COVID-19 Infection in Men on Testosterone Replacement Therapy

Amarnath Rambhatla, MD,1 Chandler J. Bronkema, BS,2,3 Nicholas Corsi, BS,2,3 Jacob Keeley, MS,3 Akshay Sood, MD,1,3 Ziad Affas, BS,2 Ali A. Dabaja, MD,1 Craig G. Rogers, MD,1 Stephen A. Liroff, MD,1 and Firas Abdollah, MD1,3

ABSTRACT

Background: Men who contract coronavirus disease 2019 (COVID-19) appear to have worse clinical outcomes compared with women which raises the possibility of androgen-dependent effects.

Aim: We sought to determine if testosterone replacement therapy (TRT) is associated with worse clinical outcomes.

Methods: 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 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.

Results: There were no statistically significant differences between the 2 groups, and TRT was not a predictor of any of the endpoints on multivariate analysis.

Conclusion: These results suggest that TRT is not associated with a worse clinical outcome in men diagnosed with COVID-19. Rambhatla A, Bronkema CJ, Corsi N, et al. COVID-19 Infection in Men on Testosterone Replacement Therapy. J Sex Med 2021;18:215–218.

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INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) demonstrates that men have less favorable disease outcomes than 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 proinflammatory 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, cardiovascular disease, chronic kidney disease, and immunosuppression status were 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.

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

| Characteristics and outcomes | 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)               | .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)                  | .7      |
| BMI, median (IQR)            | 31.5 (27.4–36.3)     | 32.7 (27.9–38.0)                | 31.2 (27.1–35.8)         | .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)                 | .9      |
| Comorbidities before COVID-19, n (%) |                  |                                 |                          | .1      |
| COPD                         | 20 (21.1)            | 4 (12.5)                        | 16 (25.4)                | .5      |
| Cardiovascular disease       | 31 (32.6)            | 12 (37.5)                       | 19 (30.2)                | .6      |
| Chronic kidney disease       | 21 (22.1)            | 6 (18.8)                        | 15 (23.8)                | .3      |
| Diabetes                     | 32 (33.7)            | 13 (40.6)                       | 19 (30.2)                | .3      |
| Hypertension                 | 56 (59.0)            | 21 (65.6)                       | 35 (55.6)                | .2      |
| Immunosuppression            | 17 (17.9)            | 8 (25.0)                        | 9 (14.3)                 |         |
| Smoking (current/former)     | 44 (46.3)            | 15 (46.9)                       | 29 (46.0)                | .9      |
| Hospital admission for COVID-19, n (%) | 60 (63.2)   | 20 (62.5)                       | 40 (63.5)                | .9      |
| ICU admission for COVID-19, n (%) | 20 (21.1)   | 4 (12.5)                        | 16 (25.4)                | .1      |
| Thromboembolic event during COVID-19, n (%) | 12 (12.6)   | 4 (12.5)                        | 8 (12.7)                 | .7      |
| Mechanical ventilation during COVID-19, n (%) | 15 (15.8)   | 3 (9.4)                         | 12 (19.1)                | .2      |
| Death due to COVID-19, n (%)  | 11 (11.6)            | 3 (9.4)                         | 8 (12.7)                 | .7      |

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

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                             |

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.
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 a 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 TRT in the era of COVID-19.

Corresponding Author: Amarnath Rambhatla, MD, Vattikuti Urology Institute (VUI), Henry Ford Hospital 2799 W Grand Blvd, Detroit, MI 48202-2689, USA. Tel: 313-717-8680; Fax: 313-982-4440; E-mail: Arambha1@hfhs.org

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Amarnath Rambhatla: Writing - Original Draft, Formal Analysis, Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition, Writing - Original Draft, Formal Analysis, Project Administration; Chandler J. Bronkema: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Nicholas Corsi: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Jacob Keeley: Writing - Original Draft, Formal Analysis, Writing - Original Draft, Formal Analysis, Project Administration; Akshay Sood: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Ziad Affas: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Ali A. Dabaja: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Craig G. Rogers: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Firas Abdullah: Writing - Original Draft, Formal Analysis, Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Stephen A. Liroff: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Amarnath Rambhatla, MD, Vattikuti Urology Institute (VUI), Henry Ford Hospital 2799 W Grand Blvd, Detroit, MI 48202-2689, USA. Tel: 313-717-8680; Fax: 313-982-4440; E-mail: Arambha1@hfhs.org

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