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COVID-19 Infection in Men on Testosterone Replacement Therapy

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Abstract

Men who contract Coronavirus Disease 2019 (COVID-19) appear to have worse clinical outcomes compared to women which raises the possibility of androgen dependent effects. We sought to determine if testosterone replacement therapy (TRT) is associated with worse clinical outcomes. Through a retrospective chart review, we identified 32 men diagnosed with COVID-19 and on TRT. They were propensity score matched to 63 men diagnosed with COVID-19 and not on TRT. Data regarding comorbidities and endpoints such as hospital admission, intensive care unit (ICU) admission, ventilator utilization, thromboembolic events, and death were extracted. Chi-square and Kruskal-Wallis tests examined differences in categorical and continuous variables, respectively. Logistic regression analysis tested the relationship between TRT status and the study endpoints. There were no statistically significant differences between the two groups and TRT was not a predictor of any of the endpoints on multivariate analysis. These results suggest that TRT is not associated with a worse clinical outcome in men diagnosed with COVID-19.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) demonstrates that men have less favorable disease outcomes when compared to women. (1) This suggests the possibility of a testosterone mediated disease process for severe disease manifestations, which has led to the formulation of polar theories. The cytokine theory proposes that a low testosterone level leads to an increase in pro-inflammatory cytokines which may facilitate a cytokine storm in men with COVID-19. (2) Conversely, the androgen driven COVID-19 theory suggests that testosterone, via activation of a transmembrane protease (TMPRSS2), promotes infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). (3) An increase in venous thromboembolism has also been associated with COVID-19 particularly in patients who are more severely affected. (4) Testosterone replacement therapy (TRT) is associated with secondary polycythemia but it is unclear whether this leads to an increase in thromboembolic events. However, some authors have suggested that men should be taken off TRT during this pandemic. (5) Our objective was to determine the impact of TRT on the clinical outcomes of COVID-19 in men.

Materials and Methods

After obtaining institutional review board approval, we performed a retrospective review identifying all men diagnosed with COVID-19 (ICD-10 code U07.1) who were on TRT from Henry Ford Health System during March to May 19, 2020. These men were propensity score matched in a ratio of 1:2 (using Greedy Nearest Neighbor method, caliper of 0.2) based on age, race, body mass index (BMI), and ZIP code (proxy for socioeconomic status), to men diagnosed with COVID-19 and not on TRT (controls).

Standardized mean difference was ≤10% for all variables after matching. Comorbidity data including smoking status, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, chronic kidney disease, and immunosuppression status was collected. COVID-19 related endpoints were extracted including hospital admission, intensive care unit (ICU) admission, mechanical ventilator utilization, thromboembolic events, and death. Chi-square and Kruskal-Wallis tests examined differences in categorical and continuous variables, respectively. Logistic regression analysis tested the relationship between TRT status and the study endpoints. Covariates consisted of age, race, BMI, ZIP code, smoking status, and comorbidity (as a cumulative number).

Results

A total of 3,697 men diagnosed with COVID-19 were identified of which 38 were on TRT. 6 men in the TRT group and 13 men in the control group had incomplete data and were excluded resulting in inclusion of 32 men in the TRT and 63 men in the control groups. Among men on TRT, 32 were diagnosed with hypogonadism (2 hypergonadotropic, 7 hypogonadotropic, and 23 mixed). 23 men received intramuscular testosterone cypionate injections while 9 were on transdermal testosterone gel. Descriptive characteristics are reported in Table 1. Median age (IQR) was 53 years (46-65) and BMI (IQR) was 31 (27.4-36.3). Mean testosterone (IQR) level for those on TRT was 397 (212.5-454.75) ng/dl. Patients on TRT had higher rates of hypertension (65.6% vs. 55.5%), cardiovascular disease (37.5% vs. 30.1%), diabetes mellitus (40.6% vs. 30.1%), immunosuppression (25% vs. 14.2%), and a lower rate of COPD compared to

controls (12.5% vs. 25.4%), none of which were statistically significant (all p≥0.1). When focusing on endpoints, patients on TRT had similar rates of hospitalization (62.5% vs. 63.4%, p=0.9), thromboembolic events (12.5% vs. 12.7%, p=0.7), and death (9.3% vs. 12.7%, p=0.7) as their counterparts not on TRT. Patients on TRT had lower rates of ICU admission (12.5% vs. 25.4%, p=0.1) and mechanical ventilator utilization (9.3% vs. 19.0%, p=0.2) than patients not on TRT but none were statistically significant. TRT was not an independent predictor of any of the examined endpoints on multivariable analysis (Table 2).

Discussion

To our knowledge, this is the first study looking at outcomes of men on TRT who developed COVID-19. In our cohort, the thromboembolic and death rates were similar in both groups. Despite having a higher rate of baseline comorbidities, there were lower rates of ICU admission and mechanical ventilator utilization that were observed in the TRT group, although not statistically significant.

Androgens are needed for the SARS-CoV-2 to infect cells via activation of TMPRSS2 which serves to prime the spike protein needed for entry into cells. (3) Based on this, clinical trials have begun with anti-androgens and TMPRSS2 inhibitors as prophylactic agents. There may also be a role for 5-**α** reductase inhibitors and luteinizing hormone releasing hormone agonists/antagonists in this setting. (6) In fact, it was found that even though cancer patients have an increased risk of contracting COVID-19, men on androgen deprivation therapy for prostate cancer had a lower risk of developing an infection. (7)

Once an infection occurs, testosterone may serve a protective role by decreasing the risk of a cytokine storm. (2) A recent report observed lower levels of testosterone in men who were admitted to the ICU with SARS-CoV-2 infections. (8) It is unknown whether these men had a low testosterone level at baseline or if they developed a low testosterone level in response to the infection. There is evidence to suggest that the majority of men admitted to acute care units have a transient suppression of testosterone to below the normal range. (9) A decreased testosterone level is associated with an increase in pro-inflammatory markers such as IL-1**β**, IL-6, and TNF-**α**. (10) Testosterone may facilitate cell infection with the SARS-CoV-2 but also be protective of worse clinical outcomes during active infections. A study measuring testosterone levels of men at baseline and at various times during COVID-19 may help further delineate this relationship.

Androgens appear to play an important role in COVID-19 but the overall clinical picture is a much more complex interplay between exposure risks, age, comorbidities, genetic predisposition, and socioeconomic status. A combination of these factors may be responsible for the differences in disease severity between men and women. Limitations of this study include small sample size, which limits the statistical power of the study. Other limitations are unknown testosterone levels in men of the control cohort, and the retrospective nature of this study with the potential for residual bias caused by unobserved confounders, even after propensity score matching. In conclusion, our study failed to demonstrate a statistically significant difference in COVID-19 outcomes among men treated with TRT and those not on TRT. Future studies are needed to help further

guide clinicians on the optimal management of hypogonadism with testosterone replacement therapy in the era of COVID-19.

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206

Table 1. Baseline characteristics and outcomes of 95 men diagnosed with COVID-19, stratified by testosterone replacement status

	All patients (*n* = 95)	**Testosterone replacement (*n* = 32)**	**Matched controls (*n* = 63)**	**P value**
Age, years, median (IQR)	53 (46-65)	52 (45-66)	54 (47-64)	0.3
Race, *n* (%)				
White	70 (73.7)	22 (68.8)	48 (76.2)	
Black	16 (16.8)	6 (18.8)	10 (15.9)	
Others	9 (9.5)	4 (12.5)	5 (7.9)	0.7
BMI, median (IQR)	31.5 (27.4 – 36.3)	32.7 (27.9 – 38.0)	31.2 (27.1 – 35.8)	0.2
Zip code, *n* (%)				
480	16 (16.8)	5 (15.6)	11 (17.5)	
481	39 (41.1)	13 (40.6)	26 (41.3)	
482	10 (10.5)	4 (12.5)	6 (9.5)	
483	16 (16.8)	4 (12.5)	12 (19.1)	
492	14 (14.7)	6 (18.8)	8 (12.7)	0.9
Comorbidities prior to COVID-19, *n* (%)				0.1
COPD	20 (21.1)	4 (12.5)	16 (25.4)	0.5
Cardiovascular disease	31 (32.6)	12 (37.5)	19 (30.2)	0.6
Chronic kidney disease	21 (22.1)	6 (18.8)	15 (23.8)	0.3
Diabetes	32 (33.7)	13 (40.6)	19 (30.2)	0.3
Hypertension	56 (59.0)	21 (65.6)	35 (55.6)	0.2
Immunosuppression	17 (17.9)	8 (25.0)	9 (14.3)	
Smoking (current/former)	44 (46.3)	15 (46.9)	29 (46.0)	0.9
Hospital admission for COVID-19, *n* (%)	60 (63.2)	20 (62.5)	40 (63.5)	0.9
ICU admission for COVID-19, *n* (%)	20 (21.1)	4 (12.5)	16 (25.4)	0.1
Thromboembolic event during COVID-19, *n* (%)	12 (12.6)	4 (12.5)	8 (12.7)	0.7
Mechanical ventilation during COVID-19, *n* (%)	15 (15.8)	3 (9.4)	12 (19.1)	0.2
Death due to COVID-19, n (%)	11 (11.6)	3 (9.4)	8 (12.7)	0.7

Legend:

BMI: body mass index; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease

Table 2- Multivariable logistic regression analysis testing the impact of testosterone replacement therapy on the clinical outcomes of men with new coronavirus infection 2019 (COVID-19)

Endpoints	**Odds Ratio**	**95% confidence interval**	**Hosmer and Lemeshow Goodness of Fit**
Hospital admission	0.997	(0.34-2.86)	0.750
Intensive care unit admission	0.323	(0.07-1.34)	0.981
Mechanical ventilator utilization	0.465	(0.10-2.08)	0.650
Thromboembolic event	0.540	(0.09-3.13)	0.895
Death	1.713	(0.13-21.24)	0.611

Legend: all multivariable analyses were adjusted to age, race, body mass index, smoking status, comorbidity (as a cumulative number), and ZIP code. The control group was set as the reference category.