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ASSOCIATION BETWEEN TESTOSTERONE SUPPLEMENTATION THERAPY AND THROMBOTIC EVENTS IN ELDERLY MEN

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Abstract

Objective—To determine the prevalence of thrombotic events and all-cause mortality in men older than 65 years with hypogonadism treated with testosterone therapy (TST).

Methods—We retrospectively reviewed the charts of 217 hypogonadal men >65 years. We compared men who received TST (n=153) to hypogonadal men (n=64) who did not receive TST. We evaluated all-cause mortality, prevalence of myocardial infarction (MI), transient ischemic attack (TIA), cerebrovascular accident (CVA, or 'stroke'), and deep vein thrombosis / pulmonary embolism (DVT/PE). All events were verified by contacting patients. We excluded men with previous thrombotic events, men previously on androgen deprivation therapy and men who had used TST prior to age of 65.

Results—Median age and Charlson Comorbidity Index of men on TST (74y; 5.1) was similar between hypogonadal men not on TST (73y, p=0.48; 5.3, p=0.36). Median follow-up was 3.8 vs. 3.5 years (TST vs. no TST). No man on TST died, whereas 5 hypogonadal men who did not receive TST died (p=0.007). There were 4 thrombotic events (1 MI, 2 CVA/TIA, 1 PE) in men who received TST and 1 event (CVA/TIA) among men who did not receive TST (p = 0.8). All events (1 death, 6 months follow-up) occurred at least after 2 years of follow-up.

Conclusions—There was increased all-cause mortality in hypogonadal men not treated with testosterone compared to men who received testosterone therapy. There was no difference in prevalence of MI, TIA/CVA, or PE between patients treated with testosterone and hypogonadal men not treated with testosterone.

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Conflicts of interest:

Ranjith Ramasamy, Jason M. Scovell, Michael Mederos, Renzhong Ren, Lakshay Jain – None

Larry I. Lipshultz –Clinical trials, Consultant, Speaker: Endo

INTRODUCTION

Low serum testosterone is a marker of poor health [1] and remains an independent risk factor for cardiovascular morbidity and mortality [2]. The goal of TST is to ameliorate hypogonadal symptoms and improve quality of life with minimal adverse effects. Previously, elderly hypogonadal men reported marked improvement in libido, energy, and sexual function after receiving TST. Men receiving TST have reported improvement in mood, energy, memory, increases in fat-free body mass, and bone density [3, 4]

Despite several studies demonstrating the beneficial effect of testosterone supplementation therapy (TST) [5, 6] for cardiovascular health, two epidemiologic studies within the past year have spawned debate surrounding the association between TST and thrombotic risk in elderly men [4, 7]. We evaluated the prevalence of thrombotic events and mortality in men older than 65 years old with symptomatic hypogonadism treated with TST in our clinical practice. We compared men treated with testosterone to an age and comorbidity matched cohort of hypogonadal men not treated with TST.

PATIENTS AND METHODS

After IRB approval, we retrospectively reviewed the charts of 217 hypogonadal men who were evaluated at a tertiary care academic urology practice. We included men older than 65 years who had 2 separate blood draws of early morning total serum testosterone < 300ng/dl associated with ≥ 3 hypogonadal symptoms verified on the Androgen deficiency in Aging Male questionnaire. We excluded men who had thrombotic events prior to initiation of testosterone therapy. We also excluded men with active malignancies, men who previously took androgen deprivation therapy and men who were on TST prior to the age of 65.

Of the 217 men, 153 men received TST (injections n=53; gel n=47; pellets n=53). We compared men receiving TST to 64 hypogonadal men who did not receive testosterone therapy (men with lower urinary tract symptoms). A power calculation was performed based on study by Basaria et al. [8] since men over 65 years were included and men in the control group did not receive any testosterone therapy. In this study, 23% of subjects on supplemental testosterone were noted to have a cardiac event compared to 5% of patients not given testosterone[8]. Setting the p-value to 0.05 and the beta value at 0.20 (80% power), we require 49 subjects in each group to detect a difference. Our study was powered at 85% to detect a difference in the number of cardiovascular events.

We evaluated all-cause mortality (social security death index), prevalence of myocardial infarction (MI), transient ischemic attack (TIA), cerebrovascular accident (CVA, or ‘stroke’), and deep vein thrombosis / pulmonary embolism (DVT/PE). All thrombotic events and deaths were verified by calling patients / family members. Data are represented as medians ± interquartile range. P-values were calculated using Mann- Whitney U test and chi-squared test.

RESULTS

Both median age (74 vs. 73 y, p=0.48) and Charlson Comorbidity Index (5.1 vs. 5.3 p = 0.36) of men treated with TST was similar to hypogonadal men not on TST. As expected, testosterone levels obtained during follow-up were higher in men receiving TST. The median follow-up in men receiving TST was 3.8 years and median follow-up in men not receiving TST was 3.4 years. No man who received TST died (follow-up range 6 months to 9.5 years), whereas 5 hypogonadal men who did not receive TST died (p=0.007). There were 4 thrombotic events (1 MI, 2 CVA/TIA, 1 PE) in men who received TST compared to 1 event (CVA/TIA) among men who did not receive TST (p = 0.8). None of hypogonadal men died due to thrombotic events. The OR for risk of mortality in hypogonadal men who did not receive testosterone was 28.3 (CI 1.5 – 52.1, z statistic = 2.2, p = 0.02). The OR for risk of a thrombotic event in men who received TST was 1.7 (CI 0.18 – 15.4) but did not reach statistical significance (z statistic = 0.46, p=0.64). Of the five hypogonadal men not on testosterone, three died due to metastatic lung cancer, one man died due to metastatic prostate cancer and one man died due to respiratory failure secondary to chronic obstructive pulmonary disease. All events (except one death which took place after 6 months of follow-up) occurred 2 years or more after follow-up.

COMMENT

The use of TST in elderly men is reasonable given that hypogonadism is an independent risk factor for cardiovascular disease and all-cause mortality [2, 9]. Furthermore, improvements in risk factors for cardiovascular disease such as body weight, waist circumference, HbA1c, and total cholesterol levels after initiating TST [10] can contribute to decrease in thrombotic events. However, recent studies have raised concerns regarding the safety of TST in elderly (≥65 years old) men.[4, 7, 8] Our study demonstrated no increased risk of mortality or thrombotic events among elderly men who received TST. Although we identified more thrombotic events in men who received TST than men that did not receive TST, the difference was not statistically significant. A power calculation (85% power), though done retrospectively, confirmed that the sample size was adequate to identify a difference in prevalence of thrombotic events. It is difficult to speculate whether we would have arrived with a different result had we studied a larger sample size.

Some of the weaknesses of the larger population studies include lack of adequate control group, lack of availability of testosterone levels before and after therapy and short follow-up. For example, the study by Finkle and colleagues[7] utilized a control group of men who received PDE5i, a known cardioprotective agent. The follow-up was limited to 3 months after testosterone prescription was filled and no serum hormone levels were available for comparison. In the Vigen et al. study, only men who underwent a coronary angiogram were included. Typically, men who undergo a coronary angiogram do not represent the majority of the patients presenting for testosterone therapy.

Strengths of our study include long follow-up (>3 years), availability of serum testosterone levels before and after therapy and availability of a control group (hypogonadal men not treated with TST) for comparison. All major adverse cardiovascular events were verified by

telephone with the patient (or family members if patient died). Further, we restricted our study population to men older than 65 years, a population that was not studied as part of the initial clinical trials for topical testosterone. We painstakingly attempted to provide a more comprehensive study population, albeit smaller, that can provide credible evidence on this controversial issue. Limitations included retrospective study design, lack of baseline testosterone levels before treatment, lack of information on type of TST, and a small sample size (that limited from performing a logistic regression analysis). Because this was a retrospective study, we are not certain as to why hypogonadal men included in the control group did not receive TST. It could either be either provider or patient preference and could be a potential source of selection bias. In addition a sensitivity analysis that could increase the robustness of the study could not be performed since we only included men who had at least two office visits that included serum testosterone evaluation.

In our small retrospective cohort study, testosterone supplementation does not appear to increase the risk of thrombotic events in symptomatic hypogonadism in elderly men. Consistent with the majority of the studies in the literature, there was increased allcause mortality in hypogonadal men not treated with testosterone compared to men who received testosterone therapy. There was no statistically significant difference in prevalence of MI, TIA/CVA, or DVT/PE between patients who were treated with testosterone and hypogonadal men not treated with testosterone. Despite reassuring data from our cohort study, testosterone should be used with caution in elderly men with co-morbidities until larger randomized trials are performed.

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Table

Comparison of mortality and thrombotic events in men on testosterone supplementation with hypogonadal men not treated with testosterone. SHBG – sex hormone binding globulin, PSA – prostate specific antigen, MI – myocardial infarction, CVA – cerebrovascular accident, TIA – transient ischemic attack, PE – pulmonary embolism

	Men on TST (n=153)	Men not on TST (n=64)	P-value
Age (y)	74 ± 6.3	75 ± 6	0.48
Follow-up (y)	3.8 ± 2.7	3.4 ± 2.8	0.36
Charlson Comorbidity Index	5.1 ± 1.7	5.3 ± 1.6	0.37
Total Testosterone (ng/dL)	475 ± 342	236 ± 54	<0.001
Estradiol (ng/dL)	3.7 ± 2.1	2.6 ± 0.7	<0.001
SHBG (ng/dL)	48 ± 19	50 ± 27	0.75
PSA (ng/dL)	1.6 ± 2	1.7 ± 2.5	0.74
Hematocrit (%)	45 ± 5	42 ± 5	<0.001
Death (all-cause)	0	5	0.007
Thrombotic events	4	1	0.8
MI	1	0	1
CVA/TIA	2	1	1
PE	1	0	1