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# ABSTRACT

**Background** Low serum testosterone is a common condition in aging associated with decreased muscle mass and insulin resistance. This study evaluated whether low testosterone levels are a risk factor for mortality in male veterans.

**Methods** We used a clinical database to identify men older than 40 years with repeated testosterone levels obtained from October 1, 1994, to December 31, 1999, and without diagnosed prostate cancer. A low testosterone level was a total testosterone level of less than 250 ng/dL (<8.7 nmol/L) or a free testosterone level of less than 0.75 ng/dL (<0.03 nmol/L). Men were classified as having a low testosterone level (166 [19.3%]), an equivocal testosterone level (equal number of low and normal levels) (240 [28.0%]), or a normal testosterone level (452 [52.7%]). The risk for all-cause mortality was estimated using Cox proportional hazards regression models, adjusting for demographic and clinical covariates over a follow-up of up to 8 years.

**Results** Mortality in men with normal testosterone levels was 20.1% (95% confidence interval [CI], 16.2%-24.1%) vs 24.6% (95% CI, 19.2%-30.0%) in men with equivocal testosterone levels and 34.9% (95% CI, 28.5%-41.4%) in men with low testosterone levels. After adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34-2.63; $P<.001$) while equivocal testosterone levels were not significantly different from normal testosterone levels (hazard ratio, 1.38; 95% CI, 0.99%-1.92%; $P=.06$). In a sensitivity analysis, men who died within the first year (50 [5.8%]) were excluded to minimize the effect of acute illness, and low testosterone levels continued to be associated with elevated mortality.

**Conclusions** Low testosterone levels were associated with increased mortality in male veterans. Further prospective studies are needed to examine the association between low testosterone levels and mortality.

Testosterone levels decline with aging, with an average decrease in total serum testosterone levels of approximately 1.5% per year.[1] The prevalence of low serum total testosterone levels is approximately 20% by the age of 50 years and 50% by the age of 80 years. Manifestations of low testosterone include decreased muscle mass and bone mineral density, increased fat mass, central obesity, insulin resistance, decreased libido and energy, irritability, and dysphoria.[2] In contrast to menopause, in which all women undergo a nearly complete cessation of gonadal estrogen secretion, in men, gonadal androgen secretion decreases gradually and progressively after the age of 30 years, but does not generally cease, and androgen levels remain highly variable in older men. The prevalence of clinical androgen deficiency (symptoms plus low testosterone levels) was recently reported to be about 6% to 12% in middle-aged and elderly men.[3] Testosterone levels also decrease with acute and chronic illnesses and with medications such as glucocorticoids and opiates.[2] Because of the aging of our society, many older men are affected by age-associated low testosterone levels.[2] In addition, the use of testosterone has increased significantly, with a tripling in prescriptions for testosterone over a 3-year period.[4] However, despite the marked increase in testosterone use, the overall risks and benefits remain unclear.[4 - 5]

In a recent small study[6] in a geriatric rehabilitation unit, we found that men with a low testosterone level had an increased 6-month mortality compared with men with a normal testosterone level who were of a comparable age and had comparable medical morbidity. Given these unforeseen preliminary findings, we conducted the present retrospective cohort study to examine if repeatedly low serum testosterone levels were associated with increased mortality in a larger sample of middle-aged and elderly men with a longer follow-up, of up to 8 years.

# METHODS

We used the Consumer Health Information and Performance Set computerized clinical database at the VA (Veterans Affairs) Puget Sound Health Care System to assess the relationship between low serum testosterone levels and all-cause mortality. The University of Washington Human Subjects Division approved access to the clinical database and to a national VA death registry, the Beneficiary Identification and Records Locator System (BIRLS)–Death File,[7] through December 31, 2002. The database contained demographic information, dates of clinic visits and blood draws, laboratory results, pharmacy data, and *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic codes[8] for inpatient and outpatient visits that occurred from October 1, 1994, through December 31, 1999.

The inclusion criteria were as follows: (1) 40 years or older at the initial testosterone test and (2) at least 2 testosterone levels obtained at least 1 week apart but less than 2 years apart before January 1, 2000. We required a minimum of 2 testosterone levels because a prior study[9] found that in about 33% of cases, low testosterone levels may be normal in a subsequent test. In some cases, because multiple levels were obtained on the same day (ie, free and total testosterone levels), subjects had more than 2 testosterone level results when they enrolled into the study. The exclusion criteria were as follows: (1) female sex, (2) antiandrogen treatment at baseline (ie, leuprolide, goserelin, flutamide, bicalutamide, or cyproterone acetate), and (3) documented history of prostate or testicular cancer before study enrollment.

The indications for obtaining testosterone levels were not available in the computerized database. However, in a prior manual review of nearly 300 medical records,[10] the clinical indications for obtaining testosterone levels were as follows: evaluation of sexual dysfunction (31.6%), osteoporosis (21.6%), follow-up of a prior low testosterone level (15.4%), geriatric rehabilitation (10.4%), genitourinary conditions (9.0%), cancer (3.2%), endocrine conditions (3.0%), and other or unknown reasons (5.6%) (percentages do not total 100 because of rounding).

Serum total and free testosterone levels were measured using automated platform immunoassays in the clinical laboratory of the VA Puget Sound Health Care System. The phlebotomy times for testosterone samples were not standardized. Testosterone has a diurnal variation, with peak plasma testosterone levels in the morning. However, this variation is most marked in younger men, and markedly diminished or absent in older men,[11] suggesting that the potential effect of variable phlebotomy times was minimal.

The lower limit of normal was defined as a total testosterone level of less than 250 ng/dL (<8.7 nmol/L) or a free testosterone level of less than 0.75 ng/dL (<0.03 nmol/L). These levels were used as threshold levels because they have been identified as clearly low and generally associated with symptoms of hypogonadism, even in older men.[4,12] Men were classified as having low testosterone levels if they had 2 low testosterone levels or if more than 2 levels were measured; most of the levels were low. Men were classified as having equivocal testosterone levels if they had at least 1 low and 1 normal level and if more than 2 levels were obtained, they had an equal number of low and normal testosterone levels. Men were classified as having normal testosterone levels if they had at least 2 normal testosterone levels and if more than 2 levels were obtained, most were normal.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The BMI data were missing in 124 cases (14.5%). Overall medical morbidity was estimated using an algorithm shown to be valid and reliable in VA computerized clinical databases. A VA-adapted pharmacy-based case-mix instrument (RxRisk-V)[13] algorithm estimates medical morbidity from the VA clinical database using pharmacy data. This method of determining medical morbidity is considered more accurate than using diagnostic codes because it reflects actively treated illnesses. The medical morbidity score is determined from the number of specified medical conditions treated in the prior 12 months (range of potential conditions, 0-45). We also obtained data on specific medical conditions that may be related to testosterone level and mortality and that had good reliability and validity using the VA-adapted pharmacy-based case-mix instrument (RxRisk-V) ($\kappa > 0.6$). These conditions were diabetes mellitus, chronic

obstructive pulmonary disease, human immunodeficiency virus, hyperlipidemia, and coronary artery disease (CAD).[13] In addition, we obtained data on glucocorticoid and opiate prescriptions because these may lower testosterone levels. Treatment data for intramuscular testosterone levels were available only in paper medical records and not in the computerized clinical record system included in the database.

The primary outcomes were all-cause mortality and survival from the date of the second testosterone level obtained through December 31, 2002. Subjects were followed up from the time of enrollment into the study (the date when the second testosterone level was obtained) through the end of 2002. Mortality data were obtained through 2002 from the BIRLS–Death File, which contains approximately 10.7 million records and has an estimated 94.5% to 96.5% sensitivity.[14 - 15] A review of major US mortality databases found that the BIRLS–Death File had a high accuracy rate[16] that compares favorably with other national mortality databases. However, a more recent study[17] found lower accuracy rates of 80% to 92% for the BIRLS–Death File, compared with the National Death Index or state death certificates. For more comprehensive mortality data, we also obtained mortality data from the regional VA database. In addition, we confirmed that men who were identified as survivors received care at the VA facility after 2002. Men were censored from the survival analysis as of their last clinic visit if they did not receive care after 2002. Thus, all men in the study had a death recorded in either the BIRLS–Death File or regional records, had a clinic visit documented after 2002, or were censored.

We determined baseline differences between men with low, equivocal, and normal testosterone levels with $\chi^2$ tests and analysis of variance. Kaplan-Meier survival curves were used to illustrate the association between testosterone status and all-cause mortality. Cox proportional hazards regression models were used to compare differences in survival between men with low, equivocal, and normal testosterone levels. Initially, each covariate was added to the model individually to examine the influence of the covariate on our primary outcome. Then, we conducted a partially adjusted analysis that included the covariates of age, medical morbidity, BMI, and glucocorticoid and opiate treatment, followed by a fully adjusted model in which we included all covariates. Because of missing BMI data, the sample size was decreased in the Cox proportional hazards regression analyses. To estimate if this affected our analyses, we repeated the analyses, first excluding subjects with a missing BMI and then using the mean BMI to replace missing BMI data. We found similar results in both analyses, so we used the mean BMI in the Cox proportional hazards regression analyses. We added interaction terms to test for potential interactions of each covariate with low testosterone level. Regression diagnostics were done to examine for colinearity among the covariates. Finally, because acute illness may cause a transient decrease in testosterone levels, we conducted a sensitivity analysis by excluding men who died within the first year. We had greater than 80% power to detect a 10% difference and greater than 95% power to detect a 15% difference in absolute mortality rates. All analyses were performed using a commercially available software program (SPSS, version 11.5.2.1; SPSS Inc, Chicago, Ill).

## RESULTS

From the clinical database, we identified 858 men, 40 years or older, who had repeated testosterone levels obtained and had no history of prostate or testicular cancer or antiandrogen treatment. There were 452 men (52.7%) with normal testosterone levels, 240 (28.0%) with equivocal levels, and 166 (19.3%) with low levels. Testosterone levels differed significantly between the 3 groups (Table 1). Men with low testosterone levels were older, had a greater BMI, and had a greater prevalence of diabetes mellitus compared with men with normal testosterone levels. Men with equivocal testosterone levels had a greater BMI than men with normal testosterone levels. Men with low and normal testosterone levels had more testosterone levels obtained than men with equivocal testosterone levels. There were no significant differences between the groups in marital status; medical morbidity; prevalence of chronic obstructive pulmonary disease, human immunodeficiency virus, CAD, or hyperlipidemia; and treatment with opiates and glucocorticoids (Table 1).

**Table 1. Baseline Characteristics of Men With Low, Equivocal, and Normal Testosterone Levels***

| Characteristic | Men With a Normal Testosterone Level (n = 452) | Men With an Equivocal Testosterone Level (n = 240) |
|---|---|---|
| Age, y‡ | 60.5 (10.9) | 61.4 (10.9) |
| Body mass index‡‖ | 28.4 (5.1) | 29.9 (6.3) |
| Medical morbidity‡# | 4.7 (2.9) | 4.9 (3.2) |
| No. of testosterone measurements‡ | 2.05 (0.22) | 2.00 (0.06) |
| Testosterone level, ng/dL‡ | | |
| Total | 520 (270) | 400 (440) |
| Free | 1.33 (0.55) | 0.92 (0.54) |
| White race | 328 (72.6) | 198 (82.5) |
| Married | 250 (55.3) | 138 (57.5) |
| Diabetes mellitus | 94 (20.8) | 57 (23.8) |
| COPD | 100 (22.1) | 61 (25.4) |
| HIV | 5 (1.1) | 2 (0.8) |
| Hyperlipidemia | 93 (20.6) | 43 (17.9) |
| CAD | 92 (20.4) | 50 (20.8) |
| Prescription | | |
| Narcotic | 168 (37.2) | 96 (40.0) |
| Glucocorticoid | 70 (15.5) | 38 (15.8) |

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HIV, human immuno
SI conversion factor: To convert testosterone to nanomoles per liter, multiply by 0.0347.
*Data are given as number (percentage) of each group unless otherwise indicated.
†Indicates the *P* value for the overall difference in means based on the $\chi^2$ test or the analysis of variance.
‡Data are given as mean (SD).
§Significant difference between low and normal testosterone level groups by the post hoc Scheffé test.
‖Calculated as weight in kilograms divided by the square of height in meters. Data were missing in 124 cases and index.
¶Significant difference between equivocal and normal testosterone level groups by the post hoc Scheffé test.
#Based on the Veterans Affairs–adapted pharmacy-based case-mix instrument (RxRisk-V) score for the prior 12 r
**Significant difference between equivocal and low testosterone level groups by the post hoc Scheffé test.

The mean (SD) follow-up was 4.30 (1.78) years. Fifty-six men (6.5%) had an unconfirmed vital status and were censored as of the date of their last visit. All-cause mortality was 20.1% (95% confidence interval, 16.2%-24.1%) in men with normal testosterone levels, 24.6% (95% confidence interval, 19.2%-30.0%) in men with equivocal testosterone levels, and 34.9% (95% confidence interval, 28.5%-41.4%) in men with low testosterone levels. Men with low and equivocal testosterone levels had shorter survival times than men with normal testosterone levels, as illustrated by the Kaplan-Meier survival analysis (log-rank test; $\chi^2_2 = 14.4$, $P$=.001) (Figure). The proportional hazards assumption was confirmed through visual inspection of the survival curves. In an unadjusted Cox proportional hazards regression model, men with equivocal testosterone levels did not differ from men with normal testosterone levels in mortality risk. Men with low testosterone levels had a significantly greater mortality risk than men with normal testosterone levels. After adjustment for age, medical morbidity, BMI, and glucocorticoid and opiate treatment, the adjusted hazard ratios for equivocal and low testosterone levels were elevated. In a fully adjusted model, men with low testosterone levels continued to have a greater mortality risk, although men with equivocal testosterone levels did not differ significantly from men with normal testosterone levels (Table 2). Tests for interaction did not reveal any effect modification on the hazard ratio for low testosterone level. In a sensitivity analysis, we excluded subjects with 1-year mortality (50 [5.8%]). Men with low testosterone levels continued to have an increased mortality risk in an adjusted model (Table 2).

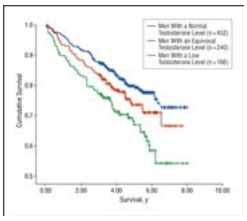

**Table 2. Crude and Multivariate-Adjusted Data for Mortality Associated With Testosterone Level**

| Group | Crude Data | | Partially Adjusted |
|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) |
| Entire sample (N = 858) | | | |
| Men with normal testosterone levels (n = 452) | 1.00 | NA | 1.00 |
| Men with equivocal testosterone levels (n = 240) | 1.31 (0.94-1.82) | .11 | 1.45 (1.04-2.02) |
| Men with low testosterone levels (n = 166) | 1.88 (1.35-2.61) | <.001 | 1.95 (1.39-2.72) |
| Sample excluding first-year deaths (N = 808) | | | |
| Men with normal testosterone levels (n = 435) | 1.00 | NA | 1.00 |
| Men with equivocal testosterone levels (n = 224) | 1.19 (0.82-1.74) | .36 | 1.36 (0.93-1.98) |
| Men with low testosterone levels (n = 149) | 1.65 (1.13-2.42) | .01 | 1.71 (1.16-2.52) |

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable.

*The partially adjusted model included the covariates of age, medical morbidity, body mass index (BMI) (calculate square of height in meters), and glucocorticoid and opiate treatment. The average BMI was used to replace missing when an analysis was done that excluded subjects with missing BMI data.

†The fully adjusted model included the covariates of age, medical morbidity, BMI, glucocorticoid and opiate treatn obstructive pulmonary disease, human immunodeficiency virus, diabetes mellitus, hyperlipidemia, and number of te was used to replace missing BMI data (n = 123). Similar results were found when an analysis was done that exclude

## COMMENT

In this study of male veterans 40 years and older, without prostate cancer, followed up for a mean of 4.3 years, men with low and equivocal serum testosterone levels had increased all-cause mortality and shorter survival times compared with men with normal testosterone levels. In an unadjusted model, low testosterone levels were associated with an increased mortality risk of 88% greater than that for men with normal testosterone levels. In the fully adjusted model, which included the covariates of age, medical morbidity, BMI, race, and other clinical factors, low testosterone level continued to be associated with an increased mortality risk of 88% greater than in men with normal testosterone levels. However, a retrospective cohort study cannot establish a causal relationship between testosterone status and mortality, and it is possible that the association is because of the mediation of some other factor that is linked to low testosterone level and mortality. Prior studies may be relevant in examining this association further.

The serum testosterone level decreases approximately 90% within 24 to 48 hours after the onset of critical illness, such as surgery, major burns, multiple trauma, and critical medical illness involving ventilator dependence.[18-21] In patients with acute stroke, a low serum total testosterone level correlated with stroke severity and size[22] and predicted 6-month mortality. Another study[21] found that a low testosterone level correlated with acute illness on admission to an intensive care unit and that survivors had an increase in testosterone levels at discharge in contrast to persistently low levels among nonsurvivors of a comparable age and with a comparable illness severity. In the sensitivity analysis, we excluded early deaths that may have been related to acute illness and continued to find persistent elevated mortality in men with low testosterone levels. Further prospective studies are needed to clarify factors other than acute illness in the association between low testosterone level and increased mortality.

Several studies[23-26] have found that low testosterone levels are associated with the metabolic syndrome, hyperinsulinemia, and diabetes mellitus. Several studies[27-29] noted that low testosterone levels are associated with multiple risk factors for CAD, including hypertension, central obesity, thrombosis, and C-reactive protein, and variable effects on lipids. In several recent studies,[30-32] testosterone treatment improved the angina threshold, increasing exercise time to ischemia in men with CAD. Low testosterone levels are also associated with sarcopenia, decreased bone mineral density, osteoporosis, anorexia, and fatigue. These are components of the frailty syndrome that is associated with significant morbidity, institutionalization, and mortality in elderly persons.[33] Thus, low testosterone levels are associated with chronic illnesses that are themselves associated with mortality. In our study, we attempted to control for the effect of chronic illness and medications that may suppress testosterone levels by controlling for age, BMI, diabetes mellitus, CAD, chronic obstructive pulmonary disease, human immunodeficiency virus, hyperlipidemia, and treatment with opiates and glucocorticoids. In addition, we excluded men who had prostate or testicular cancer before study enrollment. After controlling for overall medical morbidity and these other clinical covariates, we continued to find an association between low testosterone levels and mortality. However, it is possible that there are other chronic medical illnesses or conditions not assessed in this study that explain the association between testosterone level and mortality.

Men with hypopituitarism and untreated gonadotropin deficiency had increased cardiovascular mortality[34] and increased overall mortality[35] compared with treated subjects. Another study[36] of hypopituitarism found increased mortality in men with an unknown gonadal status compared with men who were treated with testosterone. In another study,[37] men with Klinefelter syndrome, which is characterized by hypogonadism, had increased mortality compared with that of age-matched control subjects. There have been conflicting results from studies examining the association of castration and mortality. One study[38] of legally castrated men found increased all-cause mortality but a decrease in cardiovascular mortality. A study[39] of castrated, institutionalized, mentally retarded men found decreased mortality while a study[40] of castrated male singers found no mortality differences compared with intact men. Finally, 2 longitudinal studies of older men found no association between testosterone levels and all-cause mortality[41] or cardiovascular mortality.[42] However, there have been few large prospective studies to examine the association between low testosterone levels and mortality in community-dwelling older men. Recent preliminary findings from a large prospective study[43] found increased cancer-related mortality in community-dwelling men with a total testosterone level of less than 200 ng/dL (<6.9 nmol/L). These results of increased mortality in a cohort of men who are healthier than the VA cohort suggest that the association between low testosterone level and mortality may be more generalizable.

Among several limitations to our study, the most significant is the retrospective study design with a lack of systematic assessment of a prospective cohort. This precludes establishing a causal relationship or ruling out the possibility that residual confounding may have occurred because of some other unmeasured factors that may explain the

association between low testosterone levels and mortality. Another limitation is that testosterone treatment data were not available. However, we hypothesize that testosterone treatment would bias the results toward the null because it would minimize the differences between the men with low and normal testosterone levels. Another limitation is the use of platform testosterone assays. These assays are similar to those used by most clinical laboratories, but they may be affected by alterations in sex hormone–binding globulin concentrations.[44] However, the criteria used to define low testosterone were sufficiently stringent to exclude most men with low testosterone levels because of a low sex hormone–binding globulin concentrations. Subsequent studies need to be performed using assays (eg, free testosterone by equilibrium dialysis) that are not subject to these alterations.[44] Finally, our population is not representative of community-dwelling men because it was a VA clinic–based population. This limits the generalizability of these conclusions given that VA patients have greater medical morbidity and a lower socioeconomic class.[45] Also, our cohort had a high overall mortality of 24.2% over a mean follow-up of 4.3 years. However, a recent study[46] of veterans followed up at 9 VA medical centers found a similarly high mortality (18%) over a 2-year period. Another study,[47] of more than 400 000 VA patients, found a crude mortality of 25.7% over 4 years. Thus, although the mortality rate in our study is high, it is comparable to that of other VA studies.

In conclusion, compared with men with normal testosterone levels, the covariate-adjusted mortality risk was nonsignificantly increased by 38% in men with equivocal testosterone levels and significantly increased by 88% in men with low testosterone levels. After removing first-year deaths, low testosterone levels continued to be associated with increased mortality, with a 68% greater mortality risk compared with men with normal testosterone levels. The persistence of elevated mortality risk after excluding early deaths suggests that the association between low testosterone and mortality is not simply due to acute illness. Large prospective studies are needed to clarify the association between low testosterone levels and mortality.

## AUTHOR INFORMATION

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