Published in final edited form as:

Aging Male. 2011 June ; 14(2): 132–140. doi:10.3109/13685538.2010.502269.

Testosterone is not associated with mortality in older African-American males

LENISE A. CUMMINGS-VAUGHN^{1,2}, THEODORE K. MALMSTROM³, JOHN E. MORLEY^{1,2},
and DOUGLAS K. MILLER⁴

¹Division of Geriatric Medicine, Saint Louis University School of Medicine, Saint Louis, MO, USA

²GRECC, VA Medical Center, Saint Louis Missouri, MO, USA

³Department of Neurology & Psychiatry, Saint Louis University School of Medicine, Saint Louis, MO, USA

⁴Center for Aging Research, Regenstrief Institute, Inc., Indiana University, Indianapolis, IN, USA

Abstract

Introduction—Although testosterone and its association with disease progression and mortality is a widely studied topic, no studies have evaluated mortality risks related to testosterone levels in an older African-American population. The mechanisms for known racial differences in mortality risk for certain cancers and cardiovascular risk factors are largely unknown. Elucidating a mortality risk associated with testosterone levels may give insight into the elevated risk for certain diseases in African-Americans.

Methods and results—Study data were derived from a cohort 622 African-Americans (age 80.05 ± 6.4 , range 68–102) from Saint Louis, Missouri that includes 190 males (age 79.38 ± 6.2 , range 70–102). The eligible sample for this report includes 56 of the 190 males (age 78.89 ± 6.9 , range 70–102) who donated blood at baseline in 1992–1994 and subsequently tested for total testosterone and bioavailable testosterone. Covariates for adjusted analyses were lower body functional limitations, physician visits and comorbidities, also collected at baseline. Males' mean bioavailable testosterone levels (ng/dl) were 33.33 ± 24.4 (n above 70 ng/dl = 5) and mean total testosterone levels (ng/dl) were 246.63 ± 118.7 (n above 300 ng/dl = 20). Vital status was determined through 2002; 41 males (73%) were deceased and 15 were alive. Mortality did not differ among males with testosterone levels <300 *versus* 300+ ($p = 0.42$) or with bioavailable testosterone levels <70 *versus* > 70 ($p = 0.34$). Total testosterone levels did not predict mortality when adjusted for age (Adjusted Hazard Ratio [AHR] = 0.998; 95% confidence interval [CI] 0.995–1.001; $p = 0.28$) or adjusted for age and other covariates (AHR = 0.099; 95% CI 0.996, 1.002; $p = 0.35$). Bioavailable testosterone levels did not predict mortality when adjusted for age (AHR 0.992; 95% CI .977–1.007; $p = 0.30$) or when adjusted for age and other covariates (AHR 0.991; 95% CI .976–1.006; $p = 0.261$).

Conclusion—In older African-American males, total and bioavailable testosterone levels, with and without adjustment for covariates, are not independently associated with mortality risk.

Keywords

Testosterone; mortality risk; African-American males; aging

Introduction

Testosterone levels are known to decline with increased age [1–3] and specifically with aging African-American men [4]. According to the Department of Health and Human Services, incident cancer, diabetes and heart disease and mortality are higher in African-Americans when compared to non-Hispanic Whites. Although the specific reasons are likely multi-factorial in nature, biological pathology should be investigated. Conflicting data exist regarding racial differences in androgen levels. While free testosterone and total testosterone (TT) were found to be significantly lower in Asian men and significantly higher in African-American and Hispanic men, after adjustment for body mass index (BMI) and age [5], a similar study did not find any significant racial differences in TT, bioavailable testosterone (BT), and sex hormone binding globulin (SHBG) levels between white, Hispanic and Black men [6]. Despite these differing data regarding racial differences in androgens, elevated TT and SHBG levels in young African-American men compared to non-Hispanic White men has been implicated in risk for prostate cancer [7]. In addition, higher TT levels have been associated with low serum triglycerides in African-American men aged 50–65 [8]. While these findings pose questions about disease manifestations, testosterone's association with mortality in African-American's has not been examined.

The influence of TT, dihydroepiandrosterone or dihydroepiandrosterone sulphate (DHEA or DHEAS), insulin growth factor 1 (IGF-1) and SHBG have all been evaluated in relation to disease progression and mortality. Anabolic deficiencies are common in chronic heart failure and singular and multiple hormonal deficiencies of TT, DHEAS, and IGF-1 have been shown to confer higher mortality for the chronic heart failure patients [9]. The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) showed that testosterone levels were inversely related to all cause and cardiovascular mortality. Specifically, every 6 nmol/l ($\approx$ 1 standard deviation) testosterone level increase resulted in a 14% lower risk of mortality [10]. Retrospective data have shown that men with normal testosterone levels had 20.1% mortality while participants with a low testosterone (TT level less than 250 ng/dl or free testosterone level of less than 0.75 ng/dl) had 34.9% mortality [11].

The aging in the Chianti Area Study [12] examined levels of anabolic hormones including BT, DHEAS and IGF-1 and their association with mortality. Testosterone alone was not noted to have an independent affect on mortality. Among males with CHF, a significant association between hormonal levels and mortality occurred when multiple low hormone levels or only DHEAS were low [9]. However, the Massachusetts Male Aging Study discovered weak associations between testosterone and mortality [13].

The purpose of the present study was to evaluate mortality risk related to testosterone levels in a sample of older African-American males. Since there are known racial differences in

mortality risk for certain cancers and cardiovascular risk factors, any correlation between mortality risk and testosterone levels may give insight into the elevated risk for disease.

Subjects and methods

Study Sample

Previous reports have described in detail the larger cohort from which this study sample was drawn [14–16]. In brief, a cohort of 622 African-Americans from inner-city St. Louis, Missouri (age 80.05 ± 6.4 , range 68–102) was enrolled and completed baseline evaluation in 1992–1994. The cohort of 622 African-Americans included 190 males (mean age 78.38 ± 6.2). Subjects were recruited based on stratified random sampling procedures from Medicare Enrollment Eligibility Files (with permission from the Health Care Financing Administration) and from local senior community centres and apartments. There were 408 participants from the Medicare Enrollment and 214 from the alternate sources. The analytic sample for this study includes 56/190 males (age 78.89 ± 6.9) who donated blood at baseline. The Institutional Review Board at Saint Louis University approved all procedures, and all participants gave written informed consent.

Vital status

Vital status was verified by matching through the National Death Index (NDI) for the years 1992 through 2002. Time-to-death was defined as the number of months between the date of the baseline interview (1992–1994) and date of death (1992–2002). Cases were censored at the date of the last interview (through 31 July 2003) or end date of the NDI search (through 31 December 2002).

Measures

Blood was drawn from willing volunteers and allowed to clot, and serum was decanted off immediately and frozen at -70°C until analysed. TT and BT were measured at baseline (1992–1994). The testosterone levels were measured by Geriatric Medicine laboratory at Saint Louis University. The TT COAT-A-Count radioimmunoassay (RIA) kit is from Siemens (Los Angeles, CA) and has an intra-assay percent of 6.7 and inter-assay percent of 7.3. The kit sensitivity is 4 ng/dl with a reference range for adult male is 278–1266 ng/dl. The BT in house RIA, ammonium sulphate precipitation method has an intra-assay percent of 7.5 and inter-assay percent of 10.1, sensitivity is 4 ng/dl, reference range for male adult is 70–320 ng/dl. A total of 64.3% of testosterone measurements were < 300 ng/dl.

Covariates included age, comorbidities (arthritis, hypertension, cardiopulmonary conditions, cerebrovascular disease, diabetes mellitus, cancer [malignant], and kidney disease), lower body functional limitations and physician visits. Lower body functional limitations were determined using the three-item modified Rosow-Breslau scale. The three items include doing heavy work around the house, walking half a mile and walking up and down a full flight of stairs. The participants self-reported the number of physician visits in previous 12 months (actual number truncated at 13).

Statistical analysis

Analysis was performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL). Kaplan–Meier survival curves were plotted and log-rank tests were used to compare mortality (up to 10 years after baseline) among individuals with normal *versus* low TT and with normal *versus* low BT. Cox proportional hazard (PH) regression analyses were used to model mortality risk (up to 10 years after baseline) associated with TT and BT level with adjustment for age only or for age and other covariates. Covariates were chosen in an *a priori* fashion based on variables considered likely to be independent predictors of survival and unlikely to confound the association of testosterone levels with mortality. A sensitivity analysis was performed to repeat the Cox PH regression using log-transformed value for TT and BT.

Results

Of the 56 men analysed in this study, 41 died during the study period. Table I shows baseline characteristics for survivors and decedents. TT levels adjusted for age (Adjusted Hazard Ratio [AHR] 0.998; 95% confidence interval [CI] 0.995–1.001; $p = 0.278$) and adjusted for age, lower body functional limitations, physician visits and comorbidities (AHR = 0.999; 95% CI 0.996–1.002; $p = 0.345$) were not associated with mortality risk. BT levels adjusted for age (AHR = 0.992; 95% CI 0.977–1.007; $p = 0.300$) and adjusted for age, lower body functional limitations, physician visits and comorbidities (AHR 0.991; 95% CI 0.976–1.006; $p = 0.261$) also were not associated with mortality risk. Sensitivity analyses repeating the Cox PH regression with log-transformed values of TT and BT did not change the pattern or statistical significance of these results. Figure 1 shows a Kaplan–Meier survival curve plotted by TT levels of 300 ng/dl or above ($n = 20$) *versus* below 300 ng/dl ($n = 36$) and shows that time-to-mortality did not differ between groups (logrank test, $p = 0.42$). BT levels of 70 ng/dl or less ($n = 51$) *versus* above 70 ng/dl ($n = 5$) are plotted in the Kaplan–Meier survival curve shown in Figure 2 and, also, shows that time-to-mortality did not differ between groups (logrank test, $p = 0.337$).

Discussion

Testosterone was not associated with mortality risk in this study. Are there differences between studies that could provide some insight into differing results? Tables I and II contain results of previous studies showing both associations and lack of associations between testosterone levels and mortality. One difference could be sample size. The samples size of the present study is 131 in the all male cohort and a few associations were trending toward significance. Sample sizes of other studies that did find a positive correlation ranged from 10, 423 men [10] to only 40 men [17]. Previous null studies similar to this study had sample sizes ranging from 410 men [12] to 2512 men [14]. These comparisons suggest that results are not merely an artifact of statistical power.

The relative health of the subjects may also affect the outcome of mortality risk and testosterone. The number of comorbidities can be seen as a reflection of general health. The results of this study did not show any statistically significant changes in mortality secondary to comorbid conditions. The mean number of comorbidities was 1.66. Previous studies included patients in post-hospitalisation rehabilitation [11,17], random samples from

population registries [12,13,15,16], and total sampling of a target population based on age [14]. In general, the health of the all populations studied did not differ. The only ill or recovering ill patient data analysed did find a statistically significant relationship between testosterone levels and mortality [11,17].

This study did not investigate relationships with testosterone levels and any specific disease process. However, lower testosterone levels have been associated with cardiovascular disease and cardiovascular risk factors. The Caerphilly Study [14], Table II, found an association between cortisol testosterone ratios and ischemic heart disease but not for all cause mortality. In addition, the EPIC-Norfolk studies [10], Table I, noted an association between testosterone levels and all cause mortality and cardiovascular diseases. The range of testosterone levels was much greater in the Caerphilly study, but both studies mean testosterone did not qualify as hypogonadal. The mean TT levels of this study demonstrate a largely, 64.3%, hypogonadal study population. This high percentage of hypogonadal subjects may be indicative of the mean age of this study population.

The mean age of this study population was 78.9 years. While mean ages were not available for some of the studies, two studies, Swedish Osteoporotic Fractures in Men Cohort [15] and the Rancho Bernardo Study [16], had lower but similar mean ages, 75.4 and 71.2, respectively. Age adjustment did not alter the results for the studies that did not find associated mortality risk.

There are limitations to this study. In particular, the small sample size ($n = 56$ males) relative to the larger cohort ($n = 190$ males) reduces the generalisability of the findings to the larger cohort and, also, reduces statistical power to detect effects. However, the hazard ratio point estimates suggest that if an effect is present, it is a very small one, at best. A further study limitation is the focus on all cause mortality as the primary outcome. There may be important associations between T or BT and certain specific causes of mortality that this study (by design) is unable to identify. Nonetheless, this study is unique because the participants were African-American males and mostly older than 75.

This study did not find any statistically significant association between testosterone levels and mortality. These results do not appear to be associated with the size of the study, age, health, or race of the present study subjects.

Acknowledgements

This study was supported by a grant from the National Institute on Aging to DKM (R01 AG010436).

References

1. Liu PY, Beilin J, Meier C, Nguyen TV, Center JR, Leedman PJ, Seibel MJ, Eisman JA, Handelsman DJ. Age-related changes in serum testosterone and sex hormone binding globulin in Australian men: longitudinal analyses of two geographically separate regional cohorts. *J Clin Endocrinol Metab.* 2007; 92:3599–3603. [PubMed: 17595245]
2. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab.* 2002; 87:589–598. [PubMed: 11836290]

3. Morley JE, Kaiser FE, Perry HM III, Patrick P, Morley PMK, Stauber PM, Vallas B, Baumgartner RN, Garry PJ. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism*. 1997; 46:410–413. [PubMed: 9109845]
4. Perry HM III, Miller DK, Patrick DK, Morley JE. Testosterone and leptin in older African-American men: relationship to age, strength, function, and season. *Metab Clin and Exp*. 2000; 49:1085–1091.
5. Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barret-Connor E, Cauley J, Ensrud K, Cummings S. Testosterone and estradiol among older men. *J Clin Endocrinol Metab*. 2006; 91:1336–1344. [PubMed: 16368750]
6. Litman HJ, Bhasin S, Link CL, Araujo AB, McKinlay JB. Serum androgen levels in black, Hispanic, and White men. *J Clin Endocrinol Metab*. 2006; 91:4326–4334. [PubMed: 16912139]
7. Winters SJ, Brufsky A, Weissfeld J, Trump DL, Dyky MA, Hadeed V. Testosterone, sex hormone-binding globulin and body composition in young African American and Caucasian men. *Metab Clin Exp*. 2001; 50:1242–1247. [PubMed: 11586501]
8. Haren MT, Banks WA, Perry HM, Ping P, Malmstrom TK, Miller DK, Morley JE. Predictors of serum testosterone and DHEAS in African-American men. *Int J Androl*. 2008; 3:50–59. [PubMed: 18190426]
9. Jankowski EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, Anker SD, Banasiak W, Poole-Wilson PA, Ponikowski P. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation*. 2006; 114:1829–1837. [PubMed: 17030678]
10. Khaw K-T, Dowsett M, Folkard E, Bingham S, Wareham N, Luben R, Welch A, Day N. Endogenous testosterone and mortality due to all causes, cardiovascular disease and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) prospective population study. *Circulation*. 2007; 226:2694–2701. [PubMed: 18040028]
11. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med*. 2006; 166:1660–1665. [PubMed: 16908801]
12. Maggio M, Lauretani F, Ceda GP, Bandinelli S, Ling SM, Metter E, Artoni A, Carassale L, Cazzato A, Ceresini G, et al. Relationship between low levels of anabolic hormones and 6-year mortality in older men. *Arch Intern Med*. 2007; 167:2249–2254. [PubMed: 17998499]
13. Araujo AB, Kupelian V, Page ST, Handelsman DJ, Brenner WJ, McKinlay JB. Sex steroids and all-cause and cause-specific mortality in men. *Arch Intern Med*. 2007; 167:1252–1260. [PubMed: 17592098]
14. Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caephilly study. *Circulation*. 2005; 112:332–340. [PubMed: 16009799]
15. Tivesten A, Vandenput L, Labrie F, Karlsson MK, Ljunggren O, Mellstrom D, Ohlsson C. Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab*. 2009; 94:2482–2488. [PubMed: 19401373]
16. Laughlin GA, Barrett-Conner E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab*. 2008; 93:68–75. [PubMed: 17911176]
17. Shores MM, Moceri VM, Gruenewald DA, Brodtkin KJ, Matsumoto AM, Kivlahan DR. Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men in a geriatric rehabilitation unit. *J Am Geriatr Soc*. 2004; 52:2007–2081.
18. Miller DK, Carter ME, Miller JP, Fornoff JE, Bentley JA, Boyd SD, Rogers JH, Cox MN, Morley JE, Lui LY, Coe RM. Inner-city older blacks have high levels of functional disability. *J Am Geriatr Soc*. 1996; 44:1166–1173. [PubMed: 8855994]
19. Miller DK, Wolinsky FD, Malmstrom TK, Andresen EM, Miller JP. Inner city, middle-aged African Americans have excess frank and subclinical disability. *J Gerontol A Biol Sci Med Sci*. 2005; 60:M207–M212.
20. Malmstrom TK, Andresen EM, Wolinsky FD, Miller JP, Stamps K, Miller DK. Mortality risk in older inner-city African Americans. *J Am Geriatr Soc*. 2007; 55:1049–1055. [PubMed: 17608878]

Figure 1. Mortality among males with testosterone (T) levels below 300 ($n = 36$) *versus* testosterone (T) levels 300 or above ($n = 20$). *Testosterone measurements are ng/ml.

Figure 2. Mortality among males with bioavailable testosterone (T) levels above 70 ($n = 5$) versus bioavailable testosterone (T) levels 70 or less ($n = 51$). *Bioavailable testosterone measurements are ng/ml.

Table I

Baseline characteristics of decedents and survivors.

Characteristics (mean $\pm$ standard deviation)	Decedents (<i>n</i> = 41)	Survivors (<i>n</i> = 15)
Age	79.95 $\pm$ 7.3	76.00 $\pm$ 4.5
Lower body functional limitations	1.02 $\pm$ 1.1	0.47 $\pm$ 0.7
Physician visits	5.83 $\pm$ 4.8	4.73 $\pm$ 3.6
Comorbidities	1.61 $\pm$ 1.0	1.80 $\pm$ 1.0
Total testosterone	247.12 $\pm$ 116.0	245.27 $\pm$ 130.0
Bioavailable testosterone	32.64 $\pm$ 23.5	35.21 $\pm$ 27.6

Table II

Testosterone levels associated with all cause and cause specific mortality

Study [Ref]	Sample	Tests	Length of follow up	Classification	Results
Khaw K et al. <i>Circulation</i> . 2007 [10]	EPIC-Norfolk • European Prospective Investigation into Cancer in Norfolk, United Kingdom of 11,606 men aged 40 to 79 years of age. 10,423 men without baseline cardiovascular disease or cancer • 1 to 2 age, sex and visit matched controls for each death	TT SHBG TT/SHBG ratio DHEAS	Baseline 1993 to 1997 Follow up 2003- Average 7 years	Quartile: • TT <12.5nmol/L 12.5–15.6 nmol/L 15.7 – 19.6 nmol/L >19.6	Mean TT control 16.7 nmol/L to all cause mortality mean of 15.8 nmol/L ($p < 0.01$); cardiovascular mortality mean 15.7 nmol/L ($p < 0.01$); and cancer mortality 15.6 nmol/L ($p < 0.01$) Age adjusted odds ratio for all-cause ($p < 0.001$), cardiovascular ($p < 0.01$) coronary heart disease, and cancer ($p < 0.04$) mortality decreased with increasing testosterone quartile. Every 6 nmol/L increase TT (≈ 1 SD) 14% decreased risk of mortality (OR 0.86, 95% CI 0.79 to 0.94, $p < 0.001$).
Shores MM et al. 2006 [11]	Males from the VA Puget Sound • 858 men. • 40 years or older	TT Free testosterone	Baseline 1994 to 1999 Follow up 2002 Up to 8 year follow-up	At least 2 testosterone measurements 1 week to 2 years apart Low TT < 250 ng/dL (< 8.7 nmol/L) Free testosterone < 0.75 ng/dL (< 0.03 nmol/L) Groups: Normal Equivocal Low	Mortality comparisons with normal levels, fully adjusted data for hazard ratio: Equivocal 1.38 (0.99–1.92), $p < .06$ Low TT or free testosterone 1.88 (1.34–2.63), $p < .001$
Shores MM et al. 2004 [17]	Geriatric evaluation and management unit at the VA Puget Sound – 44 men • All new admissions over 6 months • During the study decision to defer testing to after rehabilitation	TT Free testosterone Also measured depressive illness, length of stay and 6 month rehospitalization.	6 months	Low TT ≤ 3.0 ng/ml Low free testosterone ≤ 9 pg/mL	Low TT or free testosterone with higher mortality than normal levels. 31% low testosterone mortality versus 6.7% normal mortality with $p = .07$. Low testosterone and high illness severity increased mortality (4 of 6 died versus 0 or 5 died with normal testosterone). $X^2 = 5.2$, $p = .02$ Fully adjusted 6 month survival time. Hazard Ratio 27.9 (CI 2.0–384.0; $p = .01$).
Tivesten A et al. 2009 [19]	Swedish Osteoporotic Fractures in Men cohort- 3014 men • 69–80 years old • Mean follow up of 4.5 years • 383 deaths and 363 with cause of death. • Three Swedish cities. • Caucasian	SHBG TT Estradiol Free Testosterone Free Estradiol.	Mean follow up 4.5 years	Quartiles: TT (ng/ml) ≤ 3.36 3.37–4.38 4.39–5.54 ≥ 5.55 Free Testosterone (pg/ml) ≤ 61 61–79 79–99 ≥ 99 Total Estradiol (pg/ml) ≤ 16.0 16.0–20.3 20.3–25.3 ≥ 25.3	Adjusted HR for all cause mortality comparing quartile 1 (lowest) with individual and pooled quartiles 2 to 4. TT : Trend over quartiles $p < 0.001$ Pooled – HR 1.65 (CI 1.29–2.12) Total Estradiol: Trend over quartiles .033 Pooled – HR 1.54 (CI 1.22–1.95)

Study [Ref]	Sample	Tests	Length of follow up	Classification	Results
Laughlin GA et al. 2008 [20]	Rancho Bernardo Study <ul style="list-style-type: none"> • 1060 men total • 794 men with testosterone measured and full follow up. • Age 50 – 91 years old • Almost entirely Caucasian middle-to upper-middle-class 	TT, BT, Estradiol Bioavailable estradiol	Average 11.8 year follow up.	Free Estradiol (pg/ml) <= 0.27 0.27–0.35 0.35–0.44 >=0.44 Quantiles: TT(ng/dl) >370 300–370 241–299 <241 BT (ng/dl) >117 96–117 78–95 <79	538 deaths TT comparison of lowest quartile with highest : Adjusted HR 1.44 (CI 1.12–1.84), p=0.002 BT comparison of lowest quartile with highest: Adjusted HR 1.50 (CI 1.15–1.96), p < 0.001

Table III

Testosterone levels not associated with all cause mortality

Study	Sample	Tests	Length of follow up	Classification	Results
Araujo AG et al. 2007 [13]	Massachusetts Male Aging Study • Observational cohort study • 1689 of 1709 baseline respondents males aged 40 to 70 years old. • 95.3% White, 2.8% Black, and 1.9% Other.	TT Free testosterone, Dihydro-testosterone, (SHBG).	Baseline 1987–1989 and vital status obtained through 2004	Quintiles: • TT • <370ng/dL 370–<466ng/dL 466–<545ng/dL 545–<650ng/dL >=650 ng/dL • Free Testosterone • <8.0 ng/dL 8–<10.2 ng/dL 10.2–<12.2 ng/dL 12.2–<14.8 ng/dL >= 14.8 ng/dL • Dihydrotestosterone • <0.15 ng/mL 0.15–<0.20 ng/mL 0.20–<0.27 ng/mL 0.27–<0.37 ng/mL >= 0.37 ng/mL • SHBG • <21nmol/L 21–<26 nmol/L >26–32 nmol/L >32–<42 nmol/L >= 42 nmol/L	Free testosterone level and ischemic heart disease mortality RR 0.80 (0.64–0.99) per 1-SD decrease with P=.02 for trend and increased respiratory mortality 1.90 (1.24–2.92) with a P=.002 for trend. TT and SHBG no association with mortality
Maggio M et al. 2007 [12]	InCHIANTI study • 410 men 65 years and older living in Tuscany, Italy.	BT DHEAS IGF-1.	6 years	• BT < 70ng/dl • DHEA-S <50 ug/DI • IGF-1 63.9 ng/ml • Four groups according to the number of hormones with serum levels in the lowest quartile- 0, 1, 2, and 3.	126 deaths in 6-year follow-up BT Hazard Ratio 1.48 (0.89–2.46)/ P Value .13 IGF-1 Hazard Ratio 1.36 (0.78–2.38)/p value .28 DHEAS Hazard Ratio 1.38 (0.84–2.26)/p value .21 Multiple hormones 1–3 P value for trend < .001 1.04 (0.56–1.95) 1.34 (0.67–2.65) 2.44 (1.09–5.46) Mortality Rates p=.007 for trend Group 0 2.9 Group 1 6.2 Group 2 16.7 Group 3 46
Smith GD et al. 2005 [18]	Caerphilly Study • 2512 males • 2323 males with cortisol and testosterone measured. • Age range 45 to 59 • Caerphilly, South Wales	Cortisol Testosterone	Mean follow up 16.5 years	Quintiles by mean cortisol (nmol/L) /testosterone (nmol/L) ratio Lowest: 306.6/29.4 2nd: 401.7/ 25.6 3rd: 448.4/23.0 4th: 491.7/20.3\	Association between quintiles ratio/ testosterone with all cause mortality after adjustments. P trend 0.86/0.70 Risk for 1-SD Rise in Log Cortisol 1.01(0.92–1.11)/ 1.0 (0.91–1.10) Lowest : HR 1.00/1.00

Study	Sample	Tests	Length of follow up	Classification	Results
Morley JE et al. 1997 [3]	New Mexico Aging Process Study <ul style="list-style-type: none"> • 77 males • Age range 61 to 87 • 96% non-Hispanic white and 4% Hispanic 	TT, Luteinizing Hormone, Follicle Stimulating Hormone and SHBG	15 year study	Highest: 553.6/16.2 Measured decline in age group 66–70yo, 71–75yo and older than 75yo. TT lower limit of normal 245 ng/dL LH upper limit of normal > 20mIU/L	2 nd : HR 0.97/0.94 3 rd : HR 1.15/1.00 4 th : HR 1.00/1.00 Highest: HR 1.02/1.04 Mean TT levels 18 subjects that died relative to the living: 651+/-38 ng/dL vs. 639+/-18 ng/dL