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REVIEW ARTICLE

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# Why does COVID-19 kill more elderly men than women? Is there a role for testosterone?

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## Abstract

**Background:** Recent epidemiological data indicate that there may be a gender predisposition to COVID-19, with men predisposed to being most severely affected, and older men accounting for most deaths.

**Objectives:** Provide a review of the research literature, propose hypotheses, and therapies based on the potential link between testosterone (T) and COVID-19 induced mortality in elderly men.

**Materials and Methods:** A search of publications in academic electronic databases, and government and public health organization web sites on T, aging, inflammation, severe acute respiratory syndrome (SARS) due to coronavirus (CoV) 2 (SARS-CoV-2) infection, and COVID-19 disease state and outcomes was performed.

**Results:** The link between T, the immune system, and male aging is well-established, as is the progressive decline in T levels with aging. In women, T levels drop before menopause and variably increase with advanced age. Elevated IL-6 is a characteristic biomarker of patients infected with COVID-19 and has been linked to the development of the acute respiratory distress syndrome (ARDS). Thus far, half of the admitted COVID-19 patients developed ARDS, half of these patients died, and elderly male patients have been more likely to develop ARDS and die. Low T is associated with ARDS. These data suggest that low T levels may exacerbate the severity of COVID-19 infection in elderly men. It may also stand to reason that normal T levels may offer some protection against COVID-19. SARS-CoV-2 binds to the angiotensin-converting enzyme 2, present in high levels in the testis.

**Conclusion:** At present, it is not known whether low T levels in aging hypogonadal males create a permissive environment for severe responses to COVID-19 infection or if the virus inhibits androgen formation. Given the preponderance of COVID-19 related mortality in elderly males, additional testing for gonadal function and treatment with T may be merited.

KEYWORDS

acute respiratory distress syndrome, aging, inflammation, SARS-CoV-2, testis, testosterone replacement therapy

## 1 | INTRODUCTION

COVID-19 is a new human-infecting *Betacoronavirus* named 2019-nCoV by the WHO and severe acute respiratory syndrome (SARS)-CoV-2 by the International Committee on Taxonomy of Viruses. As of March 28, 2020, the spread of COVID-19 in Italy has affected primarily people over 50 years of age[1] (Instituto Superiore di Sanita). The mortality rate appears to be higher for elderly patients. In fact, for people between 70 and 79 years of age, the fatality rate has been 18.5 percent. Conversely, for patients below 50 years old, the fatality rate has been <1%. For patients older than 80 years the mortality has been about 25 percent. The WHO-China report[2] indicated that at the end of February 2020 the Death Rate (number of deaths/number of cases), the probability of dying if infected by the virus (%), was below 1% for all groups below 50 years old, 1.3% for 50-59 years old, 3.6% for 60-69 years old, 8% for 70-79 years old, and 14.8% for 80 + years old. On March 26 the CDC reported that the case-fatality percentages in the US similarly increased with age, with <1% deaths among persons aged 20-54 years, 1%-3% among persons aged 55-64 years, 3%-11% among persons aged 65-84 years, reaching 10%-27% among persons aged >85 years old.[3]

Reports from China indicate that men accounted for 60% of COVID-19 patients[4,5] and that the COVID-19 fatality rate for men was 2.8%, compared to 1.7% for women.[6] Moreover, 67% of patients admitted to the intensive care unit (ICU) were reported to be men.[7] In Italy, 70% of those who died were men.[8] In France, 73% of ICU admissions for COVID-19 have been men[9] (Sante Public France). In Norway, that figure is 75%[10] (Norwegian Institute of Public Health), and in UK it is 71%[11] (ICNARC). A Washington post-analysis of United States deaths so far also found that nearly 60% of deaths were male.[12] These data seem to indicate that there might be a gender predisposition to COVID-19, with men predisposed to being more severely affected[13] and older men accounting for most deaths.

To explain the biological basis of this gender predisposition to COVID-19, we should consider the complex biological network of testis-formed androgen, comorbidities, and infection-induced inflammation that impact several critical organs and metabolism in the aging male creating a permissive environment for SARS-CoV-2 to exert a lethal effect. Moreover, it is also likely that SARS-CoV-2 may also exert direct effects on testicular function.

## 2 | METHODS

A systematic literature review was performed by drawing on biomedical literature and academic electronic databases PubMed, ScienceDirect, and Google Scholar as well as government and public health organization web sites on T, estrogen, aging, inflammation, severe acute respiratory syndrome (SARS) due to coronavirus (CoV) 2 (SARS-CoV-2) infection, and COVID-19 disease state and outcomes. Articles included were written either in English or French.

### 2.1 | Aging, male hypogonadism, and comorbidities

Made by the Leydig cells in the testis, testosterone (T) drives the establishment and function of the male reproductive system from gestation to adulthood.[14] However, T levels decrease at a rate of 0.4% to 2% per year starting at around age 30 and can result in low levels of serum T, termed "hypogonadism", at advanced ages.[15-17] Primary hypogonadism is defined as reduced Leydig cell androgen production, when LH levels have increased, but the testicle is not responding to pituitary stimulation and producing T. In secondary hypogonadism, gonadotropin-releasing hormone (GnRH) or LH levels are reduced and become inadequate to maintain T levels. In some men, there is a mix of central (hypothalamic and/or pituitary) and gonadal deficiencies.

The progressive decline in T with aging results in 20%-50% of men over age 60 having significantly reduced T levels.[18,19] Age-related decline in T, along with associated symptoms, is referred to as late-onset hypogonadism (LOH).[20,21] LOH is symptomatically characterized by loss of libido, erectile dysfunction, and loss of muscle mass, among other symptoms, as well as a greater likelihood of both metabolic syndrome and cardiovascular disease. Moreover, there is a significant interaction between low T levels and frailty[22] as well as mortality in older men,[23] the later been more pronounced in older men with metabolic syndrome.[24] Recently the concept of functional hypogonadism has emerged. This is defined and diagnosed as the coexistence of an androgen deficiency phenotype and low serum T concentrations occurring in the absence of both intrinsic structural deficiencies and/or pathological conditions that suppress the hypothalamic-pituitary-gonadal axis.[25]

Older age has also been associated with a host of comorbidities. Older men exhibit higher prevalence of metabolic syndrome, obesity, diabetes mellitus, and other chronic health conditions that can cause hypogonadism.[16] Similarly, these same comorbidities predispose older men to a higher incidence of severe disease and mortality. As several studies have noted, a number of causes of hypogonadism in older men are modifiable and hypogonadism can be reversed with weight loss or better control of disease.[26] Thus, low T levels in older men can be attributed not only to age, but also to the presence of co-existing comorbidities and risk factors.[16,17,27] However, a series of studies showed that androgen deprivation in prostate cancer patients induces components of the metabolic syndrome[28-30] and administration of T to hypogonadal men improves insulin resistance, obesity, and dyslipidemia.[23,31]

Taken together, these data suggest that low T seen in aging men could act as either a mediator or simply a confounder of the observed comorbidities.

T replacement therapy (TRT) with exogenous T is currently the only FDA-approved therapy for the treatment of male hypogonadism. Although this treatment does have associated risks,[32-37] the indications, treatment, and follow-up for men being treated with T are well-defined and generally considered safe for treatment of male hypogonadism, LOH/functional hypogonadism.[25,38]

## 2.2 | Hormone changes in elderly women

The shift of sex steroid profile in women with a marked decline in ovarian estrogen production defines the menopausal transition. After menopause, the ovaries no longer produce estrogen and at that stage estrogen mainly come from fat tissue. In women, androgens are produced by both the ovaries and the adrenals.[39,40] In women, serum T levels decline from 20 to 40 years of age, reaching a 50% decline.[40-42] The same is true for the androgen dehydroepiandrosterone sulfate and androstenedione. There is no further decline of T following the final menstrual period.[43] In elderly 60-80 years old women, there is an increase in serum T reaching young women levels, although the extent of this increase is highly variable.[40,41] Interestingly, although T was shown to play a role in frailty in older men, its role in older women seems to be less relevant.[22]

Thus, although the age-associated decline in T occurs in both men and women, it starts much earlier in men and continues throughout the life while it reaches a maximal decrease before the menopausal transition in women. In older women, unlike men, there is a recovery in circulating T levels which although variable sometimes reaches levels close to those found in the young.[41] Moreover, the overall androgenicity ratio (androgen/estrogen) is increased with age in women since the decline of estrogen formation is dramatic.[41,43] This increase in androgenicity is likely behind the phenotypic changes seen in post-menopausal women, for example, hirsutism.[44] Whether this increase in T and androgenicity contributes to less severe outcomes and deaths in elderly women, compared to men, remains to be explored.

## 2.3 | Immune system, T and aging

The immune system is designed to protect the body against foreign pathogens in a rapid and specific manner. It does this in a highly complex manner, continuously distinguishing between normal, healthy cells, and unhealthy (because of infection of cellular damage) cells. When the immune system recognizes these "unhealthy" cells, it responds and addresses the problem. However, it is possible that dysregulation may exist, and the immune system may auto-react, causing harmful effects. When the immune system response is activated without a real threat, allergic reactions, or autoimmune diseases can result.

Inflammation is the immune system's defense mechanism against pathogens and other harmful stimuli. It can be either at the origin or the consequence of diseases that occur in the cardiovascular, respiratory, and reproductive systems. Inflammation is caused by the activation of innate and adaptive immune cells and proteins released by these cells.

Aging is associated with a progressive decline and remodeling of the immune system, resulting in an increased risk of severe outcomes from infectious diseases.[45,46] Aging is associated with elevated systemic inflammation (eg, elevated serum concentrations of IL-6 and tumor necrosis factor α (TNFα)), as well as a decreased ability to respond to specific immunological challenges.[47-49] This general impairment of overall immune function and increased inflammatory response, are responsible for increased mortality in aging. Indeed, individuals over the age of 65 account for most of all influenza-related hospitalizations and over 70% of all influenza-related deaths.[50,51] Moreover, among individuals 80 years or older, males are more likely than females to be hospitalized and succumb to influenza virus infections.[52,53]

Sex steroids, such as T, can have a significant influence on the function of inflammatory cells and regulation of the immune response. T has major effects on health and disease by altering metabolic, cardiovascular, and immune functions.[54-56] T exerts mainly a suppressive role in immune functions, acting on the androgen receptors in immune cells regulating target gene expression.[57] T suppresses immune cell activity by reducing inflammatory and promoting anti-inflammatory mediators' expression by macrophages and T cells, thus protecting against a variety of inflammation-mediated diseases.[57,58]

The role of T in the pathophysiology of inflammation was reviewed by Traish et al.[59] Low T levels have been associated with higher rates of infection-related hospitalizations and all-cause mortality in male hemodialysis patients.[60] Likewise, age-related decline in T levels have been associated with increased mortality and disease severity following influenza infections.[61] In addition, TRT administration in aged male mice decreases mortality and reduces disease severity independent of changes in viral replication or pulmonary inflammation.[61] In humans, there is data suggesting that males develop a lesser antibody response to influenza vaccination than females, and T may play a role in this.[62]

Interleukin-6 (IL-6) is a pro-inflammatory tightly regulated cytokine that is expressed at low levels, except during infection, trauma, or other stress. T is among the factors that have been shown to down-regulate IL-6 gene expression. Low T levels in young men have been associated with low-grade systemic inflammation and are believed to be part of the mechanism underlying adverse health outcomes in male hypogonadism.[63] IL-6 levels are elevated in LOH, even in the absence of infection, trauma, or stress. The age-associated increase in IL-6 is believed to account for some of the phenotypic changes of advanced male aging, particularly those that resemble chronic inflammatory disease.[47] Moreover, the levels of the inflammatory marker soluble IL-6 receptor are also increased in older men[64] and higher IL-6 levels have been shown to inhibit androgen formation.[65] TRT in hypogonadal men with chronic inflammatory conditions has been shown to reduce levels of TNFα, another inflammatory cytokine,[66] suggesting that T may attenuate the inflammatory process and reduce the burden of disease. TRT was also shown to reduce the spontaneous, but not the inducible, production of inflammatory cytokines by monocytes,[67] suggesting that the effect of TRT might be limited. In a recent paper, Bianchi reviewed the literature on the anti-inflammatory effects of T.[68] The author concluded that in general, T protects against inflammation independently of the clinical condition, although TRT was more effective in reducing inflammation in hypogonadal than eugonadal men.

Elevated IL-6 is a characteristic biomarker seen in the serum of patients infected with COVID-19.[69-71] Reports on the use of tocilizumab in COVID-19 cases, at doses similar to those used for the management of cytokine release syndrome, have shown rapid improvement in patients.[72,73] In these reports, the expeditious administration of anti-IL-6R therapy for patients in acute respiratory distress syndrome (ARDS) has been critical. The Society for Immunotherapy of Cancer encourages the use of IL-6 or IL-6-receptor blocking antibodies like tocilizumab (Actemra, Roche-Genentech), sarilumab (Kevzara, Regeneron), and siltuximab (Sylvant, EUSA Pharma) that are FDA approved for various pro-inflammatory conditions seen with cancers.[74]

## 2.4 | ARDS, aging, and T

Liu et al[75] have reported that about half of the admitted COVID-19 patients developed ARDS. Half of the ARDS patients died, and elderly patients were more likely to develop ARDS. Critical illnesses, like ARDS, are associated with neuroendocrine changes linked to increased morbidity and mortality.[76] Critical illnesses progress in two steps, the acute (hours to days) and chronic (weeks) stages. Cytokines are thought to be responsible for early response changes, and other endogenous (eg, dopamine, cortisol) and exogenous (eg, medications) factors contribute to the chronic changes.[76,77] During the early phase, T levels decrease and continue to decline during the chronic phase. T reduction seems to be independent of LH levels, indicating a dysfunction of the hypothalamic-pituitary-gonadal axis.[78,79] Fifty percent of men over 65 years old hospitalized for acute illness, such as respiratory tract infection, were found to be hypogonadal and low T levels were related with in-hospital mortality.[80,81] ARDS, a complication of severe sepsis, and sepsis-related morbidity and mortality were shown to be more prevalent in men than in women, were linked to high IL-6 levels and occurred in a manner independent of age and disease.[82] Low T levels were reported in male patients with severe sepsis and respiratory failure[83,84] suggesting that hypogonadism may create a permissive environment for severe outcomes in men. T is among the pharmacological interventions available to attenuate the catabolic response in critical illness.[85] Indeed, low T is part of the pro-inflammatory profile associated with ARDS,[86] and TRT has been shown to reduce airway inflammation in asthma.[87]

## 2.5 | Testis, a SARS-CoV-2 target

As noted above the interactions between aging, low T, comorbidities, and inflammation create a fertile environment for COVID-19 negative outcomes. However, it is also likely that SARS-CoV-2 may also exert direct effects on testicular function and T formation. Such an effect will exacerbate the effects of the virus on the aging male. The virus uses a glycosylated spike (S) protein to enter host cells and binds with high affinity to the angiotensin-converting enzyme 2 (ACE2), acting as viral receptor in humans.[88,89] Transmembrane serine protease 2 (TMPRSS2) appears to enhance ACE2-mediated viral entry.[90] The ACE2 enzyme is predominantly expressed in heart, kidney, and testis, and in lower levels in the bronchus and lung parenchyma, suggesting that it may play a critical role in cardiovascular, renal, and testicular function, as well as in the respiratory system.[91,92] Further studies have shown ACE2 to be abundantly expressed in the epithelial of the lung and serves as the receptor for the SARS coronavirus, the causative agent of SARS.[91] There is currently no published data looking at the effect of COVID-19 on testicular function, although the possibility has been brought forward.[92] Interestingly, the testis has been found to be the target organ for other viruses, including HIV, HBV, mumps, Zika, Ebola and the SARS coronavirus, causing orchitis, and occasionally hypogonadism, oligospermia, and testicular tumors.[93-103]

A search of the protein atlas database[104] showed that ACE2 RNA is expressed at high levels in male tissues and that the protein is expressed at extremely high levels in male tissues. Both ACE2 protein and mRNA are present at the highest levels in the testis in human males. Early studies by Douglas et al showed that ACE2 expression in the human testis is confined to Leydig and Sertoli cells and that it is a constitutive, luteinizing hormone (LH)-independent, product of adult Leydig cells.[105] Our findings have corroborated these, and our laboratory has found that *ACE2* transcripts are present in human Leydig-like cells differentiated from human induced pluripotent stem cells.[106] ACE2 expression is driven by the transcription factor FoxA3,[107] the only member of the Fox family of transcription factors present in adult Leydig cells.[108,109] The *TMPRSS2* transcript was also found in human Leydig-like cells.[106] These data suggest that testicular Leydig cells may be potential targets of COVID-19.

## 2.6 | Estrogen and other factors predisposing men to severe COVID-19 responses

T is probably not the only reason why more elderly men die of COVID-19 than women. Women have more robust immune systems than men and estrogen as well as genes encoded on the X chromosome may play a positive role in the development of this response.[110] The complex immunomodulating role of estrogen has been reported[58,111] and their potential role in COVID-19 has been evoked, and clinical trials are underway to evaluate their impact on the severity of COVID-19 symptoms. Although high estrogen levels in premenopausal women may be protective against COVID-19 infection, if estrogen were the primary protective factor for women, elderly post-menopausal women with COVID-19 would fare as poorly as elderly men. However, the absence of estrogen later in life does not seem to play a detrimental role in the severity of the response and outcomes of elderly women to COVID-19 compared to men. Sepsis provides the opposite model because if estrogen is protective in older men, this a rare instance where endogenous estrogen is increased. Indeed, during the acute phase of severe sepsis in men with respiratory failure in parallel with the dramatic decline in T levels, there is an increase in estrogen, mainly estrone,

levels, likely due to increased aromatization of testicular or adrenal androgen.[83,84,112] Increased estrogen levels reflect a negative outcome in sceptic shock in men.[84,112] Nevertheless, long-term treatment with estrogen, same as T, administered at youth levels may offer protection.

Gender-related lifestyle behaviors may also play a role.[110] For example, smoking is more prevalent in men than women although the limited evidence linking smoking and severity of COVID-19 is weak.[13] Genetic predisposition has also been evoked as a susceptibility factor to COVID-19.[113]

## 3 | CONCLUSION

Collectively, these data suggest low T levels may facilitate the severity of COVID-19 infection in aging men and that the testis, and most likely the Leydig cells, is a putative target organ for COVID-19. It may also stand to reason that normal T levels may offer some protection against COVID-19. At present, it is not known whether COVID-19 infection could inhibit androgen formation, or if it is the low T levels in hypogonadal men, for example, LOH/functional hypogonadism, that create a permissive environment for the virus to act. However, in support of our hypothesis, a paper published during the revision of this manuscript reported clinical data showing the prognostic role of T levels toward either severity or mortality associated with SARS-CoV-2 pneumonia.[114]

The situation with COVID-19 is still evolving and only when the pandemic is over, we will have a better characterization of the population at risk and various factors (including medications and genetics) that impart increased risk of infection and mortality. Furthermore, only when the dust settles, we will learn if the disease truly is more detrimental to elderly men compared to women. However, considering the knowledge available today on COVID-19 and in the absence of preventive or therapeutic alternatives, there are three questions that emerge: (a) Would monitoring testicular function with serum T, LH, Follicle-stimulating hormone, and sex hormone binding globulin levels in COVID-19 infected male patients allow for stratification of risk to identify and treat patients who may go on to develop ARDS or other critical illness? (b) Would treatment with TRT, in combination with the other treatments, boost the immune system and improve overall outcomes in aging men infected with COVID-19? (c) Does COVID-19 infection affect short and long-term male reproductive function?

Given the preponderance of mortality in elderly males, additional testing and treatment may be merited, particularly since the required tests and treatment are already available.

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