contaminated surface or object

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and then touches his or her mouth, nose, or eyes (Li, Guan, et al., 2020).

Pathophysiology

Named after its surface spikes that give it a crown-like appearance, the coronavirus usually first infects the cells lining the upper respiratory tract. The surfaces of these cells are rich in angiotensin-converting enzyme 2 (ACE2) receptors and the corona spikes act like a “key,” binding to the ACE2 receptor or “lock” to open an entry for the virus into the cell. Once inside the cell, the virus diverts the cell’s machinery from its normal function and turns the cell into viral factories that produce and release large numbers of new viruses that then target more cells. Early symptoms are mild, resembling the common cold, and in about 80% of individuals the immune system resolves the infection without further progression. In about 15% of individuals the virus infects the cells of the lower respiratory tract, leading to cough, fever, shortness of breath, and pneumonia (Wu & McGoogan, 2020). Lower respiratory infection triggers a heightened immune response sending signals to release cytokines, which can cause a high temperature and general malaise. If the immune function is effective, the virus can be effectively suppressed and the affected person enters the recovery phase.

Roughly 5% of individuals experience life-threatening respiratory failure and multiorgan dysfunction. If the virus disrupts the immune response and triggers excess inflammation, the lung alveoli begin to fill with fluid and severely compromise gas exchange. The virus enters the circulation from the lung and can affect other organs, which have a large number of ACE2 receptors on their cell surfaces. The risk of disease progression and developing life-threatening disease is higher if the patient is older, is immunocompromised, or has comorbidities such as hypertension and diabetes (Lin et al., 2020). The exact case fatality rate remains uncertain but is likely in the 1% to 2% range (Cascella et al., 2020; WHO, 2020b).

Epidemiology

Worldwide there have been over 12,000,000 COVID-19 cases and more than 550,000 deaths. As of July 12, 2020, the United States reported more than 3,000,000 cases and 135,000 deaths (WHO, 2020a).

Current reports continue to reflect earlier epidemiological observations that while SARS-CoV-2 infects all age groups, older men with chronic illnesses appear to be more severely affected. The first suggestion that men might be disproportionately affected emerged from an early report from China (Chen et al., 2020). Since then similar trends have been observed in other countries. In Italy, a report on 3,200 COVID-19-related deaths showed higher death rates for men than for women across all age

groups, with men accounting for about 70% of deaths (Onder et al., 2020). To date, most countries with available data also report a disproportional mortality burden among men, with the largest male-to-female ratios seen in the Dominican Republic, Netherlands, Denmark, and Philippines (GlobalHealth5050, 2020).

Not all states in the United States break down their COVID-19 reporting by sex. However, in a recent analysis of the 26 states with >2,000 COVID-19 cases, half of the states disaggregated data using sex as a variable. Similar to global findings, these 13 states reported that men are twice as likely to die from COVID-19 than women (Bischof et al., 2020). Disparities in outcomes between men and women in illnesses caused by pathogenic coronaviruses are not new. In both the SARS outbreak in 2002–2003 and the MERS of 2012, men experienced higher mortality rates (Karlberg et al., 2004).

Data from the U.S. Centers for Disease Control and Prevention on COVID-19 hospitalization and mortality rates also demonstrate disparities among racial and ethnic minorities, with mortality rates for African American and Latino men exceeding those for White or Asian males. The research literature exploring racial disparities and COVID-19 is limited (Shah et al., 2020), but after adjusting for differences in sociodemographic and clinical characteristics, race was no longer associated with increased mortality (Price-Haywood et al., 2020). These findings make it likely that the greater prevalence of conditions such as obesity, diabetes, and hypertension and socioeconomic factors including poorer access to testing and treatment account for most if not all the mortality difference among men of color (Yancy, 2020).

The reason why mortality rates differ between men and women remains uncertain. Proposed explanations include differences in ACE2 receptors, immune function, hormones, habits, coinfection rates, and gender influences related to masculinity. In this review we examine these factors and explore the rationale as to how each may impact COVID-19.

Potential Factors Impacting COVID-19

ACE2 Receptors

ACE2 receptors are found on the cell surface and help regulate a protein called angiotensin II. Angiotensin II can increase blood pressure and inflammation, potentially damaging blood vessel linings and causing other tissue injury. ACE2 plays a role in converting angiotensin II to other molecules that counteract its effects.

Infection with SARS-CoV-2 begins when the virus binds to a host cell’s ACE2 receptor, creating a cellular doorway for the virus to infect the cell (Verdecchia et al., 2020). ACE2 is commonly expressed on the epithelial

cells of the alveoli, trachea, and bronchi, and bronchial serous glands of the respiratory tract, making them targets for the SARS-CoV2 virus. Studies suggest that men have more ACE2 receptors than women do and express more ACE2 in their lungs and heart, potentially explaining the male predilection for more severe disease (Cascella et al., 2020; Sama et al., 2020). Interestingly, there are differences in ACE2 receptors in the reproductive organs, with the testes having significantly more ACE2 receptors than the ovaries (Sharma et al., 2020). Also, when the virus binds to ACE2, it inhibits the receptor's normal function, which includes inhibiting inflammation. An imbalance between proinflammatory and anti-inflammatory mechanisms can increase tissue injury, especially in the heart and lung. Differences in ACE2 receptors may adversely affect inflammatory control, leading to a more persistent viral presence and damaging inflammation in men. Some evidence suggests that ACE2 may also be higher in patients with hypertension, diabetes, and coronary heart disease and may in part explain the association of these comorbidities with COVID-19 severity and mortality (Sama et al., 2020).

Immune System Differences

Differences in immune defenses likely contribute to the discrepancies in COVID-19 outcomes between men and women. Females typically generate higher innate and adaptive immune responses when compared with males and mount a more vigorous response to most invading pathogens (Araneo et al., 1991; Barrat et al., 1997; Roberts et al., 2001). Previous studies point to better outcomes for respiratory infections in women, and men with pneumonia are more likely to come to the hospital sicker and more likely to die from pneumonia than women are, even when controlling for behaviors and chronic conditions (Reade et al., 2009). Epidemiological evidence from influenza outbreaks and pandemics also reveals a higher morbidity and mortality for men than that for women in some age groups (Klein et al., 2012). In animal studies, male animals have poorer immune responses when exposed to the coronavirus and experience more damage to their lungs (Vermillion et al., 2018). For both SARS and the MERS coronavirus outbreaks, men fared worse than women did.

A key difference in women that may explain their greater natural immune response is that women have two X chromosomes in their cells, while men have one. The X chromosome contains several important genes related to immunity and immune regulation that are extensively involved in shaping sex-specific innate and adaptive immune responses (Schurz et al., 2019). Although X chromosome inactivation might be expected to balance female and male immune gene expression, several genes on the X chromosomes can escape inactivation, which results in women producing more proteins coded by these

genes. While the mechanism of how these genes become active remains uncertain, X gene activation may account for most immune differences between the sexes. An example relevant to coronavirus infection is the X chromosome gene coding for the protein called Toll-like receptor 7 (TLR7). TLR7 helps control the innate immune response by recognizing single-stranded RNA of viral origin, like an RNA coronavirus that might be overexpressed in women and contribute to clearing the SARS-CoV2 faster (Souyris et al., 2018).

Sex Hormones

Sex hormones play a role in modulating the immune system and contribute to variations seen in the immunologic responses of men and women. They help balance the immune response between combating a viral infection and triggering harmful inflammation. In general, the male sex hormone testosterone is immunosuppressive, while the female sex hormone estrogen tends to enhance the immune response (Klein et al., 2015). However, the impact of sex hormones on the SAR-CoV-2 is complex and not fully understood. A recent German study found that critically ill male COVID-19 patients suffer from severe testosterone and dihydrotestosterone deficiencies and concluded that androgens are required to mount a strong antiviral immune response to combat infection in men (Schroeder et al., 2020). In contrast, another study found that prostate patients' androgen deprivation therapy unexpectedly had better COVID-19 outcomes (Montopoli et al., 2020). They recognized that coronavirus entry into human cells is primed by a cell surface serine protease, an enzyme encoded by the transmembrane serine protease 2 (TMPRSS2) gene (Paoloni-Giacobino et al., 1997). TMPRSS2 is an androgen-regulated gene found in the lung tissue, and Montopoli et al. (2020) speculated that testosterone stimulates TMPRSS2 gene expression, causing an increased susceptibility of men for severe SARS-CoV-2 infections. This theory suggests that androgen deprivation might block or decrease the severity of SARS-CoV-2 infections.

In contrast, some theoretical evidence suggests that low testosterone may be harmful. Inflammatory cytokines have a central role in the progression of COVID-19 infection. While a robust immune system is needed to fight an infection, unchecked, the response may be detrimental. Several studies demonstrate that hypogonadism is associated with increased proinflammatory cytokines and that testosterone may play a role in regulating the cascade of events leading to progression of COVID-19 infection due to the cytokine storm (Mohamad et al., 2019).

Since estrogen activates the immune system, an alternative explanation for the male/female difference for severe COVID-19 is that the female hormone estrogen may be protective. Evidence from both animal and human studies

supports this theory. Studies in female mice found that estrogen inhibited SARS-CoV replication, thereby protecting the mice from infection (Robinson et al., 2014). Female mice with artificially induced estrogen suppression, oophorectomy, or hysterectomy lose this protection when infected with the coronavirus and have mortality rates similar to those of male mice (Channappanavar et al., 2017). The thought that estrogen might be protective suggests that supplemental estrogen might boost the immune system. Ongoing trials are exploring whether giving men estrogen improves COVID-19 outcomes.

Reade et al. (2009) also studied immune function in the SARS-CoV-2 infection and found significant differences between men and women in their levels of tumor necrosis factor, interleukin-6, interleukin-10, antithrombin III, Factor IX, plasminogen activator inhibitor-1, and D-dimer. In some cases, concentrations for men were lower, while in others they were higher. Since sex hormones exert specific effects on male and female immunocompetence at both the cellular and the molecular level, it is not surprising to find differences in immune and inflammatory biomarkers between men and women. For example, estrogen receptors are found in most cells of the innate and adaptive immune system including T cells, B cells, neutrophils, macrophages, dendritic cells, and natural killer cells, while androgen receptors are prominent in T and B lymphocytes (Fish, 2008). Others also speculate that the different hormonal milieu could have a profound pathophysiological role in SARS-CoV-2 infection, with endogenous testosterone leaving men more prone to develop more serious complications related to the SARS-CoV-2 infection (Salonia et al., 2020). Given the range of findings and testosterone's multifaceted role in an intricate system, at this time perhaps all one can conclude is that testosterone can modulate the immune system. While in general testosterone causes a less robust immune response and estrogen helps females mount stronger immune responses, the more robust immune response in females may also lead to immunopathology resulting in fatal outcomes. Exactly how and if sex hormones positively or negatively affect outcomes in the milieu of COVID-19 remains uncertain and represents an area of future inquiry. Unraveling the exact role of the sex hormones offers the promise of developing beneficial therapeutic interventions.

Hygiene and Habits

Differences in hygiene and habits provide another explanation for the sex-related differences seen with the SARS-CoV-2 infection. Studies demonstrate that women wash their hands more often than men do, raising speculation that this might account for differences in COVID-19 between men and women (Suen et al., 2019). In this case, there should be differences in the number of COVID-19 cases as well as mortality. However, available

sex-disaggregated data for COVID-19 indicate that the number of COVID-19 cases appear to be comparable between men and women (Jin et al., 2020), making hygiene an unlikely explanation for a death rate that is two times greater for men than for women (Kocher et al., 2020).

An early theory was that higher smoking rates among men accounted for sex-related differences. Intuitively smokers would appear to be at greater risk from a respiratory infection especially since smokers are at greater risk for dying from influenza. While early studies from China suggested that smoking might account for the male-female gap, later studies did not (Cai, 2020; Zhang et al., 2020). A meta-analysis concluded that smoking was not a risk factor and surprisingly epidemiologic data from France suggested that smokers might even be at lower risk than nonsmokers (Fontanet et al., 2020; Vardavas & Nikitara, 2020).

Based on preliminary data from the United States, persons with underlying health conditions such as diabetes mellitus, chronic lung disease, and cardiovascular disease appear to be at higher risk for severe COVID-19-associated disease than persons without these conditions (CDC, 2020). Another possibility is that men tend to have higher rates of obesity, high blood pressure, diabetes, cancer, and lung and cardiovascular disease, all of which have been linked to COVID-19 severity. While most studies continue to note a male predilection (Del Rio & Malani, 2020; Lawton, 2020), one New York-based study found that when they factored these conditions into the analysis, although being male increased the risk for hospitalization, sex was no longer one of the main risk factors for severe COVID-19 (Petrilli et al., 2020). Currently sex-disaggregated data are incomplete (Shah et al., 2020), and this study highlights the need for both further study and including sex in COVID-19 data collection and reporting.

Finally, a study conducted in China found that men with COVID-19 in hospital were more likely than women to be carrying other viruses, including flu, and bacteria, suggesting that carrying more microbial pathogens may contribute to the severity of COVID-19 symptoms (Li, Zhang, et al., 2020). Typically, men have lower vaccine rates than women do for influenza and pneumonia, which might also account for a higher coinfection rate (Bergman, 2017).

Masculinity

Sex refers to the biological distinctions between males and female, while gender is the socially constructed differences between men and women that give rise to masculinity and femininity (Short et al., 2013). Masculinity is a social determinant of health (Lutfiyya et al., 2014) and aspects of masculinity intersect with biology in ways that may impact male COVID-19 mortality both currently and in the future. Toxic masculinity refers to cultural norms associated with

health-impeding behaviors and highlights engaging in risky behaviors such as the underutilization of health-care services, drinking to excess, and smoking. These and other unhealthy behaviors contribute to high blood pressure, cardiovascular disease, and other comorbidities associated with increased SARS-CoV-2-related mortality.

Alcohol misuse is already a public health concern in the United States and over 9 million adult men have an alcohol use disorder (NIH, 2020). Alcohol has the physiological potential to unfavorably complicate COVID-19 in multiple ways, including adverse effects on the immune and respiratory systems, where excessive alcohol intake can damage the epithelial cells that line the lungs (Boe et al., 2009). Ultimately, by complicating COVID-19 prevention, treatment, and recovery, excessive alcohol intake could certainly contribute to poorer outcomes in men.

While both male and females may delay seeking care, men tend to delay care more often and visit their doctors less often than women do (Mahalik et al., 2007). Arguably without the availability of effective early treatment, delaying care may not currently worsen COVID-19 but may become an important issue as new therapies merge. For example, flu antivirals work best when administered early in the disease course (Papenburg et al., 2020). If drugs active against the SARS-CoV-2 virus act similarly, then delaying care could adversely affect outcomes in the future. While not directly linked to COVID-19 mortality, delaying care for other emergencies can indirectly cause pandemic-related collateral damage (Gilligan & Gologorsky, 2020; Rosenbaum, 2020). During the COVID-19 pandemic, emergency room visits and hospitalization drastically decreased for heart disease and stroke, two potentially non-COVID-19-related life-threatening conditions (Masroor, 2020). For example, large hospital systems in California, Massachusetts, and New York City have reported 43%–50% reductions in admissions for myocardial infarction (MI) and other acute cardiovascular conditions (Lange et al., 2020). Health behavior seems to be the likely cause, since a short-term decline in the incidence of heart disease of this magnitude is biologically implausible. Early interventions for these conditions can improve outcomes and masculine behavior related to delaying or avoiding care might indirectly add to male mortality during the pandemic.

Wearing masks also seems to be a masculinity-related issue (Capraro & Barcelo, 2020). Data strongly suggest that wearing masks reduces viral transmission, yet fewer men than women wear masks (Chu et al., 2020). According to the survey of 2,459 people, men who shunned maskwearing cited concerns that face masks make them look weak and uncool (Capraro & Barcelo, 2020). Opponents of maskwearing often view not wearing masks in terms of bravery and risk-taking and, by implication, brand mask wearers as effete or cowardly. Resistance to mask wearing is not new and during the

1918 flu pandemic, men needed more convincing to wear masks than women did.

Implications

There are several reasons why understanding how COVID-19 affects men and women differently is important. One is that it can provide clues to understanding the pathophysiology of the SARS-CoV-2 infection that might lead to successful interventions. Already trials are in place to explore new options using existing drugs such as estrogen and/or progesterone therapy for men and angiotensin II receptor blockers (Healio, 2020; Sriram & Insel, 2020). The difference in TMPRSS2 gene expression suggests that drugs that inhibit the enzyme's activity might be beneficial. Differences in immune responses between men and women are often overlooked in the design and implementation of vaccination strategies (Klein & Pekosz, 2014). With multiple candidate vaccines, it will be important to disaggregate vaccine response by sex since vaccines may be more effective if matched to an individual's biological sex. Also, as new vaccines are licensed, men and women may need a different dosage to trigger immunity. Undoubtedly it will be hard to ramp up production as new vaccines come on line; therefore, vaccine availability might be extended by giving lower doses to women without compromising effectiveness. In addition to vaccines, other studies examining preventive and therapeutic treatment should include prospective sex- and gender-sensitive analyses in light of how the SARS-CoV-2 differentially affects men and women. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial reported that in patients hospitalized with COVID-19, dexamethasone reduced mortality among those patients receiving respiratory support (Rezaie, 2020). At this stage the disease is dominated more by immunopathology and less by active virus replication. The beneficial effect of dexamethasone likely depends on using the right dose, at the right time, and in the right patient. Sex-related immune response differences raise the possibility that dosing and timing might need to be tailored to biologic sex (Horby et al., 2020).

Many men believe they are less vulnerable to COVID-19 (Capraro & Barcelo, 2020), and that has consequences for how safe they really are during the pandemic. Educating men about their increased risk of dying from COVID-19 might help in developing healthier behaviors. Having male role models demonstrating and endorsing healthy habits, wearing masks, and sharing their COVID-19 stories potentially could help mitigate the spread of infection. Another noteworthy dimension of toxic masculinity is the tendency of some men to disregard the importance of personal hygiene and handwashing. Rebranding mask wearing and handwashing as altruistic, patriotic, and a service to vulnerable individuals might help men to view mask wearing, cleanliness, and hygiene as being consistent with masculinity.

Finally, a better understanding of COVID-19 risk factors can aide triage decisions, inform policy makers, and improve projections on how to distribute resources. The alarming rate at which minority men die from COVID-19 highlights the need to address the conditions of their lives and the issues of insufficient resources and inequitable testing and treatment.

Conclusions

Compared to women, men infected with COVID-19 experience more disease severity and a higher mortality. Lab and animal data indicate that men respond differently to SARS-CoV-2 infection and provide a basis for the epidemiologic findings. These results are driving new therapeutic options. Continuing to collect data disaggregated by sex can help understand why men are more likely to experience severe disease (Baker et al., 2020). These insights can direct public health policies and targeted treatment strategies such as early recognition and aggressive testing that reduce morbidity and mortality among men (Smith et al., 2020).

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