Clinical significance of sex hormones in COVID-19

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Abstract

Background: Sex hormones may play a role in excess male lethality from coronavirus disease-2019 (COVID-19).

Objective: To clarify the implications of testosterone and estradiol in the course and prognosis of COVID-19 in men and women.

Methods: PUBMED search until September 7, 2020. Search terms included: COVID-19, sex hormones, testosterone, estrogen, androgen-deprivation, mortality. Due to lack of randomized trials, we included retrospective case series, and pre-print studies.

Results: In men hospitalized with COVID-19, circulating testosterone levels are generally decreased and inversely correlated with pro-inflammatory cytokines. Low testosterone levels may be associated with severe COVID-19 and high mortality. Yet, androgen deprivation therapy as treatment of prostate cancer may be associated with decreased hospitalization and favourable clinical outcomes in COVID-19. In women hospitalized with COVID-19, high testosterone levels directly correlate with pro-inflammatory cytokines. In premenopausal women, estradiol serum levels above 70 pg/ml were associated with decreased risk of having severe COVID-19. Pre-menopausal women using combined oral contraceptives may have decreased risk of COVID-19. Conversely, post-menopausal women taking hormone replacement therapy may have increased risk. In general, pregnant women with COVID-19 seem to have similar disease course as non-pregnant women, but studies were lacking adequate control subjects.

Conclusions: Preliminary data suggest that androgen deprivation therapy and estrogen could be beneficial as potential treatment of COVID-19 in men and women, respectively. However, the possible therapeutic role of these agents will be only confirmed by randomized trials.

Introduction

Accumulating data suggest that men are disproportionally affected by COVID-19 in terms of severity and mortality [1-3]. Jin et al. [1] from China were the first to report that men had more severe COVID-19 than women. They also found that death rates were 2.4 times greater in men than in women (70.3% versus 29.7%; P = 0.016) [1]. More recent data from 7 European countries and Korea showed that overall male to female ratio of mortality per 100,000 population was 1.4 [2]. The ratio varies with different ages as follows: 1.9 in the 40-49 years age group, 2.3 in the 50-59 group, 2.6 in the 60-69 group, and 1.6 in people older than 80 years [2]. Likewise, using data from 6 countries including the USA, Green et al. [3] reported that male to female case fatality ratios were 2.53, 2.92, 2.57, 1.83, 1.57, 1.58 and 1.48 for ages 0-39, 40-49, 50-59, 60-69, 70-79, 80-89 and 90+ age groups. Ding et al. [4] have shown that sex differences in COVID-19 severity and mortality may depend on menopausal status. Thus, they did not find differences in disease severity and clinical outcomes when comparing post-menopausal women with age-matched men [4]. Yet, significant differences existed between pre-menopausal women and age-matched men, with fewer pre-menopausal women suffering severe form of COVID-19 (46% versus 75% in men, P <0.01), and death (0% versus 9.7% in men, P < 0.01) [4]. These results suggest that pre-menopausal state may have protective effect against COVID-19. Most researchers believe that excess mortality in men relative to women is largely due to higher prevalence of smoking, cardiovascular and lung disease co-morbidities [5]. Using a multinational registry formed of 14,712 patients with COVID-19, Alkhouri et al. [5] found that all-cause mortality was 8.8% in men and 4.3% in women, odds ratio (OR) 2.15, 95% CI, 1.87-2.46; P < 0.01). After propensity score matching to control for differences in age and co-morbidities, all-cause mortality was slightly attenuated but remained significantly higher in men than in women, 8.13% versus 4.60%, OR 1.81, 95% CI, 1.55-2.11; P < 0.001) [5]. Therefore, there are factors beyond co-morbidities that contribute to excess mortality in men with COVID-19. These factors may include gender differences in immune response to infections and sex hormones [6,7]. This article will focus on the possible implication of sex hormones in the clinical course of COVID-19 in men and women based on available studies.

Relevance of sex hormones to COVID-19

There are 2 opposing theories regarding the role of testosterone in COVID-19 [8]. First, low testosterone levels can cause a reduction of respiratory muscle activity and testosterone therapy improve peak oxygen consumption and functional exercise capacity [9]. In addition, testosterone has anti-inflammatory effect associated with reduction in pro-inflammatory cytokines such as interleukin- 6 (IL-6) and interferon-α (IFN-α) as well as markers of severe inflammation such as C-reactive protein [7,10]. This anti-inflammatory effect could virtually decrease severity of cytokine storm, the main cause of acute respiratory distress syndrome (ARDS) and mortality in COVID-19. On the other hand, the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) uses the angiotensin converting enzyme 2 (ACE2) as receptor

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and the transmembrane protease serine 2 (TMPRSS2) as co-receptor for host cell binding and penetration [11]. Testosterone is known to upregulate TMPRSS2, and therefore testosterone could potentially facilitate SARS-Cov-2 cell binding and spread [8]. As far as estrogen is concerned, this hormone is believed to play a protective role against COVID-19 in large part due to its anti-inflammatory effect, analogous to that of testosterone [7]. In the following sections, the authors will try to elucidate the implications of sex hormones in men and women with COVID-19 based on available data.

**Testosterone in patients with COVID-19**

**Male studies**

In one Chinese retrospective study, Ma et al. [12] compared serum levels of testosterone in 81 young men (median age 38 years) hospitalized for COVID-19 (86% of them had moderate disease) with 100 healthy control subjects. They found a non-significant trend of testosterone levels to be lower in COVID-19 patients compared with control subjects, median (interquartile range) being 397 (312-568) and 479 (349-562) ng/dl, respectively (P=0.094) [12]. Meanwhile luteinizing hormone (LH) values were significantly higher in patients compared with control individuals; median 5.9 (4.3-8.2) and 3.2 (2.5-4.6) mU/L, respectively, P < 0.0001) [12]. It follows that the testosterone/LH ratio, a marker of testicular function, was significantly lower in patients with COVID-19 compared with healthy subjects [12]. This observation suggests some degree of testicular dysfunction in men with COVID-19. Moreover, plasma levels of C-reactive protein, an index of inflammatory severity in COVID-19, were negatively associated with testosterone/LH ratio [12]. In another retrospective study from Germany, Schroeder et al. [13] measured testosterone in 35 critically ill men (median age 62 years, range 31-80) with COVID-19 admitted to the intensive care unit (ICU). They found that majority of patients (68%) had low testosterone levels, and 54% of them had very low testosterone values below 141 ng/dl (normal range in 50 years-old men 192-743 ng/dl [13]. In addition, 32% of all men and 17% of men with low testosterone had elevated LH consistent with testicular dysfunction [13]. Like the study of Ma et al. [12], Schroeder et al. [13] reported that low testosterone levels correlated with inflammatory cytokines: IL-2, and IFN-α. Furthermore, Schroeder et al. [13] observed that male patients with low testosterone appeared to have increased mortality risk compared with those with normal testosterone levels. However, the magnitude of this increased risk was not mentioned [13]. In agreement with the prior 2 studies, Rastrelli et al. [14] found that total testosterone levels were negatively associated with several indices of COVID-19 severity, namely neutrophil count, lactate dehydrogenase (LDH) and ferritin. On the other hand, using data from UK Biobank, Ghazizadeh et al. [15] showed significant direct association between free androgen index and COVID-19 susceptibility and severity in their female patients with COVID-19. Clearly, the relationship between testosterone and COVID-19 in women deserves further studies.

**Testosterone and COVID-19 mortality in men**

In a retrospective Italian study, Rastrelli et al. [14] evaluated the relationship of testosterone levels to clinical outcomes in 31 men admitted to the “respiratory” ICU with COVID-19. Median serum testosterone concentrations were significantly lower in the 4 patients whose clinical condition deteriorated and were either transferred to ICU or died compared with patients whose condition improved, 28 and 253 ng/dl, respectively [14]. In addition, compared with patients who did not develop ARDS, patients with COVID-19 complicated by ARDS had lower testosterone levels (63 versus 201 ng/dl) and higher LH levels (12.0 versus 6.9 mU/L) [14]. Moreover, these authors showed that for each 28.8 ng/dl (1 nmol/L) decrease in circulating testosterone concentrations, the probability of having worse outcome (ICU transfer or death) increased; OR 1.42, 95% CI 1.06-1.89; P=0.027 [14]. They further defined a testosterone threshold level of 144 ng/dl, below which probability of ICU transfer or death increased 10 times [14]. The results of this study are in concordance with previous investigations showing positive correlation between low testosterone levels and increase inflammatory cytokines in men with COVID-19 [12,13].

**Androgen deprivation therapy and COVID-19 mortality in men**

As mentioned earlier, there is a theory that testosterone may enhance COVID-19 infection by increasing synthesis of the co-receptor of SARS-Cov-2: TMPRSS2 [8]. Therefore, by lowering androgen levels, androgen deprivation therapy (ADT) could potentially inhibit virus cellular binding and subsequent infection. Two retrospective studies suggested that ADT may decrease susceptibility and severity of COVID-19. Montopoli et al. [19] reported that only 4 of 5273 (0.07%) patients with prostate cancer treated with ADT had COVID-19.
Furthermore, they found that these 4 patients had approximately 4 times lower risk of having COVID-19 compared with patients who did not receive ADT [19]. In addition, none of the 4 patients have died from COVID-19 [19]. In another preliminary report from New York, Patel et al. [20] found that compared with no use of ADT, use of ADT in 22 patients with prostate cancer was associated with lower rates of hospitalization (OR 0.26, 95% CI 0.06-0.79; P <0.02) and requirements for supplemental oxygen (OR 0.26, 95% CI 0.07-0.92; P 0.026) [20]. Additionally, there was a trend towards lower mortality and need for intubation on the group of patients on ADT [20]. Taken together, the results of these 2 studies suggest that achievement of extremely low testosterone levels by ADT may confer a protective effect against COVID-19 [19,20]. Meanwhile, a third study from Italy did not support the latter concept. Caffo et al. [21] reported that 36 of 194 (1.8%) with prostate cancer had COVID-19. Eleven of these 36 (30.6%) patients died from COVID-19 [21]. This lethality rate was similar and not lower than that of Italian men with similar age infected with COVID-19 [21]. Nevertheless, the increased mortality reported by Caffo et al. [21] may be partly due to the fact that their patients had advanced metastatic prostate cancer.

**Estrogen in patients with COVID-19**

**Male studies**

In the series of 81 young men (median age 38 years) hospitalized with COVID-19 reported by Ma et al. [12], estradiol levels (the main estrogen) were similar to those of healthy men (median 32 pg/ml). Shroeder et al. [13] found that 47% of men (median age 62 years) had elevated estradiol levels between 52-185 pg/ml (normal male range 27.1-52.2 pg/ml). They also found a positive correlation between estradiol levels and the pro-inflammatory cytokine IL-6 [13].

**Female studies**

In 78 pre-menopausal women hospitalized for COVID-19, Ding et al. [4] found that estradiol levels greater than 70 pg/ml were associated with decreased risk of having severe COVID-19, hazard ratio 0.30 (95% CI 0.09-1.00; P=0.05) after adjustment for age, phase of menstrual cycle and co-morbidities. In addition, there was inverse correlation between estradiol levels and the cytokines IL-6, IL-8 and TNF-α [4]. Hence, these results are consistent with estrogen protective effect in COVID-19. In a study from UK called The COVID Symptom Study Smartphone Application "app", Costeira et al. [22] reported that post-menopausal women had a higher rate of predicted COVID-19 compared with pre-menopausal women (OR 1.22, 95% CI 1.07-1.39; P =0.03) [22]. Likewise, women using combined oral contraceptives (COCOP) had a lower rate of predicted COVID-19 (OR=0.87, 95% CI 0.64-0.97; P=0.023) compared with age-matched women not taking COCP [22]. Conversely, women aged 50-65 years using post-menopausal hormone replacement therapy had higher predicted COVID-19 than age-matched women not taking such therapy (OR=1.32, 95% CI 1.16-1.49) [22]. The authors mentioned that co-morbidities, duration and use of postmenopausal hormone therapy might explain the unexpected increase in predicted COVID-19 in this group of post-menopausal women [22].

**COVID-19 in pregnancy**

Since pregnancy is characterized by extremely high levels of circulating estrogen, evaluation of susceptibility and clinical severity of COVID-19 in pregnant women may be a useful tool to examine the possible protective effect of estrogen. In general, available data suggest that severity of COVID-19 in pregnant women may not be different from non-pregnant women [23,24]. This notion is limited, however, by the lack of direct comparison with age-matched non-pregnant women with similar co-morbidities. A possible protective effect of estrogen was suggested in the study of Chen et al. [23] including 118 pregnant women hospitalized for COVID-19. In this study, 6 of the 9 pregnant women whose condition deteriorated did so following delivery when serum estrogen levels declined.

**Conclusions and current directions**

Our knowledge regarding sex hormones and COVID-19 is still in its stage of infancy. In men, low testosterone levels are generally associated with high inflammatory markers and disease severity. Whether low testosterone in men is a cause or a consequence (or both) in COVID-19 is still unclear. The preliminary observations of favorable prognosis of COVID-19 in men taking ADT supports the theory that low testosterone levels may be beneficial in COVID-19. This issue will be clarified by results of ongoing trials that compare outcomes of patients with COVID-19 randomized to ADT versus placebo. In women, preliminary data suggests that estrogen may have a beneficial effect in COVID-19. This is based on the following observations: pre-menopausal state is generally protective against COVID-19, higher serum estradiol levels are associated with less severe COVID-19, and decreased risk of COVID-19 in pre-menopausal using COCP. However, the role of estrogen will be only clarified by randomized trials. Such trials are underway to evaluate efficacy and safety of estrogen for treatment of COVID-19 in both women and men.

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