Gender differences in the battle against COVID-19: Impact of genetics, comorbidities, inflammation and lifestyle on differences in outcomes

1 | INTRODUCTION

It has been over 6 months now since the entire globe was struck by the new Coronavirus Disease 2019 (COVID-19; aka severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which has affected 215 nations.1 The medical and scientific communities continue to search for and study potential treatments for COVID-19 as well as an effective vaccine. As of 21 June 2020, 11.4 million cases have been confirmed worldwide, with approximately 530 000 deaths.1 A large number of scientific papers have been produced, hundreds of thousands of patients have been hospitalised and studied, several treatments and vaccines are being tested in randomised clinical trials, social distancing regulations have been implemented, with most of the planet in partial or full lockdown, and we have yet to control this pandemic. Of considerable interest is the observation worldwide that severe infection, organ failure, and death occur with greater frequency in men than women. Yet, from the studies conducted so far, the exposure to SARS-CoV-2 infection is similar for men and women; clearly, there must be clinical, physiological and lifestyle features that predispose men to more severe forms of infection.

2 | DIFFERENCES IN OUTCOMES BETWEEN MEN AND WOMEN INFECTED WITH COVID-19

An important piece of information about this gender disparity comes from the analysis of infected cases done by the Center for Disease Control and Prevention in China, the first affected country, showing that the mortality rate was higher in men (2.8%) than in women (1.7%).2 Another analysis of Chinese patients also revealed a case fatality rate bias, with men having a 2.4-fold higher death rate after infection than women.3 A pooled analysis of 77,932 patients infected with COVID-19 (41 510 men) showed that compared with women, men had a significant 1.71-fold higher rate of mortality.4 Among men >50 yrs and <50 yrs of age, compared with women the odds ratios for mortality were 1.94 and 1.45, respectively. In China, as of 21 June 2020, about 85 000 cases are confirmed, mostly between 30 and 69 years of age, and with 4600 deaths.1 Italy has also been seriously impacted by COVID-19, with a total of about 240 000 infected people and over 34 000 deaths as of 21 June 2020,1 and men had the most severe forms of the diseases and greater mortality than women. There was an obvious case fatality rate bias among men (1.7-2.6 times higher in men compared with women) at all ages above 30 yrs.1 In relation to the average of the last five years, in Italy during the most severe period by COVID-19 infection, which was 1 March – 4 April 2020, the increase in overall mortality was much higher in men than women (+126% vs +85%) and in those of age 65-74 and 74 and older (+110% for both).5 This is consistent with the reported older age of infected COVID-19 patients in Italy compared with China (63 yrs vs 46 years), which has been attributed to the older average age of the Italian population.6 Beyond this preliminary information, available data are now consistently showing worldwide that COVID-19 infection severity and mortality are significantly higher in men than women (eg, in Spain and Switzerland men accounted for 63% and 62% of deaths attributed to COVID-19 infection).1,8 This observed relationship of higher risk for more severe forms of infection is, however, characteristic not only of SARS-CoV-2 infection but has also been recognised for both the Middle East Respiratory Syndrome (MERS) and the Severe Acute Respiratory Syndrome (SARS) viruses.7 In the case of MERS, since April 2012 a total of 2,494 cases and 858 deaths have been recorded, with a large proportion being men, mainly those between the ages of 48-56 years (56%-87% of total cases).7 In the case of SARS, infection has been reported in 30 countries, with over 8,000 cases and 770 deaths, with men having developed the most severe forms and highest number of fatalities.10 From an evolutionary point of view, it is not yet fully elucidated what makes men so vulnerable to adverse outcomes when infected with coronaviruses, such as COVID-19, MERS and SARS. Genetics offers us some answers, but at the same time the presence of some specific habits as well as risk heightening factors such as diabetes, hypertension and coronary artery disease may at least partially explain the higher risk of infection in men than women, as well as for their greater mortality.

3 | HAND WASHING AND HYGIENE

We first wish to highlight the importance of general preventive measures, such as hand hygiene, which is the single most efficient and inexpensive method of preventing both respiratory and
gastro-intestinal infections. It is a basic hygiene measure and one of the first recommendations given to populations worldwide during the COVID-19 pandemic. There are several lines of research that show a clear difference when it comes to the frequency of hand washing between the two genders. Women tend to be more careful about their personal hygiene, washing their hands more often and longer, and their habitual environment, including food processing, cleanliness of their household, and hygiene of their clothes. In studies conducted over the years by the American Society for Microbiology and the Soap and Detergent Association on thousands of US adults, men were consistently less likely than women to wash their hands after certain activities, such as after eating, toileting, petting an animal, sneezing or coughing. Because the single most efficient method of COVID-19 prevention is hand washing, there may be a higher risk of infection for men.

4 | THE ROLE OF CIGARETTE SMOKING

Exposure to cigarette smoke may have a strong influence as well. Globally, the highest number of smokers is among men, and this is associated with a higher prevalence of lung cancer. Indeed, in developed countries a greater proportion of men compared with women are active smokers (35% vs 22%) or have a smoking habit (over 50% vs 9%). Smoking is one of the most serious public health problems worldwide, killing over 5 million people annually, mostly in developed countries. China is responsible for 40% of worldwide tobacco consumption, with about 320 million adult smokers, mostly men. The heightened risk of developing type 2 diabetes, high blood pressure, atherosclerotic cardiovascular disease and chronic obstructive pulmonary disease as well as other respiratory diseases in smokers is well known, and all these risk factors also significantly contribute to the increased risk of SARS-CoV2 infection. Given this gender disparity in smoking, this too likely contributes to a higher risk of more serious infection and death from COVID-19 in men.

5 | GENETICS

Genetics also play a prominent role. Women are more resilient to infections because of genetic background and a more efficient immune system. If we look retrospectively at other epidemics, men were consistently more affected than women, as mentioned earlier for MERS and SARS and even more for the Spanish influenza pandemic of 1918-1919 during which an estimated 40 million persons worldwide died. One of the possible explanations is that women have a more efficient immune system. The majority of genes regulating immunity localise to the X chromosome. After vaccination women experience a stronger antibody response and their immune memory is better, and this is principally why women are more inclined to develop autoimmune diseases more frequently than men (up to 80%), such as rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis or myasthenia gravis. Consistent with this, Chinese women were found to produce higher IgG titers compared with men in response to COVID-19 infection. Biological sex also relates to T cells and autoimmune response; for instance, women secrete a higher quantity of interferon-γ than men. Another aspect to consider is the role of sex hormones, since oestrogens suppress T helper cell type 1-dependent diseases, but also enhance T helper cell type 2 dependent diseases and this is one of the potential explanations why women are more susceptible to develop autoimmune diseases. Sex-related differences may also be impacted by mitochondrial DNA inheritance (all mitochondrial DNA is maternally derived), the gut microbiome, genomic imprinting (an epigenetic process insuring expression of certain genes from only one parent) and chromosomal inactivation.

Another advantage for women is the presence of the double chromosome XX, rather than men having chromosome XY, since the X chromosome contains a large number of genes regulating immunity. This gives women a more robust immune response to infections, especially those from viral agents. The impact of sex hormones on viral and microbial infections depends on secondary metabolites binding to receptors such as oestrogen receptors. It also needs to be emphasised that the immune response is directly influenced by the number of immune cell populations, and it clearly differs between the two sexes. For instance, T lymphocyte CD4 and CD8 populations fall with age uniformly between genders, though aged women show lower natural killer and memory Tregs cells as compared with aged men; these observations may at least partly explain the altered immune response and fall in cytokine production in older men.

6 | THE ROLE OF SEX HORMONES

In addition, testosterone has a suppressive effect on immunity, while oestrogens have an opposite stimulating action. Oestrogen activates macrophages, dendritic cells, and natural killer cells comprising the nasal immune system, all of which potentiate defence against viral invasion and migration into the lower airway, thereby preventing infection and viral pneumonitis. Oestrogen plays a significant role in regulating the expression of numerous chemokines and cytokines in neutrophils, macrophages, T helper cells and B cells and impacts both the innate and adaptive arms of immune responses. For instance, studies of SARS infection using animal models have shown that males are more susceptible to viral infection than females, and a recent study demonstrated the direct role of oestrogen in limiting the viral replication of influenza virus at the level of nasal epithelial cells by modulating genes that regulate the metabolic functions of such cells. In addition, the X chromosome contains loci for the androgen receptor and the angiotensin converting enzyme-2 (ACE-2) genes and, very interestingly, it has been recently shown that SARS-CoV-2 uses the ACE2 receptor for cell surface binding and penetration, as it links to the viral spike protein. Oestrogens may therefore exert a major protective role against COVID-19, although this remains to be more fully elucidated. ACE-2 is highly expressed
in lung (particularly epithelial cells), myocardium, endothelial cells, ileum, bladder and kidney. Smoking is known to augment expression of ACE-2 and, hence, may increase risk of systemic infection.

7 | CYTOKINE STORM SYNDROME AND INFLAMMATION

SARS-CoV-2 can elicit cytokine storm syndrome and greatly magnify risk for death. Men appear to have a higher inclination toward producing cytokines that promote cytokine storm syndrome, whereas women have a higher likelihood for producing chemical species that promote defence and recovery from acute viral illness. It is possible that such molecules as protectins, lipoxins and resolvins participate in this process of actively bringing resolution to the inflammatory phase of infection. In the setting of COVID-19, because of expanding viral load, there is a rapid increase in the number of inflammatory monocytes/macrophages and neutrophils in the lungs, accompanied by an increased level of cytokines and chemokines that affects the pulmonary tissue continuously and irremediably, through a cytopathic effect. If oestrogen hormones are beneficial as a potential treatment for COVID-19 patients, this remains to be tested. If testosterone suppression by various therapeutic actions (such as spironolactone) is beneficial in COVID-19 patients, this may be worth investigating during this terrible pandemic. Recently, the American Society of Preventive Cardiology emphasised the cardiovascular impact of the COVID-19 pandemic, which also correlates with gender differences in the severity and case fatality rate of SARS-CoV-2 infection.

8 | COMORBIDITIES

Comorbidities play an essential role in determining risk for serious complications and death secondary to COVID-19 infection. The presence of diabetes is associated with increased severity of symptoms and complications in COVID-19 patients. This may in part be attributable to some of the well-known manifestations of diabetes, including endothelial dysfunction, heightened systemic inflammatory tone, established micro- and macrovascular disease and increased risk for diabetic cardiomyopathy. Patients with established ASCVD who become infected with SARS-CoV-2 are at increased risk for cardiovascular complications, including myocardial infarction, malignant arrhythmias, mesenteric infarction, stroke, cardiovascular death, fulminant progression of heart failure or myocardial suppression. COVID-19 is associated with endothelitis and myocarditis. It is believed that because SARS-CoV-2 can elicit such an intense systemic inflammatory response, atherosclerotic plaque may become acutely unstable and more prone to rupture, yielding higher rates of myocardial infarction and more rapid progression of systolic dysfunction and heart failure. Acute myocarditis stemming from direct infection of myocardium by the virus may also lead to fulminant left ventricular suppression and heart failure. It is of great import that gender-related differences in vulnerability to these complications of COVID-19 be explored and quantified.

Obesity is also an important risk factor for more severe infection, need for mechanical ventilation and death. Obese patients have a higher incidence of underlying pulmonary disease, decreased diaphragmatic excursion, reduced expiratory reserve volume, functional capacity and pulmonary compliance. Obesity may increases risk of more severe infection because adipocytes in obese patients express higher levels of ACE-2, possibly rendering these cells a reservoir for persistent SARS-CoV-2 production and release. Obesity is also inextricably linked to other risk factors that predict more severe systemic manifestations of infection, such as diabetes, hypertension and atherosclerotic disease. It has been recently hypothesised that the human dipeptidyl peptidase 4 (DPP4) enzyme receptor may be a functional target for the SARS-CoV-2 spike proteins and, since DPP4-inhibitors are currently used for the treatment of patients with type-2 diabetes, there is high interest in the possibility that such treatments, and incretin-based therapies in general, may be of particular benefit during COVID-19 pandemic. Among the different agents, GLP1-receptor agonists liraglutide and semaglutide have beneficial effects on obesity and inflammatory mediators, both of which associated more severity of COVID-19, and obese patients already have heightened levels of pro-inflammatory adipokines (tumour necrosis factor-α, interleukins IL-6, IL-8, IL-12, IL18), leukotrienes, chemerin, retinol binding protein 4, among others) which may exacerbate their risk for cytokine storm syndrome and death.

9 | CONCLUSION

In conclusion, there is consistent evidence supporting gender differences for the severity of COVID-19. As recently highlighted, failing to integrate such gender differences into current research may create and/or increase health inequities in the care of patients with SARS-CoV-2 infection. Even though it is not fully clear why men are more vulnerable to the more severe consequences (cytokine storm syndrome, acute cardiovascular events, death) of COVID-19 than women, it is obvious that male sex is a negative prognostic factor, and the proposed mechanisms for this need to be further explored and validated.

DISCLOSURES

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