CORRESPONDENCE

Risks of testosterone therapy in elderly men [v1; ref status: indexed, http://f1000r.es/2oc]

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Abstract

Testosterone supplementation therapy (TST) is a widely used treatment for men with late onset hypogonadism. The benefits seen with TST, such as improved libido and energy level, beneficial effects on bone density have been well documented. Although hypogonadism remains an independent risk factor for mortality, recent studies have examined the association between testosterone therapy and cardiovascular risk.

Article Status Summary

Referee Responses

Referees	1	2
v1 published 15 Jan 2014	✓ report	✓ report

1 **Boback Berookhim**, Memorial Sloan Kettering Cancer Center USA

2 **Matthew S. Wosnitzer**, Weill Cornell Medical College of Cornell University USA

Latest Comments

No Comments Yet

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Ranjith Ramasamy, James M. Dupree and Jason R. Kovac do not have any competing interests to disclosure. Larry I. Lipshultz has reported being a clinical trials participant, consultant, and speaker for Auxlium and Endo.

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Correspondence

Vigen *et al.*[1] examined the association between testosterone supplementation and cardiovascular morbidity in men older than 60 years. They performed a retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. The absolute rate of atherosclerotic events (myocardial infarction, stroke and mortality) was 19.9% in men who did not receive testosterone vs 25.7% in the men who were treated with testosterone. Men on testosterone supplementation were reported to have higher risk of adverse events than men not on testosterone, despite being younger and having less comorbidity.

One of the most important messages to glean from the study is that hypogonadism could be an adverse prognostic factor for cardiovascular and cerebrovascular morbidity and mortality. This message is also found in other studies about hypogonadism, including a large study on male veterans that showed that hypogonadism could be an important risk factor for increased mortality[2]. Further, in men with hypertension[3], low testosterone levels were shown to be associated with increased risk of major cardiovascular adverse events.

In the Vigen *et al.* study men who received testosterone had lower pre-therapy testosterone levels, suggesting that they were even more hypogonadal than men who did not start testosterone therapy. In addition, it is unclear how much testosterone the men in the treatment arm actually received. Based on prescription refills, most men were on testosterone therapy for less than one year, and their mean post-treatment testosterone level was 332 ng/dL. With serum testosterone less than 300 ng/dL defined as biochemical hypogonadism by the Endocrine Society[4], we are concerned that a significant proportion of men could have remained hypogonadal, in spite of testosterone treatment.

Additionally, the reasons for starting testosterone therapy cannot be determined from this retrospective analysis. Because of the uncertain reasons for starting therapy in some hypogonadal men and not in others, and because of the variability in the amount of total testosterone that the patients actually received, there may be confounding factors that could also explain the higher risk of adverse events in men treated with testosterone. It is unclear whether the minimal exposure to testosterone in this elderly population (as evidenced by the post-treatment levels and duration of treatment) was responsible for such a dramatic difference in mortality and morbidity.

The association between testosterone therapy and mortality has remained controversial with studies demonstrating conflicting results[5,6]. Until larger randomized studies demonstrate clear causation, physicians prescribing testosterone therapy to elderly men with co-morbidities should use it prudently with close follow-up.

Author contributions

RR chose the article for correspondence and evaluated the data in the manuscript. JD wrote a part of the commentary. JK wrote the abstract and introduction. LIL supervised the process and critically edited the manuscript. All authors discussed the implications and commented on the manuscript at all stages.

Competing interests

Ranjith Ramasamy, James M. Dupree and Jason R. Kovac do not have any competing interests to disclosure. Larry I. Lipshultz has reported being a clinical trials participant, consultant, and speaker for Auxlium and Endo.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. Vigen R, O'Donnell CI, Baron AE, *et al.*: **Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels.** *JAMA: the journal of the American Medical Association.* 2013; **310**(17): 1829–1836.
PubMed Abstract | Publisher Full Text
2. Shores MM, Matsumoto AM, Sloan KL, *et al.*: **Low serum testosterone and mortality in male veterans.** *Arch Intern Med.* 2006; **166**(15): 1660–1665.
PubMed Abstract | Publisher Full Text
3. Vlachopoulos C, Ioakeimidis N, Terentes-Printzios D, *et al.*: **Plasma total testosterone and incident cardiovascular events in hypertensive patients.** *Am J Hypertens.* 2013; **26**(3): 373–381.
PubMed Abstract | Publisher Full Text
4. Bhasin S, Cunningham GR, Hayes FJ, *et al.*: **Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.** *J Clin Endocrinol Metab.* 2010; **95**(6): 2536–2559.
PubMed Abstract | Publisher Full Text
5. Shores MM, Smith NL, Forsberg CW, *et al.*: **Testosterone treatment and mortality in men with low testosterone levels.** *J Clin Endocrinol Metab.* 2012; **97**(6): 2050–2058.
PubMed Abstract | Publisher Full Text
6. Basaria S, Coviello AD, Travison TG, *et al.*: **Adverse events associated with testosterone administration.** *N Engl J Med.* 2010; **363**(2): 109–122.
PubMed Abstract | Publisher Full Text | Free Full Text

Current Referee Status:

Referee Responses for Version 1

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Approved: 23 January 2014

Referee Report: 23 January 2014
This correspondence from the Baylor group accurately summarizes many of the questions surrounding the Vigen *et al.* article which describes an increased cardiovascular risk profile with testosterone replacement in a highly select group of VA patients. The majority of prior studies have not detected significant increases in cardiovascular risks, except for the randomized TOM trial (Basaria *et al.* 2010 NEJM), which had many of its own issues with *"differences detected between the two trial groups possibly...due to chance alone."*

One key criticism of the Vigen *et al.* study, described in this correspondence, is that hypogonadism alone may portend adverse cardiovascular and cerebrovascular outcomes and that the T treatment group in this study had lower pre-treatment T values. This issue is most recently highlighted in the JCEM article by Yeap *et al.* from Australia in 2013 describing older Australian men with reduced mortality when testosterone was in mid-range normal levels.

Other issues with the Vigen *et al.* study include the heterogeneous preparations of testosterone, and varied/unknown compliance with regimens. Only 60% of patients had follow-up testosterone labs after starting therapy which is particularly important since T response differs from regimen to regimen and patient to patient. Additionally for those who had testosterone checked, were they done appropriately in the morning or at other times? Additionally, known mean post-treatment testosterone levels were barely in eugonadal range, further highlighting possible compliance issues. Certainly, additional randomized controlled trials are required to discern whether the findings in this population are generalizable to any other population.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Boback Berookhim
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Approved: 22 January 2014

Referee Report: 22 January 2014

Dr. Ramasamy and colleagues present a well-researched brief summary on a topic which has received great attention among physicians treating low testosterone. The authors provide a nice summary of a newsworthy publication by Vigen *et al.* in JAMA in late 2013. The concerns presented with the methodology of this article, primarily regarding the efficacy of likely sub-therapeutic testosterone replacement therapy in an elderly veteran population, are relevant and worthy of further study. Given the conflicting studies within the literature, further research is required to clearly delineate the cardiovascular risks (or lack thereof) in elderly men receiving testosterone replacement therapy.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.