



BESINS HEALTHCARE SCIENTIFIC LITERATURE REVIEW – June 2021

Must Read Articles in Men’s Health

Testosterone Target Therapy: Focus on Immune Response, Controversies and Clinical Implications in Patients With COVID-19 Infection.

Therapeutic Advances in Endocrinology and Metabolism 2021:12:1-8

Salciccia S. et al.

Pubmed Link: [PMC8072920](https://pubmed.ncbi.nlm.nih.gov/35311120/)

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Serum Testosterone is Inversely and Sex Hormone Binding Globulin is Directly Associated with All-Cause Mortality in Men.

The Journal of Clinical Endocrinology and Metabolism 2021: 106: 2: e625 -e637

Yeap B.B et al

PubMed link: [10.1210/clinem/dgaa743](https://pubmed.ncbi.nlm.nih.gov/35311120/)

Other Articles of Interest - Men’s Health

Evaluation of the Efficacy of Transdermal and Injection Testosterone Therapy in Klinefelter Syndrome: A Real-Life Study	Journal of the Endocrine Society. 2021:5:1–11 <i>Kabilan A et al</i>	TRT, irrespective of route of administration, leads to similar effects based on androgen-responsive variables in KS patients.
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Title	Authors	Journal and Issue	Article Type
Testosterone target therapy: focus on immune response, controversies and clinical implications in patients with COVID-19 Infection	Salciccia S. et al	<i>Therapeutic Advances in Endocrinology and Metabolism</i> 2021:12:1-8	Review

What this review brings: This review raises important questions about the impact of low testosterone levels on the immune system and how this may contribute to poorer outcomes in men with Covid 19 Infection.

Background:

- Older age, male sex and comorbidity are the main risk factors contributing to morbidity from COVID-19.
- Differences in immune responses between men and women are well documented and it has been postulated that hormonal differences may contribute to differences in clinical outcome between men and women.

Aim:

- This review looks at the role of testosterone in immunity and examines why there are higher incidents of COVID-19 in elderly men and usually worse clinical outcomes.

Discussion and hypothesis:

- Testosterone may have an immunosuppressive role on different components and perhaps different phases of the immune system.
- Testosterone may act negatively on the immune response in both bacterial and viral infections and this strong immunosuppressive effect may contribute to the susceptibility of men to COVID-19 infection. Exceptions to this assumption have been reported.

The author speculates that testosterone could work in two ways with COVID-19 infection.

1. The immunosuppressive action of testosterone could explain men's greater susceptibility to infection when compared with women in all age groups.
2. In elderly males who frequently develop ARDS, lower testosterone levels related to age could result in a lower immunosuppressive effect and thus a more robust cytokine response.

Current evidence indicates that low testosterone levels in patients who have contracted COVID-19 leads to a more severe clinical outcome and were negatively associated with ICU admission.

- Hypogonadism represents a significant risk factor for unfavorable results when infection has occurred.
- As regards men with prostate cancer and Androgen Deprivation Therapy (ADT) there are many studies examining the effect of ADT therapy in men with prostate cancer who have contracted COVID-19:
 - If testosterone potentially has a double-edged role the Natural History of Covid 19 infection it is possible that ADT would be contraindicated in critically ill patients as the loss of immunosuppressive effect of circulating testosterone could exacerbate the cytokine syndrome.
 - If low testosterone levels give an advantage in the susceptibility phase of infection due to restoration of immunological function and through the blocking of Transmembrane Serine Protease 2 (TMPRSS2) it is possible that ADT could represent a prevention strategy for patients at increased risk of mortality from COVID-19.
- Two studies are currently looking at the use of ADT in the treatment of COVID-19 patients.
- Dutasteride a 5 α reductase inhibitor for BPH is also currently being investigated to explore its protective role in patients with Covid -19 infection not hospitalized.
- It is advocated in this article that Testosterone replacement therapy should be tested in hypogonadal patients with COVID-19 infection in randomized control trials.

Practice Points:

- Low T levels and their effect on the immune system may explain the higher incidence of mortality in males with COVID-19.
- Low Testosterone may be protective against initial susceptibility to COVID-19 but lead to a worse clinical course in advanced infection with COVID-19.

Title	Authors	Journal and Issue	Article Type
Serum Testosterone is Inversely and Sex Hormone Binding Globulin is Directly Associated With All-cause Mortality in Men	Yeap B.B <i>et al</i>	<i>The Journal of Endocrinology and Metabolism</i> 2021:106:625 637	Prospective Cohort Study

What this study brings: This study is the largest long term cohort study examining testosterone and correlation with mortality. It highlights that men with the lowest testosterone levels, have higher risks of dying from any cause and cancer but not from CVD and men with lower SHBG have lower risks of dying from any cause, CVD and cancer.

Background:

- Serum testosterone concentrations decline in aging men and concentrations of sex hormone binding globulin (SHBG) increase.
- Conflicting evidence exists regarding the impact of testosterone concentrations on all-cause mortality, CVD and Cancer.
- Similarly, conflicting evidence exists around SHBG concentrations and their impact on male mortality.

Aim:

- To determine if lower testosterone and lower SHBG were associated with higher mortality in men and if calculated free testosterone (cFT) provides additional information to predict mortality risk in men.

Results:

- 149,436 men aged 40-69 from a UK Biobank met inclusion criteria and were followed up for a median period of 11.3 years for all-cause mortality, and 11.2 years for CVD and Cancer.

Testosterone

- Men with the lowest serum testosterone levels had the shortest average times to death from all-cause mortality, CVD and Cancer on survival plots.
- In multivariable analysis, men with lower serum testosterone had higher all cause and cancer related mortality but not CVD.

SHBG

- Men with lower SHBG had a longer average time to death from all cause or from cancer
- Men with lower SHBG had the longest average time to CVD death and those with the highest SHBG had the shortest time to death.

cFT

- Men with the lowest level of cFT had the shortest time to death from any cause, CVD or cancer on survival plots.
- In univariable analysis, as cFT levels decreased the risk of death from CVD and cancer mortality was increased stepwise.
- In multivariable analysis lower cFT levels were associated with all cause and cancer related mortality but not with CVD deaths

Discussion:

This study demonstrated that:

- Serum testosterone and cFT are inversely associated with overall and cancer related mortality but not CVD related mortality.
 - The inverse association between serum testosterone levels with all-cause mortality was independent of SHBG. It was mostly limited to men with the lowest T levels and had a modest (14%) increased risk of death from all-causes.
 - The inverse association between serum testosterone levels and cancer mortality was limited to men with the lowest serum T levels which increased their risk of mortality by 20%.
- Direct relationships between serum SHBG and overall mortality and CVD and cancer related mortality are also demonstrated.
 - Lower SHBG concentrations are associated with obesity and insulin resistance, however, this study found that serum SHBG was associated with all-cause mortality directly and in a linear fashion, independent of testosterone.

Practice Points:

- There have been many studies trying to understand correlation with testosterone, free testosterone and SHBG levels with mortality rates, these were smaller studies and showed conflicting results.
- This study is the largest long term cohort study examining testosterone and correlation with mortality: 149,436 men aged 40-69 from a UK Biobank met inclusion criteria were followed up for a median period of 11.3 years for all-cause mortality, and 11.2 years for CVD and Cancer.
- Men with the lowest testosterone levels have higher risks of dying from any cause and cancer but not from CVD.
- Men with lower SHBG, across the range of SHBG values, have lower risks of dying from any cause, CVD and cancer.