Testosterone Treatment and Mortality in Men with Low Testosterone Levels

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Context: Low testosterone levels in men have been associated with increased mortality. However, the influence of testosterone treatment on mortality in men with low testosterone levels is not known.

Objective: The objective of the study was to examine the association between testosterone treatment and mortality in men with low testosterone levels.

Design: This was an observational study of mortality in testosterone-treated compared with untreated men, assessed with time-varying, adjusted Cox proportional hazards regression models. Effect modification by age, diabetes, and coronary heart disease was tested *a priori*.

Setting: The study was conducted with a clinical database that included seven Northwest Veterans Affairs medical centers.

Patients: Patients included a cohort of 1031 male veterans, aged older than 40 yr, with low total testosterone [≤250 ng/dl (8.7 nmol/liter)] and no history of prostate cancer, assessed between January 2001 and December 2002 and followed up through the end of 2005.

Main Outcome Measure: Total mortality in testosterone-treated compared with untreated men was measured.

Results: Testosterone treatment was initiated in 398 men (39%) during routine clinical care. The mortality in testosterone-treated men was 10.3% compared with 20.7% in untreated men ($P<0.0001$) with a mortality rate of 3.4 deaths per 100 person-years for testosterone-treated men and 5.7 deaths per 100 person-years in men not treated with testosterone. After multivariable adjustment including age, body mass index, testosterone level, medical morbidity, diabetes, and coronary heart disease, testosterone treatment was associated with decreased risk of death (hazard ratio 0.61; 95% confidence interval 0.42–0.88; $P = 0.008$). No significant effect modification was found by age, diabetes, or coronary heart disease.

Conclusions: In an observational cohort of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment. These results should be interpreted cautiously because residual confounding may still be a source of bias. Large, randomized clinical trials are needed to better characterize the health effects of testosterone treatment in older men with low testosterone levels. **(*J Clin Endocrinol Metab* 97: 2050–2058, 2012)**

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Abbreviations: BMI, Body mass index; CI, confidence interval; HR, hazard risk; VA, Veterans Affairs.

Low testosterone levels are common in older men and are associated with adverse outcomes such as diabetes, obesity, cardiovascular events, sarcopenia, osteoporosis, and decreased libido (1, 2). We previously reported that men with low testosterone levels had increased mortality with an approximate doubling in mortality risk compared with men with normal testosterone levels (3). These results were confirmed in several other studies (4–7), whereas some studies (8, 9) did not find this association. The negative studies generally differed from the other studies in that they examined younger men with higher testosterone levels.

Over the past decade, testosterone prescriptions have increased markedly in the United States from 700,000/yr in 2000 to 2,700,00 in 2008 (10). Given the dramatic increase in the use of testosterone, a major public health issue is to clarify the risks and benefits of testosterone treatment in the health of older men with low testosterone levels. Some testosterone treatment trials in older men with low testosterone levels have shown beneficial effects, such as increased strength, muscle mass, bone mineral density, insulin sensitivity, and libido (11–14). Although these testosterone treatment trials reported positive results, there is ongoing concern about the risk of incident prostate cancer or prostate cancer mortality because studies have not been large enough or long enough to address this. In addition, a recent testosterone treatment trial in frail, elderly men was stopped early due to a greater occurrence of cardiovascular-related events in testosterone-treated men (15). This was an unexpected finding because a testosterone treatment trial in a similar population of frail elderly men found no increased cardiovascular risk (11), and a meta-analysis of testosterone treatment trials reported no increased cardiovascular risks with testosterone treatment (16). The report of adverse cardiovascular events associated with testosterone treatment highlights the need for further data on the risks and benefits of testosterone treatment in older men, particularly given the large numbers of older men who are prescribed testosterone. The purpose of this study was to examine whether testosterone treatment influences mortality risk in men with low testosterone levels and whether this association is modified by age, diabetes mellitus, or coronary heart disease.

Materials and Methods

Study design

This was an observational, retrospective cohort study based on data obtained from seven Veterans Affairs (VA) medical centers in the Northwest United States [Anchorage, AK; Boise, ID; Portland, OR; Roseburg, OR; White City, OR; Puget Sound (Seattle and Tacoma, WA); and Spokane, WA]. The cohort included veterans who received both outpatient and inpatient care at these facilities from January 1, 2001, to December 31, 2005. The electronic medical records included demographic information, laboratory results and dates, pharmacy data and fill dates, *International Classification of Diseases*, ninth edition diagnostic codes and procedure codes, and dates of clinic visits and hospitalizations. The VA Institutional Review Board approved this study.

Subjects

We used a VA clinical database, the Consumer Health Information and Performance Set, to identify men older than 40 yr who were treated on an inpatient or outpatient basis at one of the VA medical centers and had a serum total testosterone level 250 ng/d or less (8.7 nmol/liter) measured between January 1, 2001, and December 31, 2002. We identified 5714 men who had testosterone levels obtained during that time. Of these men, 1273 men (22%) had low testosterone levels less than 250 ng/dl and were older than 40 yr. We then excluded men who had a history of prostate cancer or treatment with testosterone or antiandrogens (*e.g.* leuprolide, goserelin, flutamide, and bicalutamide). This resulted in a sample size of 1093.

Testosterone measurements

Due to the observational study design, blood sampling was not standardized for the time of day. Most of the blood samples were obtained in the morning and the average time for sampling was 1112 h. Serum total testosterone levels were measured in the clinical laboratory at each medical center using an automated platform immunoassay, with a lower threshold for normal of 280 ng/dl (9.7 nmol/liter). For this cohort, we used a lower testosterone threshold level of 250 ng/dl (8.7 nmol/liter) to enhance the probability that the men in the cohort had clinically significant low testosterone levels that would be associated with signs and symptoms of androgen deficiency based on findings from previous studies (17, 18).

Testosterone treatment

We obtained data from VA pharmacy records on testosterone prescriptions, which included drug formulation (im, patch, or gel), date of initial pharmacy release, date of refills, testosterone dose, and the amount dispensed. Intramuscular testosterone consisted of im testosterone cypionate and testosterone enanthate, which are typically administered every 2 wk. We also obtained information from clinical notes and procedure codes when testosterone was administered as a single im dose in the shot clinic. Subjects who initiated testosterone treatment during the course of the study were classified as treated at the time treatment was initiated. A subject was classified as having stopped testosterone treatment 90 d after his final refill of testosterone was finished.

Outcome

The outcome was total mortality through December 31, 2005, which was ascertained from three mortality databases: the VA BIRLS (Beneficiary Identification Records Locator Subsystem)-Death File, the Social Security Administration-Death Master File. When the BIRLS Death File is used in conjunction with another mortality database, the concordance with the National

Death Index (the gold standard for mortality data) is greater than 95% (19, 20).

Covariates

Testosterone levels and testosterone treatment occurred during the course of routine clinical care, and the specific indications for obtaining testosterone levels and for treatment were not available in the electronic database. However, we were able to obtain data from the electronic medical record on variables that could influence testosterone prescribing patterns and mortality, thereby confounding the association of interest. Variables included potential indications for testosterone treatment, such as a low testosterone level, osteoporosis, or sexual dysfunction, and contraindications for testosterone treatment, such as a high prostate-specific antigen level (≥4.0 ng/ml), high hematocrit (≥50), and sleep apnea. Other covariates were the VA medical center site and subject baseline characteristics such as age, body mass index (BMI), and prevalent diabetes mellitus and coronary heart disease. Coronary heart disease was defined as a history of angina, myocardial infarction, coronary artery disease, or a history of coronary artery bypass graft or percutaneous transluminal coronary angioplasty procedures. Information on medical conditions and procedures were obtained using *International Classification of Diseases*, ninth edition, codes. Overall medical morbidity was estimated with the RxRisk-V algorithm, which is a pharmacy-based instrument that estimates overall medical morbidity based on the number of medical conditions treated per pharmacy records in the previous 12 months. The RxRisk-V has been validated as an index of overall medical morbidity in VA clinical databases (21, 22). As another indicator of medical morbidity, we identified hospitalizations in the year before testosterone measurement.

Statistical methods

We used time-to-event models to describe the relationship between testosterone treatment initiation and risk of death. Subjects entered the analysis at the time of testosterone measurement and were unexposed to testosterone treatment at that time. A subject was reclassified as treated when testosterone treatment was initiated during the follow-up, through December 31, 2005. A subject was censored from the analysis at the end of follow-up, at the time of death, or their last clinic visit date, whichever came first. Our primary analysis was based on an intent-to-treat approach: once subjects initiated treatment, they were considered treated throughout follow-up. A secondary analysis was based on current treatment status, and subjects who stopped treatment during follow-up were censored from the analysis 90 d after their last dose of testosterone.

Kaplan-Meier survival curves were used to illustrate unadjusted survival times for the testosterone-treated and untreated men. In Cox regression modeling, we used testosterone treatment as a time-varying exposure to account for the variability in time-to-initiate testosterone treatment. Hazard ratios and 95% confidence intervals for mortality risk were calculated to compare testosterone-treated and untreated men. The Cox regression models were adjusted for age, site, baseline testosterone level, BMI, overall medical morbidity, hospitalization in the past year, diabetes mellitus, and coronary heart disease. We also conducted a sensitivity analysis in which we excluded men who died within the first year of follow-up to minimize the potential bias for nontreatment in the most seriously ill men.

In addition to the analyses described above, which adjust individually for potential confounding factors, we also conducted a propensity score analysis as another way to adjust for limitations of the observational study design. The propensity score analysis is a statistical method to adjust for nonrandomization in observational studies and is defined as the estimated probability that a subject will be treated based on a given set of covariates (23). The propensity scores were generated using a multivariate logistic regression model, which included covariates of age, overall medical morbidity, hospitalization, BMI, testosterone level, osteoporosis, sleep apnea, sexual dysfunction, and hematocrit. The predictive ability of the propensity scores was moderate at 0.66. The logistic regression analysis found that testosterone treatment was more likely in men who were younger (<60 yr), had lower testosterone levels, a prostate-specific antigen in the normal range (<4.0 ng/dl), and a higher BMI. Factors that did not predict testosterone treatment were medical morbidity, hospitalization, sexual dysfunction, osteoporosis, and sleep apnea. All tests were two sided, and an alpha of 0.05 or less was considered statistically significant. Analyses were performed using STATA 11.1 (Stata Corp., College Station, TX). Finally, we tested *a priori* effect modification of the testosterone treatment-mortality association by age (<60 yr old compared with those older), diagnosed diabetes mellitus (yes, no), and diagnosed coronary heart disease (yes, no).

Results

Cohort characteristics

Results are reported as mean (±SD) unless indicated otherwise. The cohort consisted of 1031 men with low total testosterone levels of 250 ng/dl (8.7 nmol/liter) who entered the study on or after January 1, 2001, and were followed up through December 31, 2005. The average age in the cohort at entry was 62.1 (10.6) yr, average BMI was 32.0 (6.4) kg/m^2, and the average testosterone level was 181 (60) ng/dl. The cohort had a high degree of medical morbidity with an average of 6.7 (3.8) pharmacologically treated medical conditions. Common medical conditions in the cohort were diabetes (38%), sexual dysfunction (36%), and coronary heart disease (21%). Lower testosterone levels were associated with higher medical morbidity ($P = 0.037$). Thirty-nine percent of the men (n = 398) initiated testosterone treatment during follow-up. The testosterone formulations prescribed were im testosterone (88.6%), testosterone patch (9.1%), and testosterone gel (2.3%). The median time to initiation of testosterone treatment after the testosterone measurement was 3.3 months, and the median duration of treatment (from first to last dates of treatment) was 16.6 months, with a mean of 20.2 (16.7) months of treatment. The baseline characteristics of the cohort members are listed in Table 1. Testosterone-treated men were younger, had lower baseline testosterone levels, and had a higher BMI than untreated men. Both groups of men were similar in clinical treatment

TABLE 1. Characteristics of men with low testosterone levels by testosterone treatment status

	Untreated (n = 633)	Treated (n = 398)	*P* value
Demographics			
Age, mean (SD) (yr)	62.8 (10.8)	60.9 (10.2)	0.007
Age categories, No. (%)			0.035
41–49	73 (11.5)	44 (11.1)	
50–59	187 (29.5)	150 (37.7)	
60–69	197 (31.1)	117 (29.4)	
70+	176 (27.8)	87 (21.9)	
BMI, mean (SD), kg/m^2	31.4 (6.3)	33.0 (6.5)	<0.001
BMI categories			0.021
BMI < 25	89 (14.0)	37 (9.3)	
BMI 25–29.9	165 (26.1)	92 (23.1)	
BMI ≥ 30	379 (59.9)	269 (67.6)	
Medical morbidity, mean (SD)[a]	6.6 (3.9)	6.9 (3.7)	0.18
Medical morbidity categories[a]			0.32
0–2	92 (14.5)	46 (11.6)	
3–5	171 (27.0)	114 (28.6)	
6–8	189 (29.9)	107 (26.9)	
9–11	110 (17.4)	85 (21.4)	
12+	71 (11.2)	46 (11.6)	
Recent hospitalization, No. (%)[b]	64 (10.1)	49 (12.3)	0.27
Diabetes mellitus No. (%)	250 (39.5)	143 (35.9)	0.44
Coronary heart disease, No. (%)[c]	146 (23.1)	80 (20.1)	0.26
Potential indications for treatment			
Total T ng/dl, mean (SD)	193 (54)	160 (62)	<0.001
Sexual dysfunction, No. (%)	221 (34.9)	149 (37.4)	0.41
Osteoporosis, No. (%)	45 (7.1)	32 (8.0)	0.58
Potential contraindications for treatment			
Average PSA, ng/ml (n = 299)	1.90 (2.73)	1.27 (1.17)	0.008
PSA categories			
High PSA ≥ 4.0 ng/ml, No. (%)	20 (3.2)	8 (2.0)	<0.001
PSA < 4.0 ng/ml, No. (%)	196 (31.0)	175 (44.0)	
Missing PSA, No (%)	417 (65.9)	215 (54.0)	
			0.004
Average Hct (n = 832)	40.7 (5.4)	42.1 (4.9)	
HCT categories			
Hct ≤ 50, No. (%)	508 (80.3)	324 (81.4)	
High Hct > 50, No. (%)	8 (1.3)	15 (3.8)	
Missing Hct, No. (%)	117 (18.5)	59 (14.8)	
Sleep apnea, No. (%)	82 (13.0)	49 (12.3)	0.76
VA Medical Centers			0.93
Puget Sound, No. (%)[d]	318 (50.2)	208 (52.3)	
Portland, No. (%)	131 (20.7)	83 (20.8)	
Boise, No. (%)	57 (9.0)	35 (8.8)	
Anchorage, No. (%)	49 (7.7)	30 (7.5)	
Roseburg, No. (%)	45 (7.1)	23 (5.8)	
White City, No. (%)	28 (4.4)	14 (3.5)	
Spokane, No. (%)	5 (0.8)	5 (1.3)	

T, Testosterone; Hct, hematocrit; PSA, prostate-specific antigen.

[a] Medical morbidity was estimated with the RxRiskV (22), which estimates medical morbidity based on the number of medical conditions treated with medication in the prior year.

[b] Hospitalization is defined as hospitalization at any Northwest VA Medical Center in the year prior to the testosterone measurement.

[c] Coronary heart disease is defined as a diagnosis prior to the testosterone measurement of angina, myocardial infarction, coronary artery disease, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or heart failure.

[d] Puget Sound consists of VA Medical Centers in Seattle, WA and Tacoma, WA.

site, overall medical morbidity, hospitalization rates, prevalent diabetes mellitus, coronary heart disease, sexual dysfunction, osteoporosis, and sleep apnea.

Outcome data

The average follow-up time in the study was 40.5 (15.0) months with a follow-up time of 38.0 (15.8) months for untreated subjects and 42.8 (13.3) months for subjects who initiated treatment. Fifty-one men (4.9%) were lost to follow-up and were censored as of the date of their last clinic visit. Higher mortality was correlated with lower baseline testosterone levels and a shorter duration of testosterone treatment ($P < 0.001$ for both). In unadjusted

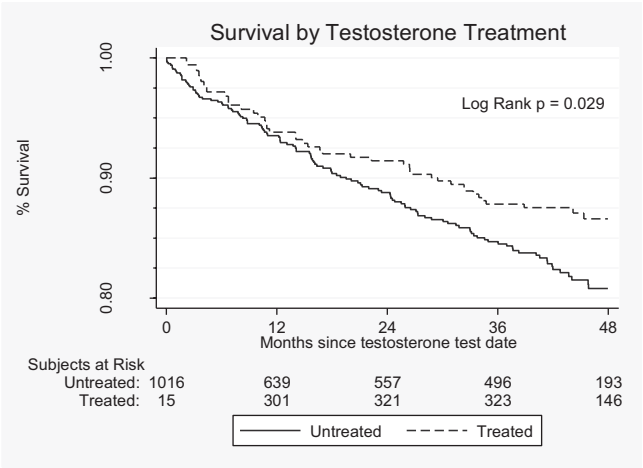

Fig. 1. Unadjusted Kaplan-Meier survival curves illustrate that testosterone-treated men had a longer survival time than untreated men ($P = 0.029$).

TABLE 3. Mortality in testosterone-treated compared to -untreated men by age, diabetes, and cardiac disease

Subgroups[a]	Hazard ratio (95% CI) and *P* value	*P* value for interaction
Age		
41–59 yr (n = 454)	0.43 (0.20–0.92); 0.03	0.30
60+ years (n = 577)	0.68 (0.45–1.03); 0.07	
Prevalent diabetes		
Yes (n = 393)	0.44 (0.23–0.84); 0.013	0.21
No (n = 638)	0.72 (0.46–1.13); 0.155	
Prevalent cardiac disease		
Yes (n = 226)	0.82 (0.42–1.61); 0.56	0.32
No (n = 805)	0.55 (0.36–0.84); 0.006	

[a] Fully adjusted for age, site, medical morbidity, baseline testosterone level, BMI, prevalent cardiac disease, prevalent diabetes, and hospitalization in the year prior to testosterone measurement.

analyses, the overall mortality in testosterone-treated compared with untreated men was 10.3 and 20.7% ($P < 0.001$), respectively, with a mortality rate of 3.4 deaths per 100 person-years in the testosterone-treated men and 5.7 deaths per 100 person-years in the untreated men. Unadjusted Kaplan-Meier survival curves illustrated that testosterone treated men had a longer survival time than untreated men ($P = 0.029$) (Fig. 1). In a time-varying Cox regression model based on treatment initiation, adjusted for age, site, BMI, baseline testosterone level, overall medical morbidity, hospitalization, clinical treatment site, coronary heart disease, and diabetes mellitus, testosterone-treated men had a 39% reduction in mortality risk [hazard risk (HR) 0.61; 95% confidence interval (CI) 0.42–0.88, $P = 0.008$] compared with untreated men (Table 2). We conducted a secondary analysis in which testosterone-treated men who stopped treatment were censored 90 d after their last treatment date and continued to find that testosterone treatment was associated with decreased mortality (HR 0.65; 95% CI 0.39–1.08; $P = 0.098$). We also conducted a sensitivity analysis, in which men who died within the first year of follow-up (n = 69) were excluded from the analysis and we continued to find that testosterone treatment was associated with decreased mortality (HR 0.47; 95% CI 0.29–0.76, $P = 0.003$). In a propensity score analysis, we found a similar reduction in mortality in the testosterone-treated men (Table 2). There was no significant effect modification by age, diabetes, or cardiovascular disease, although testosterone treatment appeared to be associated with a greater mortality reduction in younger men (<age 60 yr), diabetic men, and men without coronary heart disease (Table 3). Diagnoses of incident prostate cancer during follow-up were similar between the two groups with 1.6% incident prostate cancer in the treated men compared with 2.0% incident prostate cancer in the untreated men ($P = 0.68$).

Discussion

In a retrospective, observational study using clinical data from seven VA medical centers, we found that testosterone treatment in middle-aged and elderly men with low testosterone levels was associated with decreased mortality in a time-varying Cox regression analysis. In our primary analysis, testosterone-treated subjects remained classified as treated, even if they stopped treatment. In that analysis,

TABLE 2. Mortality in testosterone-treated and -untreated men

Testosterone exposure	Person-years	Deaths	Mortality per 100 person-years	Fully adjusted HR (95% CI)[a]	Sensitivity HR (95% CI)[b]	Propensity score HR (95% CI)[c]
Untreated (n = 633)	2290	131	5.73	1.00 (reference)	1.00 (reference)	1.00 (reference)
Treated (n = 398)	1190	41	3.44	0.61 (0.42–0.88); $P = 0.008$	0.47 (0.29–0.76); $P = 0.003$	0.64 (0.44–0.95); $P = 0.026$
Total (n = 1031)	3480	172	4.95			

[a] Adjusted for age, site, medical morbidity, baseline testosterone level, BMI, prevalent coronary heart disease, prevalent diabetes mellitus, and hospitalization in the year prior to testosterone measurement.

[b] Sensitivity analysis excluding men who died within the first year (n = 62).

[c] Adjusted for propensity scores by quintiles.

adjusted for age, BMI, baseline testosterone level, overall medical morbidity, hospitalizations, diabetes, coronary, heart disease, and medical center site, testosterone treatment was associated with a hazard ratio of 0.61, with a 39% decreased mortality risk. In a secondary analysis with similar adjustments, men who stopped testosterone treatment were censored from the cohort 90 d after the last dose of testosterone and testosterone treatment continued to be associated with decreased mortality risk, with a similar hazard ratio of 0.65. However, the results no longer reached statistical significance ($P = 0.098$), which likely was related to a loss of power due to a smaller number of events. We also conducted a sensitivity analysis, in which we excluded men who died within the first year, to minimize the impact that severe illness might have on our results and continued to find that testosterone treatment was associated with decreased mortality. In addition, we conducted a propensity score analysis and continued to find that testosterone treatment was associated with decreased mortality. Finally, we explored whether treatment effect was modified by age, diabetes, or coronary heart disease. We examined treatment effect by age because studies in women have noted a critical time period for estrogen treatment, with beneficial effects in middle-aged women and minimal beneficial effects or even deleterious effects in elderly subjects (24, 25). We examined treatment effect by diabetes because several studies have noted that low testosterone is a risk factor for incident diabetes (26–28). We examined treatment effect by coronary heart disease due to a recent study that reported a significant increase in cardiovascular-related events in frail, elderly men treated with testosterone (15). We found no significant effect modification with any of these conditions, although testosterone treatment appeared to be associated with greater mortality reduction in younger men (<age 60 yr), diabetic men, and men without coronary heart disease.

Study limitations

The observational study design limits the interpretation of the findings because subjects were treated in a clinical setting and were not randomized to treatment. This can introduce bias if we do not adequately control for confounding factors, *e.g.* those associated with both treatment initiation and with mortality. For example, it is possible that physicians may have selected healthier men for testosterone treatment or not considered treatment in men who were less well. We attempted to control for baseline health differences by adjusting for age, BMI, baseline medical morbidity, and hospitalizations; conducting a sensitivity analysis in which men who died within the first year were removed from the analysis and using a propensity score analysis (23, 29). However, despite these attempts to minimize bias, unmeasured confounders likely exist and the extent to which unmeasured variables bias the association reported is not known.

Another limitation was that entry into the study was based on a single low total testosterone level, and current clinical practice guidelines (30) recommend that two testosterone levels be obtained before initiating testosterone treatment. Repeated testosterone measures are preferable because testosterone could be transiently low due to medical illness. However, if a subject had transiently low testosterone levels and treatment was not initiated, this would tend to bias our results toward the null.

A limitation of the database was that we could not ascertain symptoms of low testosterone, which are required to make a diagnosis of hypogonadism (30). Because we could not ascertain symptoms, we used a lower testosterone threshold level, which is typically associated with signs and symptoms of hypogonadism (18) to increase the likelihood that the men had clinically significant androgen deficiency. Another limitation of the database was that we could not ascertain indications for obtaining a testosterone level or for testosterone treatment. However, in a prior study at a Northwest VA medical center, we conducted a manual chart review of nearly 300 veterans to ascertain indications for obtaining testosterone levels (31). I n that study, the most common reasons for obtaining testosterone levels were sexual dysfunction (32%), osteoporosis (22%), or urological or endocrine conditions (18%). The remaining 28% of indications included cancer, rehabilitation and current testosterone treatment, or no clearly indicated condition. In that study, the majority of clinicians ordering testosterone levels were primary care providers (60%), followed by urologists (10%) and endocrinologists (9%). This prior study suggests that at Northwest VA medical centers, the majority of testosterone levels are ordered by primary care providers as part of an assessment of sexual dysfunction, osteoporosis, and urological or endocrine conditions. Another limitation of the database is that we were unable to determine the specific indications for treatment. However, the propensity score analysis indicated that testosterone treatment was more likely in men with a lower baseline testosterone level and higher BMI, whereas age and medical morbidity were not significant predictors of testosterone treatment.

Other potential limitations are that we used total testosterone levels rather than free testosterone levels and that levels were not obtained at a standardized time. Testosterone levels were not obtained in the morning as recommended in clinical practice guidelines (30). Although there was no standardized blood sampling time, the majority of blood sampling occurred in the morning, which would tend to minimize the significance of the nonstan-

dardized blood draw time. In addition, the circadian fluctuation of testosterone is diminished in older men (32), which could also decrease the impact of the nonstandardized blood sampling time. Another limitation is the potential misclassification of testosterone-treatment if men classified as untreated obtained testosterone from a non-VA pharmacy. However, it is unlikely that subjects received testosterone from non-VA pharmacies because this would increase their medication costs. In addition, this misclassification error would tend to underestimate the association of testosterone treatment and bias the results conservatively toward the null hypothesis. Finally, we had incomplete data on follow-up testosterone levels. It would be helpful to have more complete data to ensure that testosterone treatment increased testosterone levels to the normal range. However, most men were treated with im testosterone, which typically results in testosterone levels in the mid- to high-normal range. The follow-up testosterone levels that were available indicated that treatment increased testosterone levels to the normal range.

A final limitation is that our cohort has a high degree of chronic medical morbidity. Specifically, the men in this study had an average of seven pharmacologically treated medical conditions, with a 21% prevalence of coronary heart disease and a 38% prevalence of diabetes. The high degree of medical morbidity in this cohort is consistent with prior studies that have found that veterans treated at VA medical centers have greater medical morbidity than men of comparable ages treated in a community setting (33–35). Given the high degree of chronic medical morbidity, these results may not be generalizable to a more healthy cohort of men.

Study strengths

Despite these limitations, we believe that there are several strengths to this study. The most significant strength is that this is the first study to specifically examine the association between testosterone treatment and mortality in middle-aged and older men with low testosterone levels. Another strength of the study is that the threshold for study entry required clearly low testosterone levels. Although the use of a more stringent testosterone threshold level decreased the sample size, it increased the likelihood that the men in the study had symptomatic and clinically significant androgen deficiency. An additional strength is that this is one of the first large studies to examine testosterone treatment in men with high medical morbidity (seven chronic medical conditions) who may be more susceptible to harm or benefit from testosterone treatment.

Further research

The gold standard to examine whether there is a causal relationship between testosterone treatment and mortality is a large, randomized, double-blind, placebo-controlled trial, such as the Women's Health Initiative. However, no such large prospective trials have been conducted to examine the effects of testosterone treatment in older men. There are many obstacles to conducting such a trial, including cost, size, and duration of the study and the possibility that men could be exposed to unknown risks from testosterone treatment. In the absence of data from a large, prospective, randomized clinical trial, the data from this observational study are an incremental step to address the data gap regarding the effects of testosterone treatment in older men. Additional database studies are needed in different patient populations to clarify whether there are subgroups of men who are more likely to benefit or be harmed from testosterone treatment. Based on our results, future clinical trials may want to focus enrollment on diabetic and middle-aged (40–60 yr) men because these men appeared to have a greater reduction in mortality with testosterone treatment.

Conclusions

This is the first study to specifically examine the association between testosterone treatment and mortality in men with low testosterone levels. Testosterone treatment was associated with decreased mortality in an observational cohort of middle-aged male veterans with low total testosterone levels and high chronic medical morbidity. Due to the limitations of the observational study design, these results should be viewed cautiously and cannot be interpreted as showing beneficial effects of testosterone treatment or as establishing a causal relationship between testosterone treatment and reduced mortality. However, these results do provide impetus for conducting a large-scale, double-blind, placebo-controlled clinical trial to better understand the effect of testosterone treatment on the health of older men.

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