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TESTOSTERONE, AGING AND SURVIVAL: BIOMARKER OR DEFICIENCY

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Abstract

Purpose of Review—The purpose of this paper is to review recent studies that examined the association of endogenous and exogenous testosterone (T) and mortality in older men.

Recent findings—Over the past several years, there has been a steep rise in T prescriptions. The increased use of T occurred in the context of several studies that reported an association between low serum T and increased cardiovascular events and mortality. In contrast, recent studies have reported an association between T treatment and adverse events. A T treatment trial of mobility-impaired elderly men with prevalent cardiovascular disease was stopped due to increased cardiovascular events in the T-treated men and a meta-analysis reported increased cardiovascular events in T-treated men. In two recent large observational studies, T treatment was associated with an increased risk for serious adverse cardiovascular events.

Summary—Low T is associated with mortality in multiple cohort studies; however, it is unclear if this is a causal association or due to low T being a biomarker of poor health. Given recent reports of adverse outcomes associated with T-treatment, a conservative use of T is warranted in men with cardiovascular disease who may be at greater risk for adverse outcomes.

Keywords

Testosterone; aging; mortality; androgens; biomarker

Introduction

Testosterone (T) use in the United States has risen steeply with a nearly 10-fold increase since 2000[1]. This increase occurred in the context of large increases in direct advertising

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to consumers for treatment of “low T” with nearly \$3.5 billion spent in 2012.[2, 3] The availability of T-gel formulations and the hope that T may maintain youthfulness may have also helped to fuel the increase in T use. However, T-treatment is only approved for men with symptoms of androgen deficiency and repeatedly low T levels due to pathological disorders of the reproductive axis. On a public health level the abrupt rise in T prescriptions is concerning, particularly since approximately 25% of men who received new T prescriptions did not have a T level obtained in the year prior to the T-prescription. [4]

It is also possible that the public may view T treatment as a way to prolong life, as several studies reported that low serum T levels are associated with increased mortality in older men [5–24], although others did not. [25–31]. However, it is unclear if there is a causal association between low T and mortality or if low T is merely a biomarker of poor health and survival. The purpose of this paper is to review recent studies on low T and mortality and assess current evidence regarding low T as a biomarker for poor health or as a deficiency that independently contributes to mortality. If low T is a biomarker of medical morbidity, then T levels would decrease with acute and chronic illness and low T would be a risk factor for mortality. If on the other hand, low T in older men is a deficiency that is causally associated with mortality, then low T would be an independent risk factor for mortality and T replacement would decrease mortality in men with low T levels.

Testosterone in older men

Testosterone levels in men begin to decline in middle age and continue to slowly decline with age with greater decreases in free T than in total T. [32, 33] However, in contrast to menopause, in which there is cessation of ovarian estrogen secretion, testicular T secretion decreases, but does not cease entirely. Furthermore, the decline in T levels with aging is variable with greater decreases in T in the chronically ill, obese, or men taking medications that decrease T levels, [34–37] but no decline in T in some healthy older men. [38] In addition, T levels drop abruptly with acute illness such as myocardial infarction, sepsis, or trauma. Despite the decline in T levels with aging, most healthy elderly men have T levels within the normal range for younger men.

Symptoms and signs of low T include decreased libido and erectile function, irritability, fatigue, decreased concentration, increased fat mass, decreased muscle mass, and bone loss. [39] Most of these manifestations are nonspecific and could also be due to advanced age, medical illness, chronic pain, or depression. The only approved indication for T treatment is a diagnosis of hypogonadism, which is based on repeated low T levels obtained in the morning and signs and symptoms of androgen deficiency. [40] Repeated low T levels are required as T levels may fluctuate day-to-day. Since T levels in older men are likely to be influenced by acute or chronic illness and medications, the diagnosis and management of hypogonadism in older men is more complex than in younger men, with a risk of over-diagnosis in older men if an appropriate assessment is not done. [39]

Endogenous testosterone and medical morbidity

T levels decrease in men with acute illness and normalize following recovery from illness. [41] Low T levels are also associated with chronic medical conditions, such as the metabolic

syndrome, diabetes, dyslipidemia, hypertension, renal failure, frailty, malignancy and cardiovascular (CV) events. [42–51] A meta-analysis of endogenous T and CV events found that higher T levels were associated with a decreased risk for CV events in men >70 years with a hazards ratio (HR) of 0.84 (95% confidence interval (CI), 0.76–0.92), but not in younger men, with a HR of 1.01 (95% CI, 0.95–1.08).[44] The association of T with CV outcomes may be related to its effects on insulin resistance, inflammatory markers, endothelial function, and angiogenesis. [49, 52–54]

Endogenous T and mortality

The most recent meta-analysis of T and mortality, which was published in 2011, reported that low T was associated with increased all-cause mortality with a HR of 1.35 (95% CI, 1.13–1.62).[55] Mortality risk was greater in older men and men with lower T levels. However, the studies in the meta-analysis had significant heterogeneity, which suggests that the results could have been influenced by baseline differences in the cohorts. Since the publication of this meta-analysis, several additional studies, [5–11, 13, 16, 17, 19, 20, 24–26, 29, 56–58] that include over 25,000 men, have been published, with the results summarized as follows.

From 2011–2012, nine studies were published that examined the association between T and all-cause and CV mortality. (Table 1) Seven studies found an association between low total or free T and all-cause or CV mortality, [6, 8–11, 26, 58] while two studies did not. [7, 25] In studies since then, a small study found no association between repeated measures of T, estradiol, DHEAS, LH, and FSH with mortality. [27] Another study of 963 men with prostate cancer followed for a median of 12 years, found no association between pre-diagnosis androgen levels and outcomes of prostate-cancer mortality and all-cause mortality. [28] In contrast, low total T was significantly associated with all-cause mortality in a study of diabetic men, with a HR of 2.02 (95% CI, 1.2–3.4).[5] In a large study of 3690 men total and free T had curvilinear associations with mortality [12] with the third quartile compared to the first quartile associated with the least risk, with a HR of 0.78 (95% CI, 0.65–0.94) for total T and 0.72 (95% CI, 0.60–0.87) for free T.

Testosterone treatment and medical morbidity

T treatment is associated with decreases in cholesterol, obesity, inflammatory markers, insulin resistance and improvements in sexual function, muscle mass and strength. [59–62] Until recently, clinical trials had not reported that T-treatment was associated with increased serious adverse effects. [63–65] However, a recent T treatment study of mobility-impaired elderly men, mean age 70, was stopped due to an increase in self-reported CV adverse events in the T treated men. [66, 67] The study used higher doses of T and more than 50% of the T treated men had prevalent CVD. The risk for CV events was associated with higher free T levels following treatment, but was not associated with traditional risk factors for CVD. In contrast, in another study involving a similar cohort of near-frail and frail elderly men, 65 years or older, that used a lower dose of T, there was no increase in CV adverse events. [68] While not definitive, these results suggest that frail elderly men with underlying

CVD may be at increased risk for adverse CV events and that high doses be used cautiously and T levels monitored during treatment.

Testosterone treatment, mortality, and serious CV adverse outcomes in observational studies

Over the past two years, four observational studies examined the association of T treatment with adverse CV events and mortality. [5, 69–71] Table 2. In a study conducted in a Veterans Affairs (VA) health care system of 1031 veterans with low T levels, T-treated men had a lower mortality of 10.3% vs. 20.7% compared to the untreated men. [69] These results remained significant after adjusting for age and medical comorbidities, with a HR of 0.61(95% CI, 0.42–0.88) for T-treatment compared to non-treatment. Strengths of this study are that it used a propensity score analysis to adjust for non-randomization to treatment and conducted a sensitivity analysis in which men who died within the first year were excluded from the study to minimize the potential effect of acute illness. Weaknesses of the study are that there was no information available on indications for T treatment or presence of hypogonadal symptoms and limited information on follow-up T levels. [72]

In another VA study, men with low T levels, who had cardiac catheterization, were followed for composite events of myocardial infarction (MI), stroke, and all-cause mortality. [70] After adjusting for confounders and coronary artery disease, T treatment was associated with an increased risk for adverse events with HR of 1.29 (95% CI, 1.04–1.58). Strengths of the study are that it adjusted for changes in confounders over time and that it is the largest observational study of T-treated men with low T levels. Weaknesses of the study are that there was no information available on indications for T treatment or presence of hypogonadal symptoms and limited information on follow-up T levels. Another limitation is that the men had high medical morbidity with more than 50% with coronary artery occlusion, diabetes and obesity, which makes it difficult to generalize these results to healthier men. The different results of the two VA studies may be related to differences in prevalent heart disease, as the study that reported increased CV risks associated with T treatment had a high prevalence of heart disease of 59% [70] while the study that reported no increased risk with T treatment had a 21% prevalence of heart disease. [69]

A small observational study examined mortality in T treated and untreated men with low T level, type II diabetes and CVD (42% prevalence). Men who died within the first 6 months or who had less than one year of T-treatment were excluded from the study. T levels were monitored following treatment to achieve levels in the mid-upper normal range, and 67% of the men had levels > 519 ng/dl (18nmol/L). In unadjusted analyses, the untreated men had a higher mortality of 19.2% vs. 8.4% in the T-treated men. [5] After adjusting for medical morbidity, the untreated men had a greater risk for all-cause mortality with a HR of 2.3 (95% CI, 1.3–3.9). Strengths of this study were that T-treated men had symptoms of hypogonadism and serum T levels were monitored to achieve physiologic levels. Limitations were the small number of treated men (n=64), lack of adjustment for the propensity for treatment, and exclusion of men treated for less than one year, which may create a survivor bias as it eliminates men who died within the first year of T-treatment.

Finally, a recent large cohort study of 55,593 men examined non-fatal MI occurring 1 year pre-prescription and 90 days post an initial T- prescription. [71] The risk for MI was significantly greater following T-treatment than in the year prior to T treatment with a greater risk in older men (>65) and in men who had a history of coronary heart disease. (Table 2). Strengths of this study are that it is the largest study to date of T treatment and that it adjusted for confounding by utilizing each subject as its own control by comparing pre to post treatment events. Limitations of this study are that T levels pre- treatment were unknown, time window of evaluation post-T prescription was relatively short, compliance with T prescription was not known, and there was no information regarding indications for T treatment, symptoms of hypogonadism or T levels during treatment.

Testosterone treatment and mortality in clinical trials

Three meta-analyses of T treatment trials [63–65] found no association between T treatment and mortality or major adverse events. In contrast, a recent meta-analysis [73] of nearly 3000 men found a significant association between T treatment and composite CV events with an overall HR of 1.54 (95% CI, 1.09–2.18).[73] A similar HR of 1.42 (95% CI, 0.7–2.89) was reported for CV mortality, but due to a loss of power the estimate was no longer significant. There was no association with baseline serum T level and adverse outcomes. Industry-sponsored trials reported less risk for composite CV events with a HR of 0.89 (95% CI, 0.50–1.60) than non-industry funded trials with a HR of 2.06 (95% CI, 1.34–3.17).

Summary of studies of testosterone and mortality

Since 2011, 13 studies of endogenous T and mortality were published, with 9 studies reporting an association between low total or free T and mortality [5–12, 26] while 4 did not. [7, 25–28] A noteworthy result from observational studies was that endogenous T had a nonlinear association with mortality, suggesting an optimal range for androgens. [12] In two large observational studies T treatment was associated with increased CV events. [70, 71] with short-term T prescription associated with MI, particularly in older men (>65) and younger (<65) and older men with CAD, while younger men without CAD did not have an increased risk for MI following T prescription. [71] In a T-treatment trial, elderly, mobility impaired men with prevalent CVD who were treated with high dose T had increased self-reported CV adverse events, while another trial in a similar group of older men did not. [66, 67]. Finally, in a recent meta-analysis of T treatment trials, T treatment was associated with an increased risk for adverse CV events. [73] Although existing studies have limitations, the results of these studies suggest that older men and men with underlying CVD may be at greater risk for serious adverse CV events associated with T treatment.

Is low testosterone in older men a biomarker of poor health or a deficiency?

Low T appears to be a biomarker of poor health in older men as it is associated with acute and chronic medical conditions [41–43] and is a risk factor for mortality. [5–24] Testosterone may act as a biomarker of illness, similar to other hormones that are biomarkers of illness, such as thyroid hormone (free T3), which declines with illness

severity and predicts mortality. [74, 75] Although past cohort studies of low T and mortality have attempted to adjust for medical morbidity, due to the observational study design, there may be some unmeasured marker of medical illness, which explains the association between low T and mortality.

In some older men low T levels could also reflect a deficiency state. Men with severely low levels of T, such as in hypopituitarism or Klinefelter's syndrome, benefit clinically from T replacement. [76, 77] However, in older men with borderline low T levels, it is less clear if T treatment is beneficial. First, the exact threshold for low T in older men remains controversial. [78] Second, in older men low T is likely to be related to potentially reversible medical conditions and in such men efforts should first be made to treat the underlying medical condition. [39] Finally, consensus recommendations are that T-treatment be reserved for hypogonadal men with repeated low T levels plus signs and symptoms of low T. However, on a public health level, T-treatment in older men is problematic as a recent study found that many T-treated men (25%) did not have a T level obtained prior to treatment. [4] Finally, it is likely that risks related to T-treatment in older men differ from risks in younger men and the risks for serious adverse outcomes, such as CV events, aggressive prostate cancer and mortality are unclear at this time. [79]

Based on current research, it is not clear whether the association between low T and mortality indicates that low T is a biomarker for poor health and survival or if low T is a deficiency that is causally linked to mortality. Existing evidence provides the most support for low T being a biomarker of poor health and perhaps mortality. However, it is less clear that T is causally associated with mortality or if T replacement provides a survival benefit. Ongoing studies that may help to clarify this question include an NIA-sponsored multi-site testosterone treatment trial in older hypogonadal men. However, this trial was not designed or powered to assess CV risks or mortality. In addition, the NIA has sponsored three pharmaco-epidemiological studies to assess adverse effects of T treatment in differing patient populations. The results of these studies should help to clarify if there are subsets of men who may be more likely to benefit or be harmed from T treatment and help to inform the design of subsequent randomized controlled trials.

Conclusion

Although low serum T levels are associated with increased mortality in several observational studies, the significance of this is unclear, as observational studies cannot establish a causal relationship, due to the possibility of residual confounding. A long-term, prospective, randomized, controlled trial is needed to clarify the risks and benefits of T-treatment. These are significant public health questions given the increasing number of older men with low T levels and the "epidemic" in T prescribing which has occurred over the past several years [80].

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Major Points

1. Most observational studies have reported an association between low testosterone (T) and increased mortality.
2. Endogenous T may have an optimal serum range, with increased mortality risk at levels above or below this range.
3. In recent observational studies, T-treated men had an increased risk for CV events, with greater risks in older men (>65) and men with prevalent heart disease.
4. A conservative use of T is warranted in men with prevalent CVD due to recent reports of increased adverse CV events in T-treated men with prevalent CVD.
5. Current research cannot establish if low T is causally associated with mortality or is merely a marker of poor health.

Table 1

Studies from 2011–2013 of Serum T levels and Mortality

Study Author	Study year	Number FU-yrs	Outcome (n)	Hazard Ratio (95% CI)	T Thresholds
Wehr [9]	2011	2078 8 yrs	CHF mortality (n=77) Other cardiac death (419)	0.38 (0.17; 0.87) NS	FT: hi free T vs low Q4 vs Q1 Q1 <0.23nmol/L
Ohlsson [58]	2011	241 5 yrs	CV events (485) Including CV mortality	0.70 (0.56; 0.88) [*]	Hi TT >19.1 nmol/L
Kyriazis [6]	2011	111 3 yrs	Total mortality (48)	2.81 (1.2; 6.4) 2.62(1.3; 5.4) [*]	TT<8.0nmol/L FT<0.21nmol/L
Friedrich [26]	2011	3942	Total Mortality (330)	1.54 (1.18; 1.98) [*]	Low TT or IGF1 Age specific 10th percentile
Haring [8]	2011	117/1822 10 yrs	Total mortality in men with kidney dysfunction	2.52 (1.08; 5.85) [*]	Low TT, Age specific 10th percentile
Hyde [6]	2012	3637 5 yrs	Total mortality (605) CV mortality (207)	1.62 (1.20; 2.19) [*] 1.71 (1.12; 2.62) [*]	Low FT<2.88 ng/dL
Phillips [25]	2012	4225 15 yrs	Total mortality (236)	NS, NR	TT< 15.4 nmol/L
Haring [11]	2012	2039 men 5.5 yrs	All cause mortality (321) CV mortality (NR)	1.82 (1.30; 2.55) [*] 2.25 (1.30; 3.90) [*]	Low TT Age specific 10th percentile
Schneider [7]	2012	1892 men 10 yrs	Total mortality (204) CV mortality (58)	NS, NR	Low TT <10.4 nmol/L
Haring [27]	2013	254 5 & 10 yrs	Total mortality 42 & 104 deaths	0.74 (0.56; 0.98) yr 5 NS due to multiple tests	TT per quartile base & traject.
Gershman [28]	2013	963 12	PCa Mortality (148) Total Mortality (421)	TT 0.98 (0.58; 1.67) TT 1.07 (0.8; 1.44)	TT Q4/Q1 Also NS FT, DHT
Muraleedharan [5]	2013	581 6 yrs	Total Mortality (72)	TT 2.02 (1.2; 3.4) [*]	Low TT 10.4 nmol/L
Yeap [12]	2013	3690 7 yrs	Total Mortality (974)	TT 0.78 (0.65; 0.94) [*] FT 0.72 (0.63-0.91) [*] DHT 0.76 (0.63; 0.91) [*]	Q3 lowest risk TT 12.6–15.8 nmol/L FT 183–216 pmol/L DHT 1.34–1.83 nmol/L

Abbreviations: CHF-congestive heart failure; CV-cardiovascular; DHT-dihydrotestosterone; FT-free T; NS- not significant;

NR – not reported; PCa- Prostate Cancer; TT-total T; Q-quartile

^{*} Significant

Table 2

Cohort Studies of T Treatment from 2012–2014

	N of Men with Low T/T-treatment	Mean Duration T treatment (mos)	Outcome	HR (95% CI)	T Threshold
Shores [69]	1031/398	20 months	Total mortality	Treated vs not 0.61 (0.42–0.88)	TT 9.7 nmol/L
Muraleedharan [5]	238/64 treated*	42 months	Total Mortality	Untreated vs treated 2.3 (1.3–3.9)	TT 10.4 nmol/L
Vigen [70]	8709/1223	12.5 months [#]	Composite of MI, stroke, total mortality	Treated vs not 1.29 (1.04–1.58)	TT<10.4 nmol/L
Finkel [71]	55,593 prescribed T level unknown	Mean treatment NR Followed for 90 days post-first prescription	Non-fatal MI	Post-T vs Pre-T prescription 1.36 (1.03, 1.81) overall 2.19 (1.27, 3.77) >65 yrs 2.90 (1.49, 5.62) <65, w/CAD	T level NR

CAD=coronary artery disease; N= number; NR= not reported; T=testosterone

* required T treatment >1 yr, excluded shorter T treatment

[#] after excluding men who had only 1 prescription fill (17.6% of treated men)