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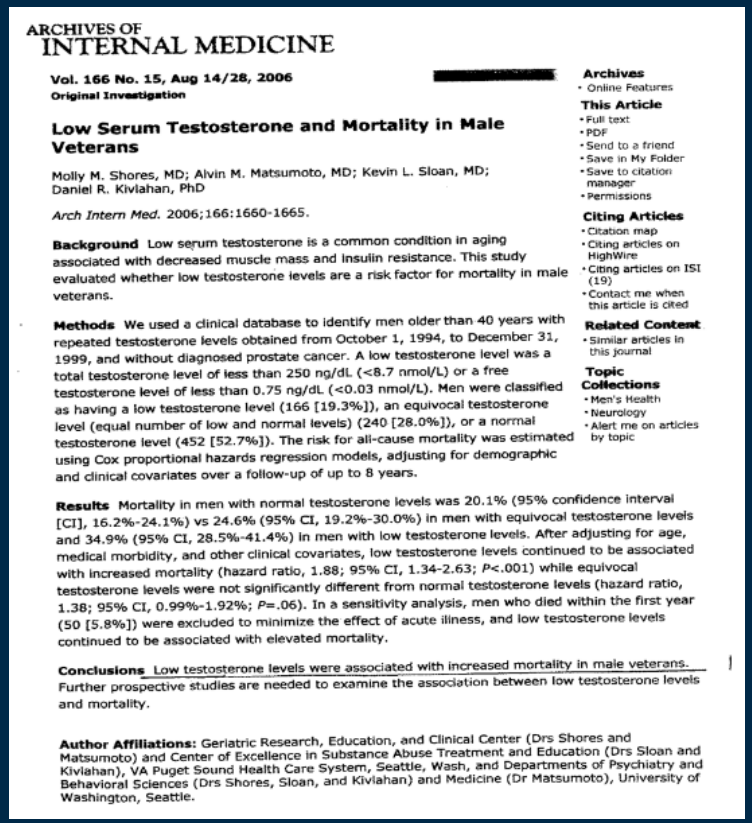
HORMONES FOR MEN

WHERE WOULD YOU LIKE YOUR TESTOSTERONE LEVELS TO BE?

BY NEAL ROUZIER

Low Serum Testosterone and Mortality in Male Veterans



ARCHIVES OF
INTERNAL MEDICINE

Vol. 166 No. 15, Aug 14/28, 2006
Original Investigation

Low Serum Testosterone and Mortality in Male Veterans

Molly M. Shores, MD; Alvin M. Matsumoto, MD; Kevin L. Sloan, MD; Daniel R. Kivlahan, PhD

Arch Intern Med. 2006;166:1660-1665.

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.

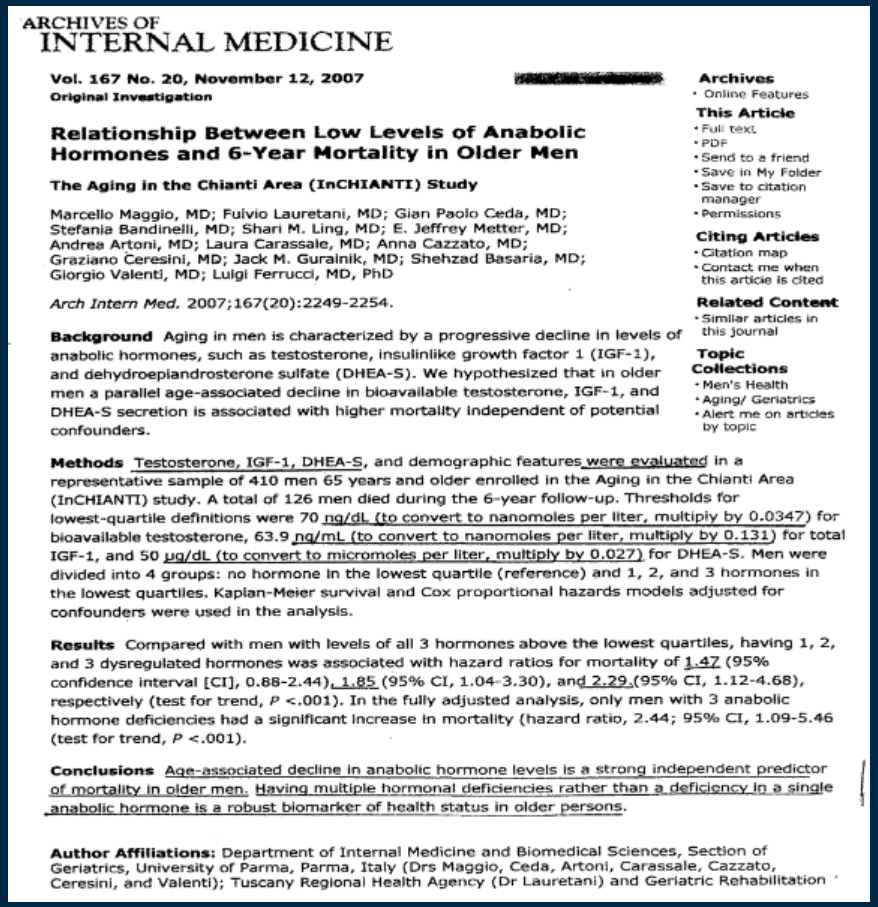
Conclusions Low testosterone levels were associated with increased mortality in male veterans. Further prospective studies are needed to examine the association between low testosterone levels and mortality.

Author Affiliations: Geriatric Research, Education, and Clinical Center (Drs Shores and Matsumoto) and Center of Excellence in Substance Abuse Treatment and Education (Drs Sloan and Kivlahan), VA Puget Sound Health Care System, Seattle, Wash, and Departments of Psychiatry and Behavioral Sciences (Drs Shores, Sloan, and Kivlahan) and Medicine (Dr Matsumoto), University of Washington, Seattle.

- Low testosterone levels were associated with increased mortality in male veterans

Shores MM, Matsumoto AM, Sloan KL, et al. Low serum testosterone and mortality in male veterans. Arch Intern Med. 2006 Aug;166(15):1660-1665.

Relationship Between Low Levels of Anabolic Hormones and 6-Year Mortality in Older Men



ARCHIVES OF
INTERNAL MEDICINE

Vol. 167 No. 20, November 12, 2007
Original Investigation

Relationship Between Low Levels of Anabolic Hormones and 6-Year Mortality in Older Men

The Aging in the Chianti Area (InCHIANTI) Study

Marcello Maggio, MD; Fulvio Lauretani, MD; Gian Paolo Ceda, MD; Stefania Bandinelli, MD; Shari M. Ling, MD; E. Jeffrey Metter, MD; Andrea Artoni, MD; Laura Carassale, MD; Anna Cazzato, MD; Graziano Ceresini, MD; Jack M. Guralnik, MD; Shehzad Basaria, MD; Giorgio Valenti, MD; Luigi Ferrucci, MD, PhD

Arch Intern Med. 2007;167(20):2249-2254.

Background Aging in men is characterized by a progressive decline in levels of anabolic hormones, such as testosterone, insulinlike growth factor 1 (IGF-1), and dehydroepiandrosterone sulfate (DHEA-S). We hypothesized that in older men a parallel age-associated decline in bioavailable testosterone, IGF-1, and DHEA-S secretion is associated with higher mortality independent of potential confounders.

Methods Testosterone, IGF-1, DHEA-S, and demographic features were evaluated in a representative sample of 410 men 65 years and older enrolled in the Aging in the Chianti Area (InCHIANTI) study. A total of 126 men died during the 6-year follow-up. Thresholds for lowest-quartile definitions were 70 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) for bioavailable testosterone, 63.9 ng/mL (to convert to nanomoles per liter, multiply by 0.131) for total IGF-1, and 50 µg/dL (to convert to micromoles per liter, multiply by 0.027) for DHEA-S. Men were divided into 4 groups: no hormone in the lowest quartile (reference) and 1, 2, and 3 hormones in the lowest quartiles. Kaplan-Meier survival and Cox proportional hazards models adjusted for confounders were used in the analysis.

Results Compared with men with levels of all 3 hormones above the lowest quartiles, having 1, 2, and 3 dysregulated hormones was associated with hazard ratios for mortality of 1.47 (95% confidence interval [CI], 0.88-2.44), 1.85 (95% CI, 1.04-3.30), and 2.29 (95% CI, 1.12-4.68), respectively (test for trend, P <.001). In the fully adjusted analysis, only men with 3 anabolic hormone deficiencies had a significant increase in mortality (hazard ratio, 2.44; 95% CI, 1.09-5.46 (test for trend, P <.001).

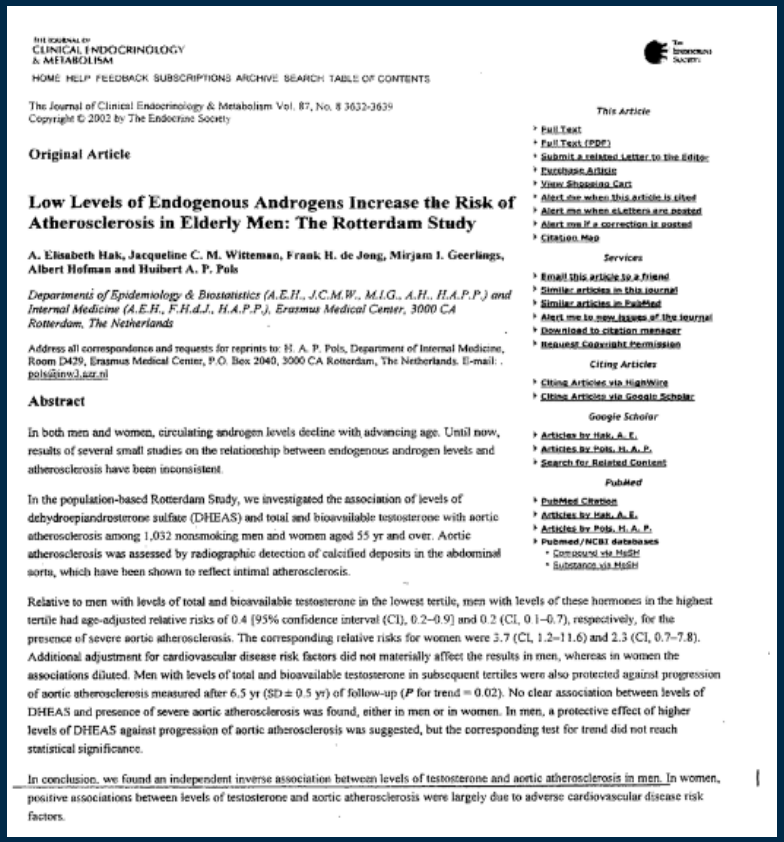
Conclusions Age-associated decline in anabolic hormone levels is a strong independent predictor of mortality in older men. Having multiple hormonal deficiencies rather than a deficiency in a single anabolic hormone is a robust biomarker of health status in older persons.

Author Affiliations: Department of Internal Medicine and Biomedical Sciences, Section of Geriatrics, University of Parma, Parma, Italy (Drs Maggio, Ceda, Artoni, Carassale, Cazzato, Ceresini, and Valenti); Tuscany Regional Health Agency (Dr Lauretani) and Geriatric Rehabilitation

- Testosterone, IGF-1, DHEA-S …….were evaluated
- Age-associated decline in anabolic hormone levels is a strong independent predictor of mortality in older men. Having multiple hormonal deficiencies rather than a deficiency in a single anabolic hormone is a robust biomarker of health status in older persons.

Maggio M, Lauretani F, Ceda GP, et al. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (In CHIANTI) study. Arch Intern Med. 2007 Nov;167(20):2249-2254.

Low Levels of Endogenous Androgens Increase the Risk of Atherosclerosis In Elderly Men: The Rotterdam Study



THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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The Journal of Clinical Endocrinology & Metabolism Vol. 87, No. 8 3632-3639

Original Article

Low Levels of Endogenous Androgens Increase the Risk of Atherosclerosis in Elderly Men: The Rotterdam Study

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Abstract

In both men and women, circulating androgen levels decline with advancing age. Until now, results of several small studies on the relationship between endogenous androgen levels and atherosclerosis have been inconsistent.

In the population-based Rotterdam Study, we investigated the association of levels of dehydroepiandrosterone sulfate (DHEAS) and total and bioavailable testosterone with aortic atherosclerosis among 1,032 nonsmoking men and women aged 55 yr and over. Aortic atherosclerosis was assessed by radiographic detection of calcified deposits in the abdominal aorta, which have been shown to reflect intimal atherosclerosis.

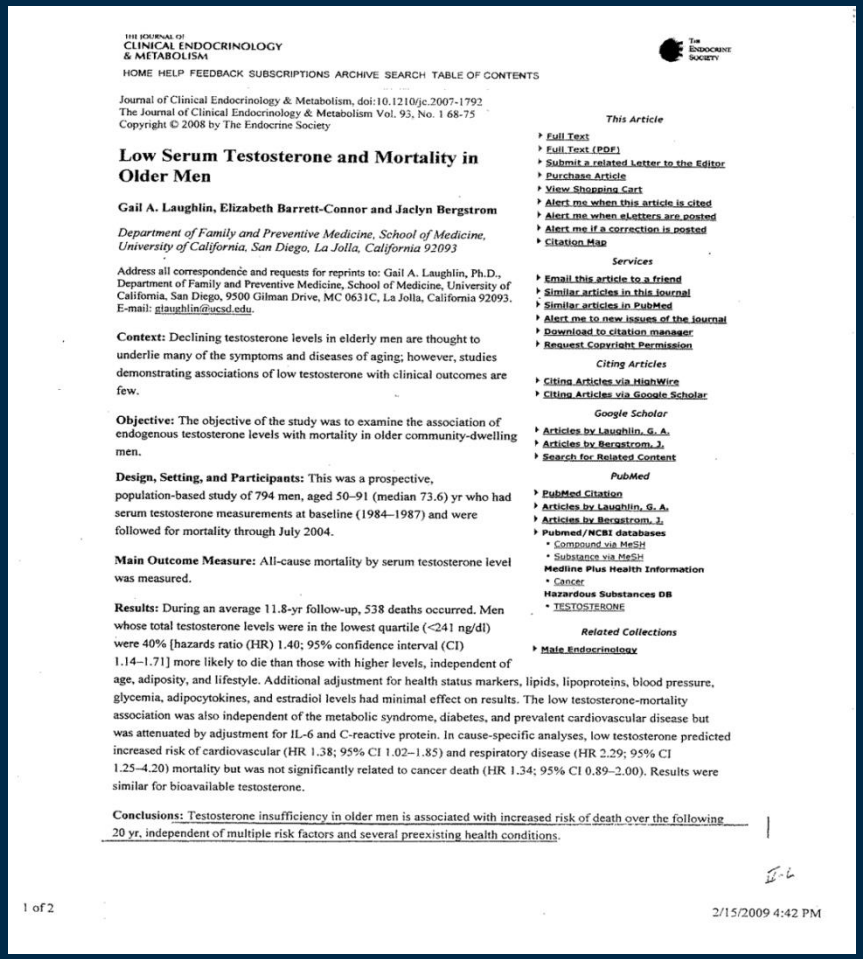
Relative to men with levels of total and bioavailable testosterone in the lowest tertile, men with levels of these hormones in the highest tertile had age-adjusted relative risks of 0.4 [95% confidence interval (CI), 0.2–0.9] and 0.2 (CI, 0.1–0.7), respectively, for the presence of severe aortic atherosclerosis. The corresponding relative risks for women were 3.7 (CI, 1.2–11.6) and 2.3 (CI, 0.7–7.8). Additional adjustment for cardiovascular disease risk factors did not materially affect the results in men, whereas in women the associations diluted. Men with levels of total and bioavailable testosterone in subsequent tertiles were also protected against progression of aortic atherosclerosis measured after 6.5 yr (SD ± 0.5 yr) of follow-up (*P* for trend = 0.02). No clear association between levels of DHEAS and presence of severe aortic atherosclerosis was found, either in men or in women. In men, a protective effect of higher levels of DHEAS against progression of aortic atherosclerosis was suggested, but the corresponding test for trend did not reach statistical significance.

In conclusion, we found an independent inverse association between levels of testosterone and aortic atherosclerosis in men. In women, positive associations between levels of testosterone and aortic atherosclerosis were largely due to adverse cardiovascular disease risk factors.

- In conclusion we found an independent inverse association between levels of testosterone and aortic atherosclerosis in men.

Hak AE, Witteman JC, de Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: The Rotterdam study. J Clin Endocrinol Metab. 2002 Aug;87(8):3632-3639.

Low Serum Testosterone and Mortality in Older Men



THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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Journal of Clinical Endocrinology & Metabolism, doi:10.1210/jc.2007-1792
The Journal of Clinical Endocrinology & Metabolism Vol. 93, No. 1 68-75

Low Serum Testosterone and Mortality in Older Men

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Address all correspondence and requests for reprints to: Gail A. Laughlin, Ph.D., Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, 9500 Gilman Drive, MC 0631C, La Jolla, California 92093. E-mail: glaughlin@ucsd.edu.

Context: Declining testosterone levels in elderly men are thought to underlie many of the symptoms and diseases of aging; however, studies demonstrating associations of low testosterone with clinical outcomes are few.

Objective: The objective of the study was to examine the association of endogenous testosterone levels with mortality in older community-dwelling men.

Design, Setting, and Participants: This was a prospective, population-based study of 794 men, aged 50–91 (median 73.6) yr who had serum testosterone measurements at baseline (1984–1987) and were followed for mortality through July 2004.

Main Outcome Measure: All-cause mortality by serum testosterone level was measured.

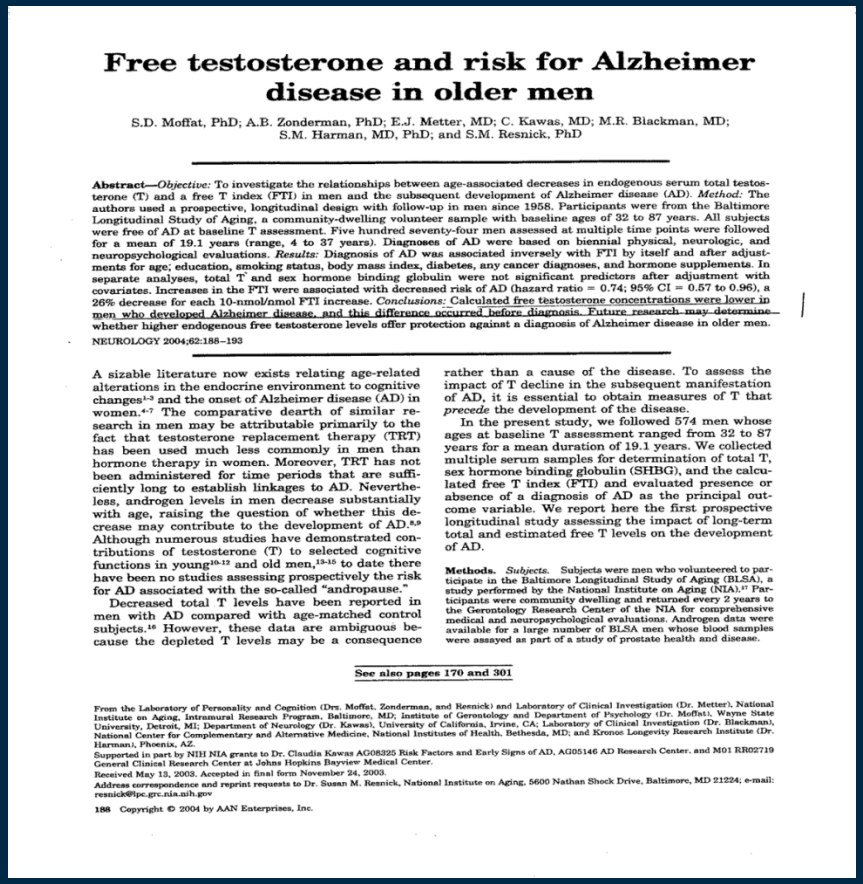
Results: During an average 11.8-yr follow-up, 538 deaths occurred. Men whose total testosterone levels were in the lowest quartile (<241 ng/dl) were 40% [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14–1.71] more likely to die than those with higher levels, independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results. The low testosterone-mortality association was also independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease but was attenuated by adjustment for IL-6 and C-reactive protein. In cause-specific analyses, low testosterone predicted increased risk of cardiovascular (HR 1.38; 95% CI 1.02–1.85) and respiratory disease (HR 2.29; 95% CI 1.25–4.20) mortality but was not significantly related to cancer death (HR 1.34; 95% CI 0.89–2.00). Results were similar for bioavailable testosterone.

Conclusions: Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple risk factors and several preexisting health conditions.

- Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple risk factors and several preexisting health conditions.

Hak AE, Witteman JC, de Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: The Rotterdam study. J Clin Endocrinol Metab. 2002 Aug;87(8):3632-3639.

Free testosterone and risk for Alzheimer disease in older men



Free testosterone and risk for Alzheimer disease in older men

S.D. Moffat, PhD; A.B. Zonderman, PhD; E.J. Metter, MD; C. Kawas, MD; M.R. Blackman, MD; S.M. Harman, MD, PhD; and S.M. Resnick, PhD

Abstract—*Objective:* To investigate the relationships between age-associated decreases in endogenous serum total testosterone (T) and a free T index (FTI) in men and the subsequent development of Alzheimer disease (AD). *Method:* The authors used a prospective, longitudinal design with follow-up in men since 1958. Participants were from the Baltimore Longitudinal Study of Aging, a community-dwelling volunteer sample with baseline ages of 32 to 87 years. All subjects were free of AD at baseline T assessment. Five hundred seventy-four men assessed at multiple time points were followed for a mean of 19.1 years (range, 4 to 37 years). Diagnoses of AD were based on biennial physical, neurologic, and neuropsychological evaluations. *Results:* Diagnosis of AD was associated inversely with FTI by itself and after adjustments for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplements. In separate analyses, total T and sex hormone binding globulin were not significant predictors after adjustment with covariates. Increases in the FTI were associated with decreased risk of AD (hazard ratio = 0.74; 95% CI = 0.57 to 0.96), a 26% decrease for each 10-nmol/amol FTI increase. *Conclusions:* Calculated free testosterone concentrations were lower in men who developed Alzheimer disease, and this difference occurred before diagnosis. Future research may determine whether higher endogenous free testosterone levels offer protection against a diagnosis of Alzheimer disease in older men.

NEUROLOGY 2004;62:188–193

A sizable literature now exists relating age-related alterations in the endocrine environment to cognitive changes[1-3] and the onset of Alzheimer disease (AD) in women.[4-7] The comparative dearth of similar research in men may be attributable primarily to the fact that testosterone replacement therapy (TRT) has been used much less commonly in men than hormone therapy in women. Moreover, TRT has not been administered for time periods that are sufficiently long to establish linkages to AD. Nevertheless, androgen levels in men decrease substantially with age, raising the question of whether this decrease may contribute to the development of AD.[8,9] Although numerous studies have demonstrated contributions of testosterone (T) to selected cognitive functions in young[10-12] and old men,[13-15] to date there have been no studies assessing prospectively the risk for AD associated with the so-called "andropause."

Decreased total T levels have been reported in men with AD compared with age-matched control subjects.[16] However, these data are ambiguous because the depleted T levels may be a consequence rather than a cause of the disease. To assess the impact of T decline in the subsequent manifestation of AD, it is essential to obtain measures of T that *precede* the development of the disease.

In the present study, we followed 574 men whose ages at baseline T assessment ranged from 32 to 87 years for a mean duration of 19.1 years. We collected multiple serum samples for determination of total T, sex hormone binding globulin (SHBG), and the calculated free T index (FTI) and evaluated presence or absence of a diagnosis of AD as the principal outcome variable. We report here the first prospective longitudinal study assessing the impact of long-term total and estimated free T levels on the development of AD.

Methods. *Subjects.* Subjects were men who volunteered to participate in the Baltimore Longitudinal Study of Aging (BLSA), a study performed by the National Institute on Aging (NIA).[17] Participants were community dwelling and returned every 2 years to the Gerontology Research Center of the NIA for comprehensive medical and neuropsychological evaluations. Androgen data were available for a large number of BLSA men whose blood samples were assayed as part of a study of prostate health and disease.

See also pages 170 and 301

From the Laboratory of Personality and Cognition (Drs. Moffat, Zonderman, and Resnick) and Laboratory of Clinical Investigation (Dr. Metter), National Institute on Aging, Intramural Research Program, Baltimore, MD; Institute of Gerontology and Department of Psychology (Dr. Moffat), Wayne State University, Detroit, MI; Department of Neurology (Dr. Kawas), University of California, Irvine, CA; Laboratory of Clinical Investigation (Dr. Blackman), National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD; and Kronos Longevity Research Institute (Dr. Harman), Phoenix, AZ.

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- Calculated free testosterone concentrations were lower in men who developed Alzheimer disease, and this difference occurred before diagnosis. Future research may determine…….

Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab. 2008 Jan;93(1):68-75.

Endogenous Testosterone and Mortality in Men: A Systematic Review and Meta-Analysis

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SPECIAL FEATURES

Endogenous Testosterone and Mortality in Men: A Systematic Review and Meta-Analysis

Andre B. Araujo, Julia M. Dixon, Elizabeth A. Suarez, M. Hassan Murad, Lin T. Guey and Gary A. Wittert

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Abstract

Context: Low testosterone levels have been associated with outcomes that reduce survival in men.

Objective: Our objective was to perform a systematic review and meta-analysis of published studies to evaluate the association between endogenous testosterone and mortality.

Data Sources: Data sources included MEDLINE (1966 to December 2010), EMBASE (1988 to December 2010), and reference lists.

Study Selection: Eligible studies were published English-language observational studies of men that reported the association between endogenous testosterone and all-cause or cardiovascular disease (CVD) mortality. A two-stage process was used for study selection. 1) Working independently and in duplicate, reviewers screened a subset (10%) of abstracts. Results indicated 96% agreement, and thereafter, abstract screening was conducted in singlicate. 2) All full-text publications were reviewed independently and in duplicate for eligibility.

Data Extraction: Reviewers working independently and in duplicate determined methodological quality of studies and extracted descriptive, quality, and outcome data.

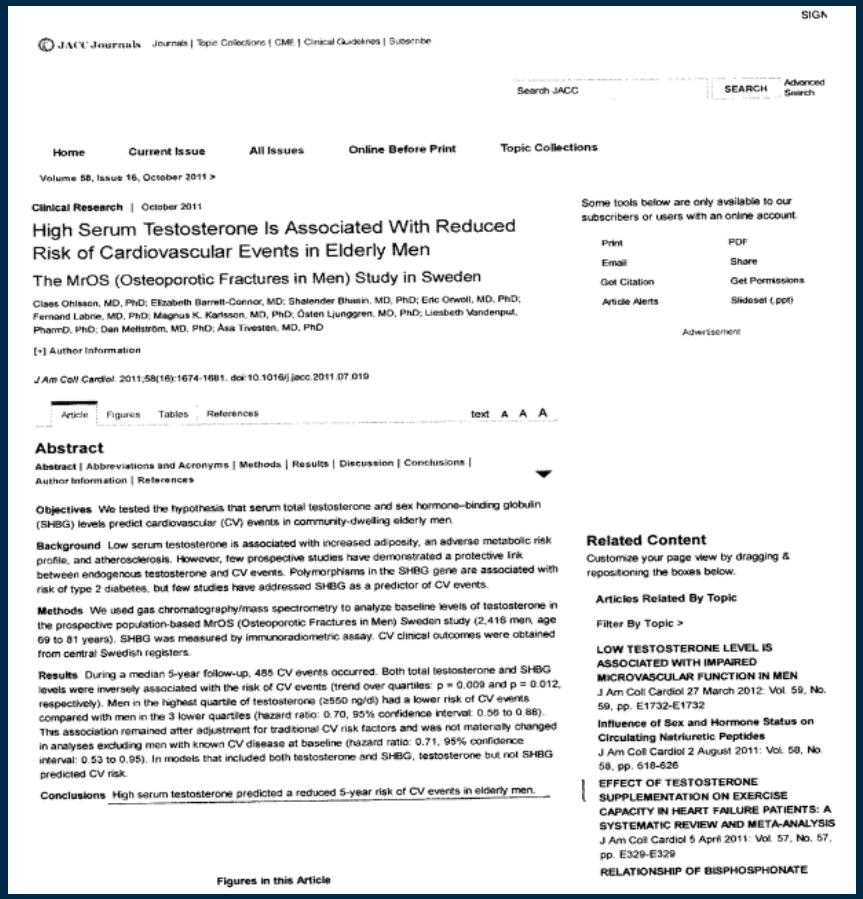
Data Synthesis: Of 820 studies identified, 21 were included in the systematic review, and 12 were eligible for meta-analysis [n = 11 studies of all-cause mortality (16,184 subjects); n = 7 studies of CVD mortality (11,831 subjects)]. Subject mean age and testosterone level were 61 yr and 487 ng/dl, respectively, and mean follow-up time was 9.7 yr. Between-study heterogeneity was observed among studies of all-cause ($P < .001$) and CVD mortality ($P = 0.06$), limiting the ability to provide valid summary estimates. Heterogeneity in all-cause mortality (higher relative risks) was observed in studies that included older subjects ($P = 0.020$), reported lower testosterone levels ($P = 0.018$), followed subjects for a shorter time period ($P = 0.010$), and sampled blood throughout the day ($P = 0.030$).

Conclusion: Low endogenous testosterone levels are associated with increased risk of all-cause and CVD death in community-based studies of men, but considerable between-study heterogeneity, which was related to study and subject characteristics, suggests that effects are driven by

- Low endogenous testosterone levels are associated with increased risk of all-cause and CVD death in community based studies of men.

Araujo AB, Dixon JM, Suarez EA, et al. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Oct;96(10):3007-3019.

High Serum Testosterone Is Associated With Reduced Risk of Cardiovascular Events in Elderly Men



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Clinical Research | October 2011

High Serum Testosterone Is Associated With Reduced Risk of Cardiovascular Events in Elderly Men

The MrOS (Osteoporotic Fractures in Men) Study in Sweden

Claes Ohlsson, MD, PhD; Elizabeth Barrett-Connor, MD; Shalender Bhasin, MD, PhD; Eric Orwoll, MD, PhD; Fernand Labrie, MD, PhD; Magnus K. Karlsson, MD, PhD; Östen Ljunggren, MD, PhD; Liesbeth Vandenput, PharmD, PhD; Dan Mellström, MD, PhD; Åsa Tivesten, MD, PhD

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J Am Coll Cardiol. 2011;58(16):1674-1681. doi:10.1016/j.jacc.2011.07.019

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Abstract

Abstract | Abbreviations and Acronyms | Methods | Results | Discussion | Conclusions | Author Information | References

Objectives We tested the hypothesis that serum total testosterone and sex hormone–binding globulin (SHBG) levels predict cardiovascular (CV) events in community-dwelling elderly men.

Background Low serum testosterone is associated with increased adiposity, an adverse metabolic risk profile, and atherosclerosis. However, few prospective studies have demonstrated a protective link between endogenous testosterone and CV events. Polymorphisms in the SHBG gene are associated with risk of type 2 diabetes, but few studies have addressed SHBG as a predictor of CV events.

Methods We used gas chromatography/mass spectrometry to analyze baseline levels of testosterone in the prospective population-based MrOS (Osteoporotic Fractures in Men) Sweden study (2,416 men, age 69 to 81 years). SHBG was measured by immunoradiometric assay. CV clinical outcomes were obtained from central Swedish registers.

Results During a median 5-year follow-up, 485 CV events occurred. Both total testosterone and SHBG levels were inversely associated with the risk of CV events (trend over quartiles: $p = 0.009$ and $p = 0.012$, respectively). Men in the highest quartile of testosterone (≥550 ng/dl) had a lower risk of CV events compared with men in the 3 lower quartiles (hazard ratio: 0.70, 95% confidence interval: 0.56 to 0.88). This association remained after adjustment for traditional CV risk factors and was not materially changed in analyses excluding men with known CV disease at baseline (hazard ratio: 0.71, 95% confidence interval: 0.53 to 0.95). In models that included both testosterone and SHBG, testosterone but not SHBG predicted CV risk.

Conclusions High serum testosterone predicted a reduced 5-year risk of CV events in elderly men.

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J Am Coll Cardiol 5 April 2011: Vol. 57, No. 57, pp. E329-E329

RELATIONSHIP OF BISPHOSPHONATE

- High serum testosterone predicted a reduced 5-year risk of CV in elderly men.

Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. J Am Coll Cardiol. 2011 Oct;58(16):1674-1681.

toward an inverse association between serum testosterone and incident CHD events in the Caerphilly study (10), and other large population-based studies addressing testosterone as a predictor of CV events (Rancho Bernardo [(15)], Framingham [(16)], Tromsö [13]) show no association. Thus, our findings of a significant inverse association between testosterone levels and risk of combined fatal and nonfatal CV events in men support and extend previous work showing an association between testosterone and CV mortality (7- 10,14). Our study differs from previous studies that all used immunoassay-based hormone assay methods; ours is the first study addressing the association between CV events and serum testosterone assessed by a mass spectrometry–based technique, which provides more accurate assessment of testosterone than immunoassay-based techniques (30).

In the present study, testosterone levels in the highest quartile were associated with reduced CV risk compared with lower levels (quartiles 1 to 3). It is biologically plausible that serum testosterone less than a certain serum level confers increased cardiometabolic risk. Adverse effects of testosterone deficiency on, for example, body composition, insulin sensitivity, and systemic inflammation, may mediate such an effect (1,6). This notion is further supported by the fact that androgen-deprivation therapy in prostate cancer patients increases CV risk (31). In line with previous studies (6), we found that men with high serum testosterone levels had lower BMI and ApoB/A1 ratio, were more physically active, and had a lower frequency of reported diabetes, hypertension, and prevalent CV disease. Although testosterone is associated with an adverse metabolic risk profile, the association between testosterone and risk of CV events remained statistically significant, albeit slightly attenuated, after adjustment for traditional risk factors for CV disease. This may suggest that other mechanisms, such as endothelial regeneration, could be important (32).

Although there are several possible mechanisms by which testosterone potentially reduces CV risk, it is important to note that any severe illness can suppress testosterone production (3,33). Thus, any acute or chronic illness may concomitantly reduce testosterone production and increase the risk of a CV event. Because the elderly are more likely than younger adults to have CV or other diseases, a high testosterone level in elderly men may be a sign of good general health and thereby associated with reduced risk of CV events. However, the absence of statistical evidence of an interaction with age does not support this thesis, but the age range was fairly narrow. Further, exclusion of the first 2.6 years of follow-up did not attenuate the association, arguing against an important role for baseline (sub)acute systemic disease. In addition, excluding men with prevalent CV disease did not materially change the HRs for CV risk. Nevertheless, studies addressing testosterone levels, assessed by mass spectrometry–based techniques, as predictors of CV events in relatively younger and presumably healthier men are of continued interest.

In the present study, low SHBG levels predicted an increased risk of CV events. Ours is the first study demonstrating an association between SHBG and the risk of combined fatal and nonfatal CV events. Two previous studies found an association between low SHBG levels and mortality from CV disease and/or CHD (11,19), whereas other studies found no similar association (12,14,20). Yeap et al. (14) found no association between SHBG and incident stroke/transient ischemic attack. In the present study, the association between SHBG and CV risk was no longer significant after adjustment for testosterone levels, suggesting that the covariation of SHBG with testosterone levels may explain some or all of its association with cardiometabolic risk (18).

In the present study, free testosterone levels were weakly and not significantly associated with CV risk, despite a trend toward an inverse association. Most previous studies of testosterone and CV endpoints did not study free or bioavailable testosterone (8- 10,16). Some studies (7,14) found similar associations for free (or bioavailable) and total testosterone, whereas others (11- 12) found discordant results. The Massachusetts Male Aging Study (11) reported a direct association between free testosterone and mortality from ischemic heart disease. Thus, data regarding free testosterone and CV events are inconsistent. There are differing opinions regarding the merits of calculated free testosterone values because these estimates show larger variability (34). However, they are mainly influenced (80% of attributable variance) by the variability of the total testosterone assay and less influenced (14%) by the equations used (35). Thus, if sensitive and accurate measurements of testosterone are used, calculated free testosterone should provide an accurate estimate of free testosterone (36). The Vermeulen formula used in the present study has been shown to be in good agreement with equilibrium dialysis measurements (25- 27).

Study limitations

The results are based on single measurements of sex steroids and SHBG and may underestimate the true associations. Given the diurnal variation in serum testosterone levels (37), the use of some nonmorning samples may contribute to increased variability and underestimation of serum testosterone levels in the present study. However, the diurnal variation of serum testosterone is less in older men (70 years; 10% lower levels at 4 PM than at 8 AM) (37), and the hour of day was adjusted for in these analyses. Another limitation is that baseline diabetes, hypertension, and CV disease were at least in part self-reported. More important, older adults are often treated with medications that might alter CV risk and/or testosterone levels, which were not examined in this report. In addition, our results are limited to elderly Swedish men. Further, our post-hoc analyses using a dichotomous variable comparing quartile 4 with quartiles 1 to 3 were not adjusted for multiple comparisons. The study also has considerable strengths, including the mass

- Thus our findings of a significant inverse association between testosterone levels and risk of combined fatal and nonfatal CV events in men support and extend previous work showing an association between testosterone and CV mortality.
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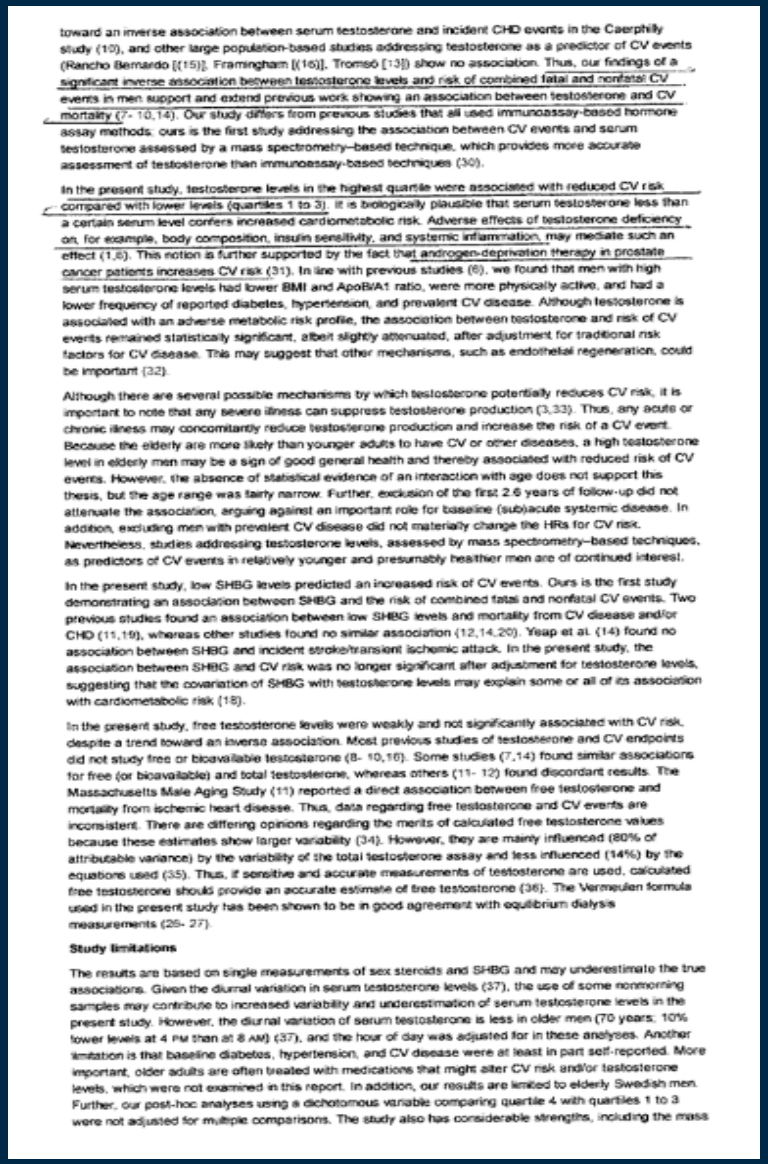
Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. J Am Coll Cardiol. 2011 Oct;58(16):1674-1681.



toward an inverse association between serum testosterone and incident CHD events in the Caerphilly study (10), and other large population-based studies addressing testosterone as a predictor of CV events (Rancho Bernardo [(15)], Framingham [(16)], Tromsö [13]) show no association. Thus, our findings of a significant inverse association between testosterone levels and risk of combined fatal and nonfatal CV events in men support and extend previous work showing an association between testosterone and CV mortality (7- 10,14). Our study differs from previous studies that all used immunoassay-based hormone assay methods; ours is the first study addressing the association between CV events and serum testosterone assessed by a mass spectrometry–based technique, which provides more accurate assessment of testosterone than immunoassay-based techniques (30).

In the present study, testosterone levels in the highest quartile were associated with reduced CV risk compared with lower levels (quartiles 1 to 3). It is biologically plausible that serum testosterone less than a certain serum level confers increased cardiometabolic risk. Adverse effects of testosterone deficiency on, for example, body composition, insulin sensitivity, and systemic inflammation, may mediate such an effect (1,6). This notion is further supported by the fact that androgen-deprivation therapy in prostate cancer patients increases CV risk (31). In line with previous studies (6), we found that men with high serum testosterone levels had lower BMI and ApoB/A1 ratio, were more physically active, and had a lower frequency of reported diabetes, hypertension, and prevalent CV disease. Although testosterone is associated with an adverse metabolic risk profile, the association between testosterone and risk of CV events remained statistically significant, albeit slightly attenuated, after adjustment for traditional risk factors for CV disease. This may suggest that other mechanisms, such as endothelial regeneration, could be important (32).

Although there are several possible mechanisms by which testosterone potentially reduces CV risk, it is important to note that any severe illness can suppress testosterone production (3,33). Thus, any acute or chronic illness may concomitantly reduce testosterone production and increase the risk of a CV event. Because the elderly are more likely than younger adults to have CV or other diseases, a high testosterone level in elderly men may be a sign of good general health and thereby associated with reduced risk of CV events. However, the absence of statistical evidence of an interaction with age does not support this thesis, but the age range was fairly narrow. Further, exclusion of the first 2.6 years of follow-up did not attenuate the association, arguing against an important role for baseline (sub)acute systemic disease. In addition, excluding men with prevalent CV disease did not materially change the HRs for CV risk. Nevertheless, studies addressing testosterone levels, assessed by mass spectrometry–based techniques, as predictors of CV events in relatively younger and presumably healthier men are of continued interest.

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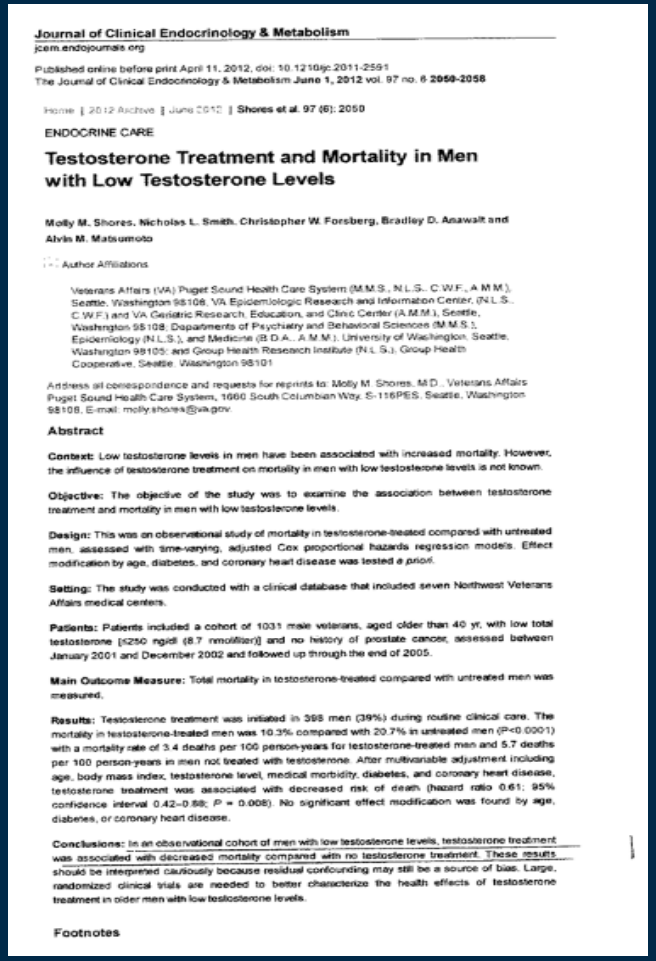
Testosterone Treatment and Mortality in Men with Low Testosterone Levels



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ENDOCRINE CARE

Testosterone Treatment and Mortality in Men with Low Testosterone Levels

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Abstract

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.

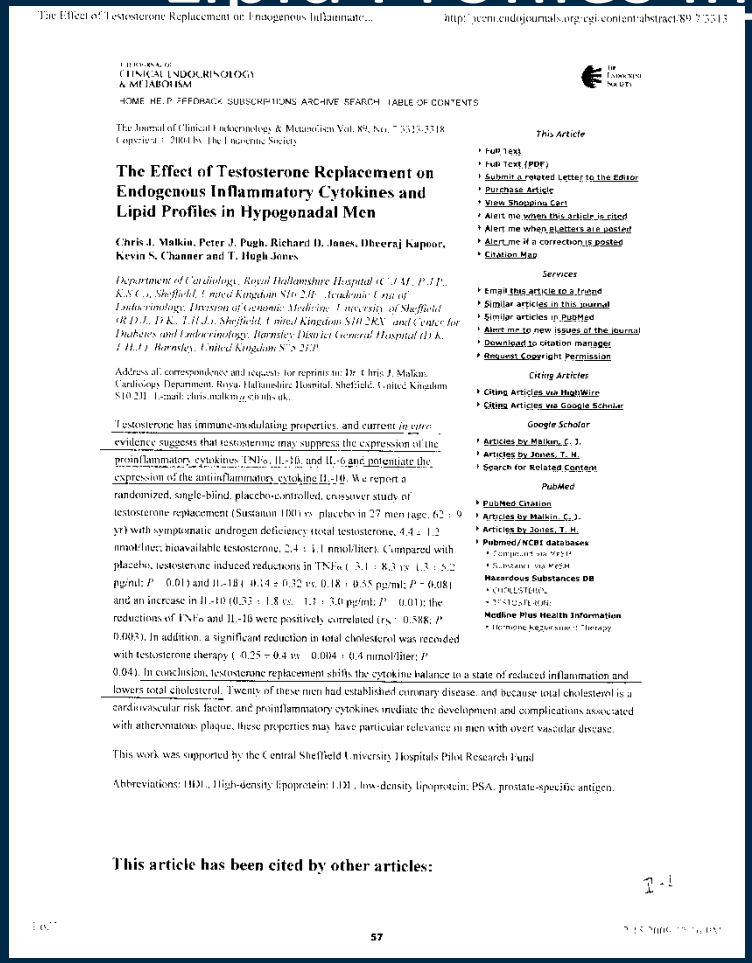
Conclusions: In an observational cohort of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment. These results should be interpreted cautiously because residual confounding may still be a source of bias. Large, randomized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

Footnotes

- In an observational cohort of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment

Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab. 2012 Jun;97(6):2050-2058.

The Effect of Testosterone Replacement on Endogenous Inflammatory Cytokines and Lipid Profiles in Hypogonadal Men



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The Effect of Testosterone Replacement on Endogenous Inflammatory Cytokines and Lipid Profiles in Hypogonadal Men

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Testosterone has immune-modulating properties, and current *in vitro* evidence suggests that testosterone may suppress the expression of the proinflammatory cytokines TNFα, IL-1β, and IL-6 and potentiate the expression of the antiinflammatory cytokine IL-10. We report a randomized, single-blind, placebo-controlled, crossover study of testosterone replacement (Sustanon 100) *vs.* placebo in 27 men (age, 62 ± 9 yr) with symptomatic androgen deficiency (total testosterone, 4.4 ± 1.2 nmol/liter; bioavailable testosterone, 2.4 ± 1.1 nmol/liter). Compared with placebo, testosterone induced reductions in TNFα (−3.1 ± 8.3 *vs.* −1.3 ± 5.2 pg/ml; $P = 0.01$) and IL-1β (−0.14 ± 0.32 *vs.* 0.18 ± 0.55 pg/ml; $P = 0.081$) and an increase in IL-10 (0.33 ± 1.8 *vs.* −1.1 ± 3.0 pg/ml; $P = 0.01$); the reductions of TNFα and IL-1β were positively correlated ($r_s = 0.588$; $P = 0.003$). In addition, a significant reduction in total cholesterol was recorded with testosterone therapy (−0.25 ± 0.4 *vs.* 0.004 ± 0.4 nmol/liter; $P = 0.04$). In conclusion, testosterone replacement shifts the cytokine balance to a state of reduced inflammation and lowers total cholesterol. Twenty of these men had established coronary disease, and because total cholesterol is a cardiovascular risk factor, and proinflammatory cytokines mediate the development and complications associated with atheromatous plaque, these properties may have particular relevance in men with overt vascular disease.

This work was supported by the Central Sheffield University Hospitals Pilot Research Fund

Abbreviations: HDL, High-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate-specific antigen.

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Malkin CJ, Pugh PJ, Jones RD, et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab. 2004 Jul;89(7):3313-3318

Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men

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Epidemiology

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

Kay-Tee Khaw, MBBChir, FRCP; Mitch Dowsett, PhD; Elizabeth Folkerd, PhD; Sheila Bingham, PhD; Nicholas Wareham, MBBS, PhD; Robert Luben, BSc; Ailsa Welch, PhD; Nicholas Day, PhD

From the Department of Public Health and Primary Care (K.-T.K., R.L., A.W., N.D.), Institute of Public Health, University of Cambridge School of Clinical Medicine, Cambridge, UK; Academic Department of Biochemistry (M.D., E.F.), Royal Marsden Hospital, London, UK; and MRC Dunn Human Nutrition Unit (S.B.) and MRC Epidemiology Unit (N.W.), Cambridge, UK.

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Received June 1, 2007; accepted September 11, 2007.

Background— The relation between endogenous testosterone concentrations and health in men is controversial.

Methods and Results— We examined the prospective relationship between endogenous testosterone concentrations and mortality due to all causes, cardiovascular disease, and cancer in a nested case-control study based on 11 606 men aged 40 to 79 years surveyed in 1993 to 1997 and followed up to 2003. Among those without prevalent cancer or cardiovascular disease, 825 men who subsequently died were compared with a control group of 1489 men still alive, matched for age and date of baseline visit. Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes (825 deaths), cardiovascular disease (369 deaths), and cancer (304 deaths). Odds ratios (95% confidence intervals) for mortality for increasing quartiles of endogenous testosterone compared with the lowest quartile were 0.75 (0.55 to 1.00), 0.62 (0.45 to 0.84), and 0.59 (0.42 to 0.85), respectively ($P<0.001$ for trend after adjustment for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, diabetes mellitus, alcohol intake, physical activity, social class, education, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin). An increase of 6 nmol/L serum testosterone (≈1 SD) was associated with a 0.81 (95% confidence interval 0.71 to 0.92, $P<0.01$) multivariable-adjusted odds ratio for mortality. Inverse relationships were also observed for deaths due to cardiovascular causes and cancer and after the exclusion of deaths that occurred in the first 2 years.

Conclusions— In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.

CLINICAL PERSPECTIVE

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Khaw KT, Dowsett M, Folkerd E, et al. 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 Dec;116(23):2694-2701.

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

IMPORTANCE Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.

OBJECTIVES To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.

DESIGN, SETTING, AND PATIENTS A retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011.

MAIN OUTCOMES AND MEASURES Primary outcome was a composite of all-cause mortality, MI, and ischemic stroke.

RESULTS Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography. Of the 1710 outcome events, 748 men died, 443 had MIs, and 519 had strokes. Of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. The absolute rate of events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI, −1.4% to 13.1%) at 3 years after coronary angiography. In Cox proportional hazards models adjusting for the presence of coronary artery disease, testosterone therapy use as a time-varying covariate was associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% CI, 1.04 to 1.58). There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, $P = .41$).

CONCLUSIONS AND RELEVANCE Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.

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Author Video Interview at jama.com

JAMA Patient Page 1872

Supplemental content at jama.com

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JAMA. 2013;310(17):1829-1836. doi:10.1001/jama.2013.280386

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Testosterone Treatment and Mortality in Men with Low Testosterone Levels

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2. Nicholas L. Smith,
3. Christopher W. Forsberg,
4. Bradley D. Anawalt and
5. Alvin M. Matsumoto

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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.

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Clinical Study

Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes

1. Vakkat Muraleedharan1,2,
2. Hazel Marsh1,
3. Dheeraj Kapoor1,
4. Kevin S Channer3,4 and
5. T Hugh Jones1,2

Abstract

Objective Men with type 2 diabetes are known to have a high prevalence of testosterone deficiency. No long-term data are available regarding testosterone and mortality in men with type 2 diabetes or any effect of testosterone replacement therapy (TRT). We report a 6-year follow-up study to examine the effect of baseline testosterone and TRT on all-cause mortality in men with type 2 diabetes and low testosterone.

Research design and methods A total of 581 men with type 2 diabetes who had testosterone levels performed between 2002 and 2005 were followed up for a mean period of 5.8±1.3 S.D. years. Mortality rates were compared between total testosterone >10.4nmol/l (300ng/dl; n=343) and testosterone ≤10.4nmol/l (n=238). The effect of TRT (as per normal clinical practise: 85.9% testosterone gel and 14.1% intramuscular testosterone undecanoate) was assessed retrospectively within the low testosterone group.

Results Mortality was increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; P=0.003) when controlled for covariates. In the Cox regression model, multivariate-adjusted hazard ratio (HR) for decreased survival was 2.02 (P=0.009, 95% CI 1.2-3.4). TRT (mean duration 41.6±20.7 months; n=64) was associated with a reduced mortality of 8.4% compared with 19.2% (P=0.002) in the untreated group (n=174). The multivariate-adjusted HR for decreased survival in the untreated group was 2.3 (95% CI 1.3-3.9, P=0.004).

Conclusions Low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.

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Epidemiology

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

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Abstract

Background— The relation between endogenous testosterone concentrations and health in men is controversial.

Methods and Results— We examined the prospective relationship between endogenous testosterone concentrations and mortality due to all causes, cardiovascular disease, and cancer in a nested case-control study based on 11 606 men aged 40 to 79 years surveyed in 1993 to 1997 and followed up to 2003. Among those without prevalent cancer or cardiovascular disease, 825 men who subsequently died were compared with a control group of 1489 men still alive, matched for age and date of baseline visit. Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes (825 deaths), cardiovascular disease (369 deaths), and cancer (304 deaths). Odds ratios (95% confidence intervals) for mortality for increasing quartiles of endogenous testosterone compared with the lowest quartile were 0.75 (0.55 to 1.00), 0.62 (0.45 to 0.84), and 0.59 (0.42 to 0.85), respectively ($P<0.001$ for trend after adjustment for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, diabetes mellitus, alcohol intake, physical activity, social class, education, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin). An increase of 6 nmol/L serum testosterone (≈1 SD) was associated with a 0.81 (95% confidence interval 0.71 to 0.92, $P<0.01$) multivariable-adjusted odds ratio for mortality. Inverse relationships were also observed for deaths due to cardiovascular causes and cancer and after the exclusion of deaths that occurred in the first 2 years.

Conclusions— In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.

Key Words:
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ENDOCRINE RESEARCH

Low Free Testosterone Predicts Mortality from Cardiovascular Disease But Not Other Causes: The Health in Men Study

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Abstract

Context: Low testosterone is associated with all-cause mortality, but the relationship with cause-specific mortality is uncertain.

Objective: Our objective was to explore associations between testosterone and its related hormones and cause-specific mortality.

Design: This was a population-based cohort study.

Setting and Participants: Demographic and clinical predictors of mortality, and testosterone, SHBG, and LH were measured from 2001–2004 in 3637 community-dwelling men aged 70–88 yr (mean, 77 yr).

Main Outcome Measure: Cause of death was obtained via electronic record linkage until December 31, 2008.

Results: During a mean follow-up period of 5.1 yr, there were 605 deaths. Of these, 207 [34.2%; 95% confidence interval (CI) = 30.4–38.1%] were due to cardiovascular disease (CVD), 231 to cancer (38.2%; 95% CI = 34.3–42.1%), 130 to respiratory diseases (21.5%; 95% CI = 18.2–24.8%), and 76 to other causes (12.6%; 95% CI = 9.9–15.2%). There were 39 deaths attributable to both cancer and respiratory diseases. Lower free testosterone (hazard ratio = 1.62; 95% CI = 1.20–2.19, for 100 *vs.* 280 pmol/liter), and higher SHBG and LH levels were associated with all-cause mortality. In cause-specific analyses, lower free testosterone (sub-hazard ratio = 1.71; 95% CI = 1.12–2.62, for 100 *vs.* 280 pmol/liter) and higher LH predicted CVD mortality, while higher SHBG predicted non-CVD mortality. Higher total testosterone and free testosterone levels (sub-hazard ratio = 1.96; 95% CI = 1.14–3.36, for 400 *vs.* 280 pmol/liter) were associated with mortality from lung cancer.

Conclusions: Low testosterone predicts mortality from CVD but is not associated with death from other causes. Prevention of androgen deficiency might improve cardiovascular outcomes but is unlikely to affect longevity otherwise.

Since time immemorial, the ability to resist the effects of aging and prolong life has been a universal human desire. For millennia, alchemists sought in vain for an elixir of life, while more recently, 19th-century physicians attempted to produce a rejuvenating tonic from animal testicular extracts (1).

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REVIEW

Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study

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Abstract

Objective To verify whether hypogonadism represents a risk factor for cardiovascular (CV) morbidity and mortality and to verify whether testosterone replacement therapy (TRT) improves CV parameters in subjects with known CV diseases (CVDs).

Design Meta-analysis.

Methods An extensive Medline search was performed using the following words 'testosterone, CVD, and males'. The search was restricted to data from January 1, 1969, up to January 1, 2011.

Results Of the 1178 retrieved articles, 70 were included in the study. Among cross-sectional studies, patients with CVD have significantly lower testosterone and higher 17-β estradiol (E_2) levels. Conversely, no difference was observed for DHEAS. The association between low testosterone and high E_2 levels with CVD was confirmed in a logistic regression model, after adjusting for age and body mass index (hazard ratio (HR)=0.763 (0.744–0.783) and HR=1.015 (1.014–1.017), respectively, for each increment of total testosterone and E_2 levels; both $P<0.0001$). Longitudinal studies showed that baseline testosterone level was significantly lower among patients with incident overall- and CV-related mortality, in comparison with controls. Conversely, we did not observe any difference in the baseline testosterone and E_2 levels between case and controls for incident CVD. Finally, TRT was positively associated with a significant increase in treadmill test duration and time to 1 mm ST segment depression.

Conclusions Lower testosterone and higher E_2 levels correlate with increased risk of CVD and CV mortality. TRT in hypogonadism moderates metabolic components associated with CV risk. Whether low testosterone is just an association with CV risk, or an actual cause-effect relationship, awaits further studies.

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SPECIAL FEATURES

Endogenous Testosterone and Mortality in Men: A Systematic Review and Meta-Analysis

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Abstract

Context: Low testosterone levels have been associated with outcomes that reduce survival in men.

Objective: Our objective was to perform a systematic review and meta-analysis of published studies to evaluate the association between endogenous testosterone and mortality.

Data Sources: Data sources included MEDLINE (1966 to December 2010), EMBASE (1988 to December 2010), and reference lists.

Study Selection: Eligible studies were published English-language observational studies of men that reported the association between endogenous testosterone and all-cause or cardiovascular disease (CVD) mortality. A two-stage process was used for study selection. 1) Working independently and in duplicate, reviewers screened a subset (10%) of abstracts. Results indicated 96% agreement, and thereafter, abstract screening was conducted in singlicate. 2) All full-text publications were reviewed independently and in duplicate for eligibility.

Data Extraction: Reviewers working independently and in duplicate determined methodological quality of studies and extracted descriptive, quality, and outcome data.

Data Synthesis: Of 820 studies identified, 21 were included in the systematic review, and 12 were eligible for meta-analysis [n = 11 studies of all-cause mortality (16,184 subjects); n = 7 studies of CVD mortality (11,831 subjects)]. Subject mean age and testosterone level were 61 yr and 487 ng/dl, respectively, and mean follow-up time was 9.7 yr. Between-study heterogeneity was observed among studies of all-cause ($P < .001$) and CVD mortality ($P = 0.06$), limiting the ability to provide valid summary estimates. Heterogeneity in all-cause mortality (higher relative risks) was observed in studies that included older subjects ($P = 0.020$), reported lower testosterone levels ($P = 0.018$), followed subjects for a shorter time period ($P = 0.010$), and sampled blood throughout the day ($P = 0.030$).

Conclusion: Low endogenous testosterone levels are associated with increased risk of all-cause and CVD death in community-based studies of men, but considerable between-study heterogeneity, which was related to study and subject characteristics, suggests that effects are driven by

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Low serum testosterone, arterial stiffness and mortality in male haemodialysis patients

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Abstract

Background. In the general population, accumulating data support a link between low testosterone levels and mortality by all causes, but especially by cardiovascular disease (CVD). Also, accelerated arterial stiffness has been recognized as an important cardiovascular risk factor. Here, we explored the association between testosterone levels and risk of death in male haemodialysis (HD) patients, whose arterial system is characterized by generalized stiffening.

Methods. In this three-centre prospective observational study, 111 male HD patients after completion of baseline assessment, including measurement of male sex hormones and pulse wave velocity (PWV), were followed up for CVD and all-cause mortality.

Results. Of the 111 patients studied, 54 were found with and 57 without testosterone deficiency, defined as testosterone levels <8 nmol/L. During a median follow-up period of 37 months, 49 deaths occurred, 28 (57%) of which were caused by CVD. Testosterone deficiency patients had increased CVD and all-cause mortality [crude hazard ratio: 3.14 [95% confidence interval (CI), 1.21-8.16] and 3.09 (95% CI, 1.53-6.25), respectively], even after adjustment for age, body mass index, serum albumin and C-reactive protein, prevalent CVD and HD vintage. The association of testosterone with CVD mortality, but not with all-cause mortality, was lost after adjusting for PWV, an index of arterial stiffness. Testosterone levels were inversely related to PWV ($r = -0.441$; $P < 0.001$).

Conclusion. We showed that testosterone deficiency in male HD patients is associated with increased CVD and all-cause mortality and that increased arterial stiffness may be a possible mechanism explaining this association.

Key words cardiovascular disease male hypogonadism mortality pulse wave velocity testosterone

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Testosterone deficiency syndrome (TDS) and the heart

This editorial refers to 'Low testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79'†, by R. Haring *et al.*, on page 1494

A low testosterone [hypogonadism or testosterone deficiency syndrome (TDS)] may be present in 30% of men and present in a number of different ways.[1] One of the problems in detecting TDS is the lack of awareness of its existence amongst the general medical community including cardiologists. In addition, the signs and symptoms may unhelpfully not be specific to TDS (*Table 1*). With the accumulating evidence of an association between TDS and cardiovascular co-morbidities and an increased risk of mortality when compared with men with normal testosterone levels, there is a compelling need to screen men at risk of low testosterone levels.[2]

View this table:
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Table 1
Signs and symptoms indicative of TDS

There is increasing evidence that TDS is associated with all-cause mortality and in particular cardiovascular death. Haring and colleagues add to the growing evidence of the importance of a link in a prospective population-based study (mean follow-up 7.2 years) showing in a sample of men aged 20–79 years that a testosterone level <8.7 nmol/L (250 ng/dL) doubled the risk of all-cause mortality independently of age, waist circumference, cigarette smoking, excess alcohol, and decreased physical activity.[3]

A recent observational prospective study from Florence investigated the relationship between low total testosterone levels in 1687 men with erectile dysfunction (ED) and fatal or non-fatal major adverse cardiovascular events (MACEs).[4] Men with a testosterone <8 nmol/L (230 ng/dL), after adjusting for age and chronic diseases, at a mean follow-up of 4.3 ± 2.6 years had a significantly increased incidence of fatal MACEs [hazard ratio (HR) = 7.1 95% confidence interval (CI) (1.8–28.6), P <0.001). In the 6 year CHIANTI study, the same unit suggested that declining testosterone levels were a strong independent predictor of mortality in men.[5]

The EPIC-Norfolk (European Prospective Investigation into Cancer in Norfolk) study performed in the UK was a nested case-control study designed to evaluate any association between testosterone levels and all-cause cardiovascular disease (CVD) and death from cancer.[6] During follow-up, 1489 men lived from entry between 1993 and 1997 to 2003 [illegible] vidence of

and controls were matched for age and date of baseline visit. Total testosterone concentrations at baseline were found to be inversely related to all-cause mortality (n = 825), CVD deaths (n = 369), and deaths from cancer (n = 304). After adjusting for confounding variables, an increase of 6 nmol/L (173 ng/dL) in serum testosterone was associated with a 14% decrease in death rate regardless of age (above or below 65 years of age). Men in the highest testosterone quartile had a 30% lower risk of death compared with those in the lowest. As occult illness at entry may have distorted the findings, in an additional analysis all those who died in the first 2 years of the study were excluded and the findings were unchanged. The study can be criticized for only including a single testosterone sample and not free or bioavailable testosterone which binds to the androgen receptor, but single measures are believed to be accurate for population studies.[7]

The Rancho-Bernardo area study prospectively followed up 794 men aged 50–91 years, evaluating the link between testosterone levels and all-cause mortality over a 20 year period.[8] Men in the lowest quartile of testosterone levels were 40% more likely to die than those in the highest quartile—mainly from CVD and respiratory disease. These findings were independent of age, obesity, hyperlipidaemia, and lifestyle, and were in line with the Norfolk study. The authors concluded that low testosterone levels (<12.5 nmol/L) could be a predictive marker for men at high risk of CVD.

In a retrospective study of 858 male veterans over 40 years of age without a diagnosis of prostate cancer, ~20% had total testosterone levels <10.4 nmol/L (300 ng/dL) and the survival rate decreased, as did the testosterone level (HR 1.88: 95% CI 1.34–2.63; P <0.001) after adjustments for clinical co-variables over an 8 year period.[9]

Whilst some cross-sectional and prospective studies have found no significant relationship between testosterone levels and CVD, the evidence overall, particularly from the large recent studies, does point to testosterone having a pathogenic role in CVD.[2,10] As TDS is associated with type 2 diabetes, metabolic syndrome, visceral fat accumulation, abnormalities of coagulation, inflammatory cytokines, and dyslipidaemia, its importance is clearly integral to other CVD risk factors,[2,10,11]

Whilst there is no evidence that testosterone replacement reduces CVD risk or all-cause mortality (randomized trials are needed), we have good evidence that replacement may be symptomatically beneficial in hypogonadic men with angina or heart failure.[12,13] Importantly, there is no evidence that replacement increases CVD risk.

In practice consider measuring testosterone (before 11 a.m. to avoid diurnal variation) in those who appear symptomatic or have a chronic illness or erectile dysfunction.[14] Total testosterone levels <8 nmol/L (2.31 ng/mL) or free testosterone (not bound to sex hormone-binding globulin and non-bioavailable, therefore a more accurate but more expensive measurement) <180 pmol/L (52 pg/mL) require replacement therapy.[15] Total levels >12 nmol/L (3.46 ng/mL) or free testosterone levels >250 pmol/L (72 pg/mL) do not, and a trial of therapy can be considered in between 8 and 12 nmol/L total testosterone. Though the link between testosterone replacement and prostate cancer is not proven, monitoring prostate-specific antigen is currently advised and urological advice sought where appropriate. Regular checks on liver function (toxicity is very rare) and polycythaemia are also advised and caution advocated in men with sleep apnoea which may worsen.[14] Oligospermia or azoospermia which may not be reversible can occur, so it is important to check men who wish to preserve their fertility. Monitoring response to replacement therapy should be at 3–6 month intervals.

TDS can symptomatically benefit from replacement therapy which is safe

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Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20–79

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Abstract

Aims Although the association of low serum testosterone levels with mortality has gained strength in recent research, there are few population-based studies on this issue. This study examined whether low serum testosterone levels are a risk factor for all-cause or cause-specific mortality in a population-based sample of men aged 20–79.

Methods and results We used data from 1954 men recruited for the prospective population-based Study of Health in Pomerania, with measured serum testosterone levels at baseline and 195 deaths during an average 7.2-year follow-up. A total serum testosterone level of less than 8.7 nmol/L (250 ng/dL) was classified as low. The relationships of low serum testosterone levels with all-cause and cause-specific mortality were analysed by Cox proportional hazards regression models. Men with low serum testosterone levels had a significantly higher mortality from all causes than men with higher serum testosterone levels (HR 2.24; 95% CI 1.41–3.57). After adjusting for waist circumference, smoking habits, high-risk alcohol use, physical activity, renal insufficiency, and levels of dehydroepiandrosterone sulfate, low serum testosterone levels continued to be associated with increased mortality (HR 2.32; 95% CI 1.38–3.89). In cause-specific analyses, low serum testosterone levels predicted increased risk of death from cardiovascular disease (CVD) (HR 2.56; 95% CI 1.15–6.52) and cancer (HR 3.46; 95% CI 1.68–6.68), but not from respiratory diseases or other causes.

Conclusion Low serum testosterone levels were associated with an increased risk of all-cause mortality independent of numerous risk factors. As serum testosterone levels are inversely related to mortality due to CVD and cancer, it may be used as a predictive marker.

Key words Testosterone All-cause and CVD mortality Men Study of Health in Pomerania (SHIP)

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ENDOCRINE CARE

Low Serum Testosterone and Mortality in Older Men

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Abstract

Context: Declining testosterone levels in elderly men are thought to underlie many of the symptoms and diseases of aging; however, studies demonstrating associations of low testosterone with clinical outcomes are few.

Objective: The objective of the study was to examine the association of endogenous testosterone levels with mortality in older community-dwelling men.

Design, Setting, and Participants: This was a prospective, population-based study of 794 men, aged 50–91 (median 73.6) yr who had serum testosterone measurements at baseline (1984–1987) and were followed for mortality through July 2004.

Main Outcome Measure: All-cause mortality by serum testosterone level was measured.

Results: During an average 11.8-yr follow-up, 538 deaths occurred. Men whose total testosterone levels were in the lowest quartile (<241 ng/dl) were 40% [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14–1.71] more likely to die than those with higher levels, independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results. The low testosterone-mortality association was also independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease but was attenuated by adjustment for IL-6 and C-reactive protein. In cause-specific analyses, low testosterone predicted increased risk of cardiovascular (HR 1.38; 95% CI 1.02–1.85) and respiratory disease (HR 2.29; 95% CI 1.25–4.20) mortality but was not significantly related to cancer death (HR 1.34; 95% CI 0.89–2.00). Results were similar for bioavailable testosterone.

Conclusions: Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple risk factors and several preexisting health conditions.

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Articles citing this article

Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes

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Original Articles

Testosterone Supplementation in Heart Failure

A Meta-Analysis

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Abstract

Background—Low testosterone is an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with heart failure (HF). We sought to determine whether testosterone therapy improves exercise capacity in patients with stable chronic HF.

Methods and Results—We searched Medline, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (1980–2010). Eligible studies included randomized controlled trials (RCTs) reporting the effects of testosterone on exercise capacity in patients with HF. Reviewers determined the methodological quality of studies and collected descriptive, quality, and outcome data. Four trials (n=198; men, 84%; mean age, 67 years) were identified that reported the 6-minute walk test (2 RCTs), incremental shuttle walk test (2 RCTs), or peak oxygen consumption (2 RCTs) to assess exercise capacity after up to 52 weeks of treatment. Testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo. The mean increase in the 6-minute walk test, incremental shuttle walk test, and peak oxygen consumption between the testosterone and placebo groups was 54.0 m (95% CI, 43.0–65.0 m), 46.7 m (95% CI, 12.6–80.9 m), and 2.70 mL/kg per min (95% CI, 2.68–2.72 mL/kg per min), respectively. Testosterone therapy was associated with a significant increase in exercise capacity as measured by units of pooled SDs (net effect, 0.52 SD; 95% CI, 0.10–0.94 SD). No significant adverse cardiovascular events were noted.

Conclusions—Given the unmet clinical needs, testosterone appears to be a promising therapy to improve functional capacity in patients with HF. Adequately powered RCTs are required to assess the benefits of testosterone in this high-risk population with regard to quality of life, clinical events, and safety.

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Plasma Total Testosterone and Incident Cardiovascular Events in Hypertensive Patients

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Abstract

BACKGROUND Androgen deficiency confers an independent risk for cardiovascular events and total mortality. Hypertension, a major contributory factor to the development of cardiovascular disease, has also been associated with increased prevalence of low testosterone. We investigated whether low androgen concentration predicts incident major adverse cardiovascular events (MACE) in middle-aged nondiabetic hypertensive patients without clinical atherosclerosis.

METHODS MACE in relation to total testosterone (TT) were analyzed with proportional hazards models in 228 male patients (mean age 56 years).

RESULTS During a mean follow-up of 44 months, 19 of 228 participants (8.3%) experienced a MACE. Compared to patients who did not experience MACE, hypertensive subjects who developed MACE had lower TT concentration (3.9±0.7ng/ml vs. 4.6±1.5ng/ml, $P < 0.01$) and a higher prevalence of hypogonadism (36% vs. 16%, $P < 0.05$). Subjects in the lowest TT tertile (<4.0ng/ml) had a statistically significant higher risk of MACE compared to those in the highest tertile (>4.9ng/ml) in multivariate Cox models adjusted for age, systolic blood pressure, and risk factors (all $P < 0.05$). A TT plasma level of 5.04ng/ml was associated with a negative predictive value (ability to "rule out" MACE) of 97.2%. Addition of TT to standard risk factors model yielded a net reclassification improvement of 38.8 % ($P < 0.05$).

CONCLUSIONS Our results show that low plasma testosterone is associated with increased risk for a MACE in hypertensive patients. Low endogenous androgen concentration improves risk prediction when added to standard risk factors and may represent a valuable biomarker of prediction of cardiovascular disease risk in these patients.

Key words androgen deficiency blood pressure hypertension major adverse cardiovascular events risk prediction total testosterone.

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Low free testosterone is associated with heart failure mortality in older men referred for coronary angiography

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Abstract

Aims Accumulating evidence suggests that androgen deficiency is associated with cardiovascular disease. We aimed at evaluating whether total testosterone (TT) and free testosterone (FT) are associated with specific cardiovascular events.

Methods and results We measured TT and sex-hormone-binding globulin levels in 2078 men who were routinely referred for coronary angiography between 1997 and 2000. Free testosterone was calculated according to Vermeulen. Main outcome measures were Cox proportional hazard ratios (HRs) for sudden cardiac death, fatal myocardial infarction, death from congestive heart failure (CHF), as well as other cardiac deaths according to quartiles of TT and FT. The median follow-up time was 7.7 years. Multivariable adjusted HRs (with 95% confidence intervals) in the fourth compared with the first FT quartile and per 1 SD increase in FT for CHF mortality were 0.38 (0.17–0.87) and 0.37 (0.15–0.89), respectively. We observed no independent significant association of FT with sudden cardiac death, fatal myocardial infarction, or other cardiac death. There was no independent association of TT levels with cardiovascular events or cardiac disease.

Conclusion Low levels of FT are independently associated with increased CHF mortality.

Key words Free testosterone Congestive heart failure

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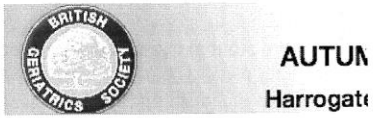

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Serum testosterone but not leptin predicts mortality in elderly men

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SIR—In men ageing is associated with a gradual progressive decline of total serum testosterone concentration [1–5]. A substantial proportion of older men, ranging from 20% in 60 years old to 50% in 80 years old, have testosterone concentrations below the normal range of younger men [4]. Low testosterone associates with occurrence of various cardiovascular risk factors [6, 7], and most epidemiological studies suggest that association of testosterone with coronary artery disease is either favourable or neutral [8]. Some studies have suggested that leptin is also an independent predictor of cardiovascular morbidity and mortality [9–11], but this association has not been seen in all studies [12]. After adjustment for age, concentration of testosterone in serum is inversely correlated with intima–media thickness of the carotid artery, whereas no such association is seen between serum leptin and carotid artery thickness [12]. Thus, endogenous testosterone may have a protective role in the development of atherosclerosis in ageing men, but information on associations between testosterone and mortality or coronary heart disease is lacking.

We performed a longitudinal 10-year study to clarify the association of endogenous testosterone and leptin with all-cause mortality in ageing men. The results suggest an association between low endogenous testosterone concentration and mortality in elderly men.

Subjects and methods

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CLINICAL STUDY

Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes

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Abstract

Objective Men with type 2 diabetes are known to have a high prevalence of testosterone deficiency. No long-term data are available regarding testosterone and mortality in men with type 2 diabetes or any effect of testosterone replacement therapy (TRT). We report a 6-year follow-up study to examine the effect of baseline testosterone and TRT on all-cause mortality in men with type 2 diabetes and low testosterone.

Research design and methods A total of 581 men with type 2 diabetes who had testosterone levels performed between 2002 and 2005 were followed up for a mean period of 5.8±1.3 S.D. years. Mortality rates were compared between total testosterone >10.4nmol/l (300ng/dl; n=343) and testosterone ≤10.4nmol/l (n=238). The effect of TRT (as per normal clinical practise: 85.9% testosterone gel and 14.1% intramuscular testosterone undecanoate) was assessed retrospectively within the low testosterone group.

Results Mortality was increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; P=0.003) when controlled for covariates. In the Cox regression model, multivariate-adjusted hazard ratio (HR) for decreased survival was 2.02 (P=0.009, 95% CI 1.2–3.4). TRT (mean duration 41.6±20.7 months; n=64) was associated with a reduced mortality of 8.4% compared with 19.2% (P=0.002) in the untreated group (n=174). The multivariate-adjusted HR for decreased survival in the untreated group was 2.3 (95% CI 1.3–3.9, P=0.004).

Conclusions Low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.

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Original Investigation

Relationship Between Low Levels of Anabolic Hormones and 6-Year Mortality in Older Men

The Aging in the Chianti Area (InCHIANTI) Study

Marcello Maggio, MD; Fulvio Lauretani, MD; Gian Paolo Ceda, MD; Stefania Bandinelli, MD; Shari M. Ling, MD; E. Jeffrey Metter, MD; Andrea Artoni, MD; Laura Carassale, MD; Anna Cazzato, MD; Graziano Ceresini, MD; Jack M. Guralnik, MD; Shehzad Basaria, MD; Giorgio Valenti, MD; Luigi Ferrucci, MD, PhD

Arch Intern Med. 2007;167(20):2249-2254.

Background Aging in men is characterized by a progressive decline in levels of anabolic hormones, such as testosterone, insulinlike growth factor 1 (IGF-1), and dehydroepiandrosterone sulfate (DHEA-S). We hypothesized that in older men a parallel age-associated decline in bioavailable testosterone, IGF-1, and DHEA-S secretion is associated with higher mortality independent of potential confounders.

Methods Testosterone, IGF-1, DHEA-S, and demographic features were evaluated in a representative sample of 410 men 65 years and older enrolled in the Aging in the Chianti Area (InCHIANTI) study. A total of 126 men died during the 6-year follow-up. Thresholds for lowest-quartile definitions were 70 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) for bioavailable testosterone, 63.9 ng/mL (to convert to nanomoles per liter, multiply by 0.131) for total IGF-1, and 50 µg/dL (to convert to micromoles per liter, multiply by 0.027) for DHEA-S. Men were divided into 4 groups: no hormone in the lowest quartile (reference) and 1, 2, and 3 hormones in the lowest quartiles. Kaplan-Meier survival and Cox proportional hazards models adjusted for confounders were used in the analysis.

Results Compared with men with levels of all 3 hormones above the lowest quartiles, having 1, 2, and 3 dysregulated hormones was associated with hazard ratios for mortality of 1.47 (95% confidence interval [CI], 0.88-2.44), 1.85 (95% CI, 1.04-3.30), and 2.29 (95% CI, 1.12-4.68), respectively (test for trend, P <.001). In the fully adjusted analysis, only men with 3 anabolic hormone deficiencies had a significant increase in mortality (hazard ratio, 2.44; 95% CI, 1.09-5.46 (test for trend, P <.001).

Conclusions Age-associated decline in anabolic hormone levels is a strong independent predictor of mortality in older men. Having multiple hormonal deficiencies rather than a deficiency in a single anabolic hormone is a robust biomarker of health status in older persons.

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Low Serum Testosterone and Mortality in Older Men

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Context: Declining testosterone levels in elderly men are thought to underlie many of the symptoms and diseases of aging; however, studies demonstrating associations of low testosterone with clinical outcomes are few.

Objective: The objective of the study was to examine the association of endogenous testosterone levels with mortality in older community-dwelling men.

Design, Setting, and Participants: This was a prospective, population-based study of 794 men, aged 50–91 (median 73.6) yr who had serum testosterone measurements at baseline (1984–1987) and were followed for mortality through July 2004.

Main Outcome Measure: All-cause mortality by serum testosterone level was measured.

Results: During an average 11.8-yr follow-up, 538 deaths occurred. Men whose total testosterone levels were in the lowest quartile (<241 ng/dl) were 40% [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14–1.71] more likely to die than those with higher levels, independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results. The low testosterone-mortality association was also independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease but was attenuated by adjustment for IL-6 and C-reactive protein. In cause-specific analyses, low testosterone predicted increased risk of cardiovascular (HR 1.38; 95% CI 1.02–1.85) and respiratory disease (HR 2.29; 95% CI 1.25–4.20) mortality but was not significantly related to cancer death (HR 1.34; 95% CI 0.89–2.00). Results were similar for bioavailable testosterone.

Conclusions: Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple risk factors and several preexisting health conditions.

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Perspectives

Welcoming low testosterone as a cardiovascular risk factor

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Male hypogonadism now has a new spectrum of complications. They are mainly cardiometabolic in nature. Low serum testosterone levels are a risk factor for diabetes, metabolic syndrome, inflammation and dyslipidemia. These metabolic and inflammatory complications are not without consequences. Recent studies have shown low serum testosterone levels to be an independent risk factor of cardiovascular and all-cause mortality. It is time to welcome low serum testosterone levels as a cardiovascular risk factor.

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Keywords: hypogonadism; metabolic syndrome; diabetes; inflammation

Testosterone is the predominant sex hormone in man. A young man produces 3–10 mg of testosterone daily that results in serum levels of 300–1000 ng per 100 ml. The traditional consequences of male hypogonadism are well known. These include decreased libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, changes in mood and energy, osteoporosis and decreased sexual hair.[1] However, for the past two decades, many studies have found an association between low serum testosterone levels and various cardiovascular (CV) risk factors. In addition, some epidemiological studies have also linked low testosterone levels with CV and all-cause mortality. In this review, we will briefly touch upon the various CV risk factors that have been linked to low serum testosterone in men.

Diabetes and metabolic syndrome

Low testosterone levels have been associated with diabetes and metabolic syndrome. Epidemiological studies have reported that low testosterone levels are an independent risk factor for type-2 diabetes.[2] Interestingly, concentrations of free and bioavailable testosterone even in the low-normal range are associated with diabetes, after adjusting for adiposity.[3] Similarly, low total testosterone levels independently predict development of the metabolic syndrome in middle-aged men.[4] Interventional trials have shown that testosterone administration results in an increased glucose uptake by the muscles, thereby improving insulin sensitivity.[5] One study even showed an improvement in HbA1c in hypogonadal men with type-2 diabetes who received testosterone.[6] Another study showed that testosterone replacement inhibits incorporation of triglycerides in visceral fat (which is the most active depot metabolically and contributes to insulin resistance).[7] In addition, androgen deprivation in men with prostate cancer is associated with hyperglycemia and metabolic syndrome,[8,9] and the degree of hyperglycemia is directly related to the duration of castration.[10] Thus, even low-normal levels of testosterone appear to be a risk factor for metabolic dysregulation.

Hyperlipidemia and inflammation

In contrast to the belief of many physicians that androgen administration leads to an adverse lipid profile, research shows that physiological testosterone replacement is at least neutral (if not beneficial) to lipids. Hence, it should be differentiated from non-aromatizable androgens that do result in harm-

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ful lipid profile by lowering high-density lipoprotein. Epidemiological data suggest that testosterone levels are associated negatively with total cholesterol, low-density lipoprotein cholesterol and triglycerides, and positively with high-density lipoprotein cholesterol.[11] Trials of testosterone replacement have shown an improvement in lipid profile.[12] Similarly, there are reports of inverse associations between inflammatory cytokines and testosterone,[13] and a reduction in these cytokines is seen with testosterone replacement.[12] Furthermore, inverse associations have been found between testosterone and plasminogen activator inhibitor I, fibrinogen and factor VII.[14]

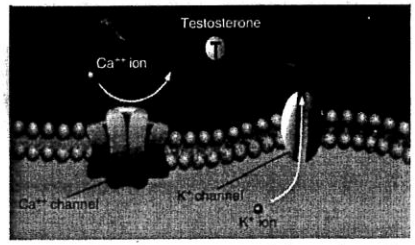

Figure 1 Action of testosterone on calcium and potassium channels.

Atherosclerosis

Studies show that low testosterone levels are associated with atherosclerosis in all major vessels. Animal experiments have shown that testosterone inhibits plaque development in rabbits and rodents fed a high-fat diet.[15] It was Phillips *et al.*[16] who first reported an inverse relationship between low total and free testosterone levels and angiographically proven coronary artery disease after adjusting for age and adiposity. A recent study confirmed these findings, showing that men with coronary artery disease had lower levels of testosterone than controls and that testosterone levels were inversely correlated to the degree of coronary atherosclerosis.[17] In the Rotterdam study, the association between total and bioavailable testosterone and aortic atherosclerosis was evaluated in 504 nonsmoking men aged ⩾55 years.[14] They found that men in the highest tertile had a risk reduction of 60–80% of severe aortic atherosclerosis after controlling for age and CV risk factors. Another prospective study of elderly men (mean age 77 years) showed free testosterone to be inversely related to the progression of intima–media thickness of the common carotid artery over 4 years.[18] Furthermore, men in the lowest tertile of testosterone experienced more progression.

Vascular tone and endothelial function

The vascular system is a target of androgen action and current evidence suggests that androgens are beneficial to vasculature. Older studies conducted more than six decades ago showed that testosterone replacement relieved symptoms of angina and peripheral vascular disease.[19] Similarly, population studies have shown that systolic and diastolic blood pressures are inversely correlated with testosterone.[20] Recent animal studies show that acute treatment with testosterone results in dilatation of the coronary and pulmonary arteries.[21] In humans, transdermal testosterone therapy improves exercise-induced myocardial ischemia (measured as time to ST depression) during an exercise stress test in men with stable angina,[22] with men having the lowest baseline testosterone levels benefitting the most. A recent study using oral testosterone in hypogonadal men with coronary artery disease showed increased myocardial perfusion.[23] These vasodilatory effects of testosterone are reflected by the fact that men with prostate cancer undergoing androgen deprivation therapy experience arterial stiffness.[24] It is believed that testosterone causes both endothelium-dependent and endothelium-independent vasodilation. The former is achieved by an increased release of nitric oxide from endothelium, whereas the latter by blocking of calcium channels and/or opening of potassium channels[25] (Figure 1). Recent studies also suggest a beneficial role for testosterone in endothelial regeneration.[26] Testosterone replacement in hypogonadal men results in an increase in the number of circulating endothelial progenitor cells.[27] This increase is androgen receptor mediated (not a result of rise in estrogen levels) as this event is abolished by androgen receptor antagonists.[28]

Mortality

Recent population studies have shown that low serum testosterone levels are associated with both CV and all-cause mortality. A retrospective study of male veterans showed that low testosterone was associated with increased mortality.[29] A prospective study of 794 men, aged 50–91 years, looked at the relationship of testosterone with all-cause mortality over two decades.[30] Men with total testosterone levels in the lowest quartile (<241 ng per 100 ml) were 40% more likely to die than men with higher androgen levels, independent of age, adiposity, lipids, adipokines and lifestyle. In cause-specific analyses, low testosterone predicted increased risk

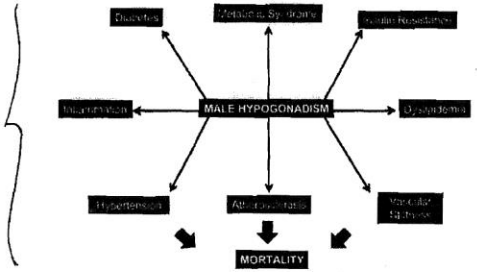

Figure 2 New spectrum of CV complications of low testosterone levels. CV, cardiovascular.

of mortality due to CV and respiratory disease. In a recent study, Khaw *et al.*[31] conducted a nested case–control study to determine the association of endogenous serum testosterone with all-cause, CV and cancer-related mortality. The authors compared 825 men who did not have any CV disease or cancer at baseline but died during the course of follow-up, with 1489 men who were still alive. The cases and controls were matched for age and date of baseline visit. The authors found that baseline testosterone levels were inversely related to deaths due to all cause, CV disease and malignancy. This protective effect of testosterone increased with increasing quartiles such that men in the highest quartile had 30% lower risk of death compared with those in the lowest quartile. Similarly, men undergoing androgen deprivation therapy for prostate cancer are also at risk of increased CV mortality compared with men not undergoing castration.[32]

Conclusion

This review shows that ample evidence has accumulated through epidemiological studies and small clinical trials showing that low androgen levels are associated with numerous CV risk factors and mortality (Figure 2). In addition to traditional CV risk factors, novel risk factors are also inversely related to testosterone levels. Indeed, a recent study showed that low testosterone levels increase oxidative stress in men and testosterone replacement reverses this pathology.[33] Similarly, the effect of testosterone treatment in men with chronic heart failure is also being explored.[34] Now what we need are long-term, double-blind, randomized, placebo-controlled trials of androgen replacement in men with low testosterone levels and evaluate its effect on CV risk factors, CV mortality and all-cause mortality. What we need is a Men's Health Initiative study and the federal funding agencies should be open to this kind of trial. In the meantime, we should consider welcoming low testosterone as a new CV risk factor in men.

Conflict of interest

The authors declare no conflict of interest.

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Editorial

Testosterone Making an Entry Into the Cardiometabolic World

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Key Words: Editorials • epidemiology • hormones • men • testosterone

Testosterone, the predominant sex hormone in men, is produced by the testes under stimulation by the gonadotrophs in the pituitary, which in turn are controlled by gonadotropin-releasing hormone neurons in the hypothalamus. A young adult man generally produces 3 to 10 mg of testosterone daily, which translates into serum values of 300 to 1000 ng/dL. The consequences of classical male hypogonadism (primary or secondary) have been long known to physicians and patients alike and include decreased libido, erectile dysfunction, osteoporosis, reduced sexual hair, and changes in body habitus. Recently, we have come to appreciate that reductions in serum testosterone resulting from aging or chronic disease have signs and symptoms similar to those seen in classical male hypogonadism, along with increased fat mass, decreased lean body mass, decreased muscle strength, and diminished quality of

life.[1] During the past decade, reports have been trickling in, mainly from laboratory and epidemiological studies (and a few clinical studies), linking differences in serum testosterone levels to various cardiovascular risk factors and also directly to cardiovascular disease and death. The article by Khaw et al[2] in this issue of *Circulation* is another link to this growing chain.

Article p 2694

Thirteen years ago, Phillips et al[3] reported that low total and free testosterone levels were inversely linked to coronary artery disease, even after adjusting for age and adiposity. This observation still holds true, as was recently supported by a study showing that men with angiographically proven coronary artery disease had lower levels of testosterone than those of controls.[4] Furthermore, testosterone levels were negatively correlated to the degree of coronary involvement. A few population-based studies have been published that relate low serum testosterone level with risk of death. A study of male veterans showed that low testosterone was associated with increased risk of death[5]; however, it was a retrospective study, and the subjects were a clinic-based Veterans Administration population, who tend to have greater medical morbidity, rather than healthy men living in the community. Recently, a prospective population-based study of 794 men, 50 to 91 years of age, in the Rancho Bernardo community, looked at the relationship of testosterone with all-cause death over the subsequent 2 decades.[6] The authors found that men whose total testosterone levels were in the lowest quartile, defined as <241 ng/dL, were 40% more likely to die than were men with higher androgen levels. These findings were independent of age, adiposity, lipids, adipokines, and lifestyle. In cause-specific analyses, low testosterone predicted increased risk of death due to cardiovascular and respiratory disease. The findings of this study are not surprising given the fact that low testosterone is independently associated with many of the individual risk factors for heart disease. For example, testosterone levels are inversely related to fat mass in men.[7] Indeed, men undergoing androgen deprivation for the treatment of prostate cancer have higher body mass index and fat mass than age and disease-matched controls.[8] This role of fat mass regulation by androgens is further supported by the fact that testosterone administration decreases adiposity in men.[9] Because fat mass is an independent predictor of cardiovascular death, it seems that testosterone is an important player in regulating this cardiovascular risk.

In addition to body mass index and fat mass, testosterone has been linked to other cardiovascular risk factors. The vascular system seems to be an important target of androgen action, and current evidence suggests that androgens are beneficial to the vascular system. Older clinical trials, though not as rigorously conducted, showed that testosterone replacement relieved symptoms of angina and peripheral vascular disease.[10] Almost half a century later, experimental studies showed that acute treatment with testosterone results in dilatation of the coronary arteries in animals.[11] Subsequently, a clinical trial showed that transdermal testosterone therapy improved exercise-induced myocardial ischemia (measured as time to ST depression) during an exercise stress test in men with stable angina.[12] These vasodilatory effects of testosterone on coronary and other vasculature are confirmed by the findings that men with prostate cancer undergoing androgen-deprivation therapy experience an increase in central arterial pressure (reflecting stiffening of large arteries).[13] Similarly, in population studies, systolic and diastolic blood pressures have been shown to be inversely correlated with testosterone level.[14]

In addition to vasomotor regulation, testosterone levels are also inversely related with arterial calcification. In the Rotterdam Study, the association between total and bioavailable testosterone with aortic atherosclerosis was evaluated in 504 nonsmoking men ≥55 years of age.[15] Compared with men with levels of total and bioavailable

testosterone in the lowest tertile, men in the highest tertile had a risk reduction of 60% to 80% of severe aortic atherosclerosis. Adjustments for age and cardiovascular risk factors did not influence these results. Given that aortic atherosclerosis was assessed by radiographic detection of calcification in the abdominal aorta, it is likely that subclinical atherosclerosis was not detected in this study. Another prospective study of elderly men (mean age 77 years) showed free testosterone concentration to be inversely related to the progression of intima-media thickness of the common carotid artery after adjustment for age and other risk factors.[16] Hence, it appears that arterial stiffening and increased atherosclerosis are 2 mechanisms by which male hypogonadism may contribute to high risk of death.

Another mechanism by which low testosterone may contribute to a higher death rate is its association with diabetes. Epidemiological studies show that low testosterone levels are independently associated with type 2 diabetes mellitus after adjusting for potential confounders.[17] In fact, lower concentrations of free and bioavailable testosterone even in the normal range are associated with diabetes, independent of adiposity.[18] Furthermore, low total testosterone levels independently predict development of the metabolic syndrome in middle-aged men.[19] A clinical model that further establishes the role of testosterone in the mediation of glucose metabolism is that of androgen deprivation in men with prostate cancer. It is seen that insulin resistance develops within a few months of initiation of androgen-deprivation therapy[13]; however, when men undergoing long-term androgen deprivation are studied, in addition to hyperinsulinemia, they have a higher prevalence of hyperglycemia and metabolic syndrome.[20,21] This relationship between hypogonadism and hyperglycemia persists even after adjustment for age and body mass index, and the degree of hyperglycemia is directly related to the duration of sex hormone suppression.[22] Thus, hypoandrogenism seems to be an early marker for disturbances in insulin and glucose metabolism and may contribute to the pathogenesis of diabetes and metabolic syndrome, thus again contributing to the cardiovascular risk.

Another risk factor linking hypogonadism to cardiovascular disease is the association of androgens with lipids and inflammatory cytokines. Epidemiological data suggest that testosterone levels are associated with a beneficial lipid profile, with negative correlations with total cholesterol, low-density lipoprotein cholesterol, and triglycerides and a positive association with high-density lipoprotein cholesterol.[23] Similarly, there are reports of inverse associations between inflammatory cytokines and testosterone.[24] These associations are further validated by clinical trials showing improvement in lipid profile and reduction in inflammatory cytokines with testosterone replacement.[25] Additionally, inverse associations between testosterone and plasminogen activator inhibitor I, fibrinogen, and factor VII have been reported in men.[15] Animal experiments also suggest beneficial effects of testosterone on plaque development.[26] In summary, these findings suggest that testosterone may influence cardiovascular disease via multiple mechanisms, including changes in body composition, fat metabolism, glucose regulation, vascular mechanisms, and clotting (see the Figure).

In this issue of *Circulation*, Khaw et al[2] provide more evidence that makes the chain linking low testosterone to risk of death even stronger.[2] The authors conducted a nested case–control study to determine the association of endogenous serum testosterone with all-cause, cardiovascular, and cancer-related death. The authors compared 825 men, who did not have any cardiovascular disease or cancer at baseline but died during the course of follow-up, with 1489 men who were still alive. The cases and controls were matched for age and date of baseline visit. The authors found that baseline testosterone levels were inversely related to deaths due to all causes, cardiovascular disease, and malignancy, after controlling for the usual confounders (plus dehydroepiandrosterone sulfate and sex hormone–binding globulin). This protective effect of testosterone increased with increasing quartiles, such that men in the highest quartile had a 30% lower risk of death than that of those in the lowest quartile. Even after excluding deaths during the first 2 years of follow-up, this inverse relationship was maintained. In fact, every 6-nmol/L (173-ng/dL) increase in serum testosterone decreased the death rate by 14%, and this benefit was irrespective of patient's age (above or below 65 years of age).

Though the study was well conducted, the findings should be interpreted with caution. First, the testosterone values were based on only a single measurement. Hence, one cannot control for any errors in measurement or transient variation in testosterone secretion. Second, the authors did not measure or calculate either free or bioavailable testosterone, the moiety that binds to the androgen receptor. These measures are more accurate than total testosterone, especially in subjects with obesity or diabetes and in older men because changes in sex hormone–binding globulin levels are expected in such patients. Finally, the authors did not measure estradiol levels. It would have been interesting to see whether these beneficial effects of testosterone are mediated by the testosterone itself or via aromatization to estradiol.

So is low serum testosterone just a marker for sickness (or wellness), or does it have a true pathogenic role? Even though Khaw et al[2] excluded men with serious disease and also those who died within the first 2 years of baseline visit (assuming that they may have had subclinical illness), the authors were cautious enough (rightly so) in mentioning that they still might have included men with subclinical disease. Nevertheless, on the basis of all the evidence cited in the present editorial, we believe that testosterone has a pathogenic role in the development of cardiovascular disease and is not simply a "marker" for illness and wellness. In terms of death related to cancer and respiratory disease (an association suggested by other reports),[27] the exact mechanism by which testosterone may cause an increased risk of death is currently unknown.

Hence, increasing evidence indicates that low androgen levels are associated with all-cause death and especially cardiovascular death. What do we do now on the basis of the reasonably substantial information discussed with regard to testosterone and cardiovascular disease? We believe the answer lies in long-term, double-blind, randomized, placebo-controlled trials of androgen replacement in men with low testosterone levels to evaluate its effects on cardiovascular disease, cardiovascular death, and all-cause death. We cannot assume that testosterone replacement will ameliorate the increased risk seen in these epidemiological studies. We still have not answered questions about the critical level for starting treatment, optimal dose, target testosterone level to be reached, or long-term safety. What we need is a Men's Health Initiative study. With all these data, androgens should no longer be considered as mediators of only sexual function or skeletal health, nor should they be discarded by defaming them as a "fountain of youth," as has been done by some critics of androgen replacement. The aim is to critically evaluate the effects of testosterone treatment by performing large trials, similar to those recently

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REVIEW

Testosterone: a metabolic hormone in health and disease

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Abstract

Testosterone is a hormone that plays a key role in carbohydrate, fat and protein metabolism. It has been known for some time that testosterone has a major influence on body fat composition and muscle mass in the male. Testosterone deficiency is associated with an increased fat mass (in particular central adiposity), reduced insulin sensitivity, impaired glucose tolerance, elevated triglycerides and cholesterol and low HDL-cholesterol. All these factors are found in the metabolic syndrome (MetS) and type 2 diabetes, contributing to cardiovascular risk. Clinical trials demonstrate that testosterone replacement therapy improves the insulin resistance found in these conditions as well as glycaemic control and also reduces body fat mass, in particular truncal adiposity, cholesterol and triglycerides. The mechanisms by which testosterone acts on pathways to control metabolism are not fully clear. There is, however, an increasing body of evidence from animal, cell and clinical studies that testosterone at the molecular level controls the expression of important regulatory proteins involved in glycolysis, glycogen synthesis and lipid and cholesterol metabolism. The effects of testosterone differ in the major tissues involved in insulin action, which include liver, muscle and fat, suggesting a complex regulatory influence on metabolism. The cumulative effects of testosterone on these biochemical pathways would account for the overall benefit on insulin sensitivity observed in clinical trials. This review discusses the current knowledge of the metabolic actions of testosterone and how testosterone deficiency contributes to the clinical disease states of obesity, MetS and type 2 diabetes and the role of testosterone replacement.

Keywords

metabolism testosterone type 2 diabetes metabolic syndrome

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Review: Testosterone and the metabolic syndrome

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Abstract

Metabolic syndrome and testosterone deficiency in men are closely linked. Epidemiological studies have shown that low testosterone levels are associated with obesity, insulin resistance and an adverse lipid profile in men. Conversely in men with metabolic syndrome and type 2 diabetes have a high prevalence of hypogonadism. Metabolic syndrome and low testosterone status are both independently associated with increased all-cause and cardiovascular mortality. Observational and experimental data suggest that physiological replacement of testosterone produces improvement in insulin resistance, obesity, dyslipidaemia and sexual dysfunction along with improved quality of life. However, there are no long-term interventional studies to assess the effect of testosterone replacement on mortality in men with low testosterone levels. This article reviews the observational and interventional clinical data in relation to testosterone and metabolic syndrome.

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Testosterone Replacement in Hypogonadal Men With Type 2 Diabetes and/or Metabolic Syndrome (the TIMES2 Study)

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Abstract

OBJECTIVE This study evaluated the effects of testosterone replacement therapy (TRT) on insulin resistance, cardiovascular risk factors, and symptoms in hypogonadal men with type 2 diabetes and/or metabolic syndrome (MetS).

RESEARCH DESIGN AND METHODS The efficacy, safety, and tolerability of a novel transdermal 2% testosterone gel was evaluated over 12 months in 220 hypogonadal men with type 2 diabetes and/or MetS in a multicenter, prospective, randomized, double-blind, placebo-controlled study. The primary outcome was mean change from baseline in homeostasis model assessment of insulin resistance (HOMA-IR). Secondary outcomes were measures of body composition, glycemic control, lipids, and sexual function. Efficacy results focused primarily on months 0–6 (phase 1; no changes in medication allowed). Medication changes were allowed in phase 2 (months 6–12).

RESULTS TRT reduced HOMA-IR in the overall population by 15.2% at 6 months (P = 0.018) and 16.4% at 12 months (P = 0.006). In type 2 diabetic patients, glycemic control was significantly better in the TRT group than the placebo group at month 9 (HbA_{1c}: treatment difference, −0.446%; P = 0.035). Improvements in total and LDL cholesterol, lipoprotein a (Lpa), body composition, libido, and sexual function occurred in selected patient groups. There were no significant differences between groups in the frequencies of adverse events (AEs) or serious AEs. The majority of AEs (>95%) were mild or moderate.

CONCLUSIONS Over a 6-month period, transdermal TRT was associated with beneficial effects on insulin resistance, total and LDL-cholesterol, Lpa, and sexual health in hypogonadal men with type 2 diabetes and/or MetS.

Footnotes

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Review

The Dark Side of Testosterone Deficiency: II. Type 2 Diabetes and Insulin Resistance

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Abstract

A considerable body of evidence exists suggesting a link among reduced testosterone plasma levels, type 2 diabetes (T2D), and insulin resistance (IR). Hypogonadal men are at higher risk for T2D. Here we evaluate the relationships between testosterone, metabolic syndrome (MetS), T2D, and IR and discuss the relationships among androgen deficiency and these factors, especially as it ultimately relates to the development of cardiovascular disease and erectile dysfunction (ED). Thus, a comprehensive literature search was carried out using PubMed, and relevant articles pertinent to androgen deficiency, T2D, IR, MetS, and ED were reviewed and discussed. Low testosterone precedes elevated fasting insulin, glucose, and hemoglobin A1c (HbA1C) values and may even predict the onset of diabetes. Treatment of prostate cancer patients with surgical or medical castration exacerbates IR and glycemic control, strengthening the link between testosterone deficiency and onset of T2D and IR. Androgen therapy of hypogonadal men improves insulin sensitivity, fasting glucose, and HbA1c levels. We suggest that androgen deficiency is associated with IR, T2D, MetS, and with increased deposition of visceral fat, which serves as an endocrine organ, producing inflammatory cytokines and thus promoting endothelial dysfunction and vascular disease.

Key words: Erectile dysfunction, androgen deficiency, metabolic syndrome, vascular disease

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Review Article

Male hypogonadism: The unrecognized cardiovascular risk factor

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KEYWORDS:
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Hormone replacement;
Hypogonadism;
Metabolic syndrome;
Testosterone

Abstract Normal levels of male sex hormones are essential to men's health. Many studies demonstrate that hypogonadal men are at higher risk for developing a host of metabolic derangements, including dyslipidemia, type 2 diabetes mellitus, obesity, and hypertension. We examined the most recent studies supporting this notion of hypogonadism as a cardiac risk factor by reviewing all relevant PubMed data. Most studies showed an increase in metabolic disorders and cardiac events in hypogonadal men compared to their eugonadal counterparts. Mechanisms explaining this increased risk include adverse cytokine profiles produced by excess adipose tissue, abnormal lipid metabolism by understimulated hormone-sensitive lipase, and abnormal cellular respiration leading to insulin resistance. In contrast, some studies have not demonstrated such an increased cardiac risk. Conflicting data between studies is expected, given the complexity of testosterone and its metabolic effects. Additionally, the interaction of testosterone with the androgen receptor differs based on an individual genome. Hypogonadism will affect individual men differently because of this genomic variance. The literature points toward true hypogonadism as a major cardiac risk factor. Men at risk of being hypogonadal should be screened and brought back to eugonadism with hormone replacement.

Testosterone serves to maintain health in every system of the body. It is produced mainly in the Leydig cells of the testes in response to luteinizing hormone release from the pituitary gland. Testosterone acts on muscle, bone, bone marrow, testes, and the central nervous system through direct effects on target tissues, as well as through the effects of its metabolites estradiol and dihydrotestosterone (DHT). Estradiol is produced by the aromatase enzyme in adipose tissue and the more potent androgen DHT is produced by the 5-α reductase enzyme in prostate and skin (see Fig. 1).

Because of its diverse effects, the task of describing testosterone's cardiovascular effects may prove to be even more difficult than the female sex hormone estrogen. The Woman's Health Initiative (WHI) attempted to establish a beneficial role for estrogens in preventing heart disease, but instead discovered an increase in heart disease during the study. In parallel, testosterone, once believed to have negative effects on heart disease, is now emerging as essential to men's health, highlighting the importance of male eugonadism.

Hypogonadism in the community

Physicians identify and treat hypogonadal men based on symptoms of low testosterone, including decreased libido,

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Original Article

Low Levels of Endogenous Androgens Increase the Risk of Atherosclerosis in Elderly Men: The Rotterdam Study

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Abstract

In both men and women, circulating androgen levels decline with advancing age. Until now, results of several small studies on the relationship between endogenous androgen levels and atherosclerosis have been inconsistent.

In the population-based Rotterdam Study, we investigated the association of levels of dehydroepiandrosterone sulfate (DHEAS) and total and bioavailable testosterone with aortic atherosclerosis among 1,032 nonsmoking men and women aged 55 yr and over. Aortic atherosclerosis was assessed by radiographic detection of calcified deposits in the abdominal aorta, which have been shown to reflect intimal atherosclerosis.

Relative to men with levels of total and bioavailable testosterone in the lowest tertile, men with levels of these hormones in the highest tertile had age-adjusted relative risks of 0.4 [95% confidence interval (CI), 0.2–0.9] and 0.2 (CI, 0.1–0.7), respectively, for the presence of severe aortic atherosclerosis. The corresponding relative risks for women were 3.7 (CI, 1.2–11.6) and 2.3 (CI, 0.7–7.8). Additional adjustment for cardiovascular disease risk factors did not materially affect the results in men, whereas in women the associations diluted. Men with levels of total and bioavailable testosterone in subsequent tertiles were also protected against progression of aortic atherosclerosis measured after 6.5 yr (SD ± 0.5 yr) of follow-up (***P*** for trend = 0.02). No clear association between levels of DHEAS and presence of severe aortic atherosclerosis was found, either in men or in women. In men, a protective effect of higher levels of DHEAS against progression of aortic atherosclerosis was suggested, but the corresponding test for trend did not reach statistical significance.

In conclusion, we found an independent inverse association between levels of testosterone and aortic atherosclerosis in men. In women, positive associations between levels of testosterone and aortic atherosclerosis were largely due to adverse cardiovascular disease risk factors.

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Age Ageing, July 1, 2008; 37(4): 461 - 464.
[Full Text] [PDF]

Androgens and Diabetes in Men

Results from the Third National Health and Nutrition Examination Survey (NHANES III)

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OBJECTIVE— Low levels of androgens in men may play a role in the development of diabetes; however, few studies have examined the association between androgen concentration and diabetes in men in the general population. The objective of this study is to test the hypothesis that low normal levels of total, free, and bioavailable testosterone are associated with prevalent diabetes in men.

RESEARCH DESIGN AND METHODS — The study sample included 1,413 adult men aged ≥20 years who participated in the morning session of the first phase of the Third National Health and Nutrition Examination Survey, a cross-sectional survey of the civilian, noninstitutionalized population of the U.S. Bioavailable and free testosterone levels were calculated from serum total testosterone, sex hormone–binding globulin, and albumin concentrations.

RESULTS— In multivariable models adjusted for age, race/ethnicity, and adiposity, men in the first tertile (lowest) of free testosterone level were four times more likely to have prevalent diabetes compared with men in the third tertile (odds ratio 4.12 [95% CI 1.25–13.55]). Similarly, men in the first tertile of bioavailable testosterone also were approximately four times as likely to have prevalent diabetes compared with men in the third tertile (3.93 [1.39–11.13]). These associations persisted even after excluding men with clinically abnormal testosterone concentrations defined as total testosterone <3.25 ng/ml or free testosterone <0.07 ng/ml. No clear association was observed for total testosterone after multivariable adjustment (*P* for trend across tertiles = 0.27).

CONCLUSIONS— Low free and bioavailable testosterone concentrations in the normal range were associated with diabetes, independent of adiposity. These data suggest that low androgen levels may be a risk factor for diabetes in men.

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Abbreviations: AAG, androstanediol glucuronide; NHANES III, Third National Health and Nutrition Examination Survey; SHBG, sex hormone–binding globulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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It has been suggested that sex steroid hormones may play a causal role in the development of insulin resistance and type 2 diabetes (1,2). There is a growing amount of literature examining the role sex steroid hormones may play in the development of diabetes and cardiovascular disease in women, but there has been relatively less attention paid to this association in men. Men with endocrine disorders that are associated with low testosterone levels (hypogonadism), such as Klinefelter's and Wolfram's syndromes, have an elevated risk of developing insulin resistance and diabetes (3,4). However, the association between sex steroid concentrations within the normal range and diabetes risk in men in the general population has not been well characterized.

Obesity, one of the most important underlying causes of insulin resistance, is associated with low testosterone levels in men (5–7) and may partially or wholly mediate the process by which endogenous sex hormones influence diabetes risk. Many previous studies have been conducted in small, highly selected populations or convenience samples and/or did not rigorously measure or control for the possible effects of adiposity. The present study was undertaken to investigate the association between sex steroid hormones and diabetes in the general adult male population in the U.S. Specifically, we hypothesized that low levels of total, free, and bioavailable testosterone would be associated with prevalent diabetes. We also hypothesized that this association would persist after controlling for the potentially confounding effects of adiposity. Estimates from this study are nationally representative of the U.S. adult male population in 1988–1991.

RESEARCH DESIGN AND METHODS

— Between 1988 and 1994, the National Center for Health Statistics conducted the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was designed as a cross-sectional study using a multistage-stratified, clustered probability sample of the U.S. civilian noninstitutionalized population. To ensure adequate

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Free testosterone and risk for Alzheimer disease in older men

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Abstract—*Objective:* To investigate the relationships between age-associated decreases in endogenous serum total testosterone (T) and a free T index (FTI) in men and the subsequent development of Alzheimer disease (AD). *Method:* The authors used a prospective, longitudinal design with follow-up in men since 1958. Participants were from the Baltimore Longitudinal Study of Aging, a community-dwelling volunteer sample with baseline ages of 32 to 87 years. All subjects were free of AD at baseline T assessment. Five hundred seventy-four men assessed at multiple time points were followed for a mean of 19.1 years (range, 4 to 37 years). Diagnoses of AD were based on biennial physical, neurologic, and neuropsychological evaluations. *Results:* Diagnosis of AD was associated inversely with FTI by itself and after adjustments for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplements. In separate analyses, total T and sex hormone binding globulin were not significant predictors after adjustment with covariates. Increases in the FTI were associated with decreased risk of AD (hazard ratio = 0.74; 95% CI = 0.57 to 0.96), a 26% decrease for each 10-nmol/nmol FTI increase. *Conclusions:* Calculated free testosterone concentrations were lower in men who developed Alzheimer disease, and this difference occurred before diagnosis. Future research may determine whether higher endogenous free testosterone levels offer protection against a diagnosis of Alzheimer disease in older men.

NEUROLOGY 2004;62:188–193

A sizable literature now exists relating age-related alterations in the endocrine environment to cognitive changes[1-3] and the onset of Alzheimer disease (AD) in women.[4-7] The comparative dearth of similar research in men may be attributable primarily to the fact that testosterone replacement therapy (TRT) has been used much less commonly in men than hormone therapy in women. Moreover, TRT has not been administered for time periods that are sufficiently long to establish linkages to AD. Nevertheless, androgen levels in men decrease substantially with age, raising the question of whether this decrease may contribute to the development of AD.[8,9] Although numerous studies have demonstrated contributions of testosterone (T) to selected cognitive functions in young[10-12] and old men,[13-15] to date there have been no studies assessing prospectively the risk for AD associated with the so-called "andropause."

Decreased total T levels have been reported in men with AD compared with age-matched control subjects.[16] However, these data are ambiguous because the depleted T levels may be a consequence rather than a cause of the disease. To assess the impact of T decline in the subsequent manifestation of AD, it is essential to obtain measures of T that *precede* the development of the disease.

In the present study, we followed 574 men whose ages at baseline T assessment ranged from 32 to 87 years for a mean duration of 19.1 years. We collected multiple serum samples for determination of total T, sex hormone binding globulin (SHBG), and the calculated free T index (FTI) and evaluated presence or absence of a diagnosis of AD as the principal outcome variable. We report here the first prospective longitudinal study assessing the impact of long-term total and estimated free T levels on the development of AD.

Methods. *Subjects.* Subjects were men who volunteered to participate in the Baltimore Longitudinal Study of Aging (BLSA), a study performed by the National Institute on Aging (NIA).[17] Participants were community dwelling and returned every 2 years to the Gerontology Research Center of the NIA for comprehensive medical and neuropsychological evaluations. Androgen data were available for a large number of BLSA men whose blood samples were assayed as part of a study of prostate health and disease.

See also pages 170 and 301

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On the first day the JAMA article was released I received 500 emails from physicians and patients requesting my opinion of the article that demonstrated an increase in heart attacks and strokes in men treated with testosterone. Today is the second day and I'm afraid to turn on the computer. First of all this was an observational study that was retrospective in nature and this type of study is fraught with compounding biases that are difficult to control as expressed in the discussion section of this study. A randomized controlled trial (RCT) would have much more power than this type of study. Also the problem with an observation study is that it does not prove causation as would an interventional study in a blinded fashion. Therefore observational studies can't prove causation as well as RCTs and what we should take away from the study is that which the researchers state in the last paragraph, that more studies are necessary before definitive conclusions can be made as to cause and effect. Also, treatment decisions should not be based solely on one study but rather on a trend of studies. Unfortunately the editorial comment section did not express this clearly.

The discussion section of this article mentions that this is the only study that showed this adverse outcome and it was in a select group of individuals. All other RCT's (this was not an RCT) have shown the opposite outcome, either no effect or protection against heart attacks. Since all other studies show the opposite, and one study does not negate all the other studies, and there were some biases in this study, I would suggest that we do not change anything that we do based on one study with flaws and biases when all other studies demonstrate protection against heart disease and stroke (see attached articles). And this was an observational study which has weaker power than a randomized controlled trial. I'm sure that other experts will voice the same opinion once they review the discussion section of this article as there were many biases and flaws in this study.

A review of the index lists the studies that demonstrate protection against heart disease and strokes. In the “Longevity Section” that I present in the Part II course, all of the articles demonstrate improved longevity in those treated with testosterone, but increased morbidity and mortality in those men not treated with testosterone. The WHI study showed that Prempro increased heart attacks and strokes in certain individuals. Subsequent studies have proven that estradiol and progesterone, particularly in younger women, don't. Perhaps there is a confounding problem in older Veterans with cardiovascular disease that is different from other studies. However, as presented in the Part II course, every study that I review (and there are many) demonstrated a significant improvement in longevity and decreased morbidity and mortality in addition to improvement in all cardiovascular risk factors in men treated with testosterone as opposed to control groups treated with placebo (see attached studies).

Had this study been published years ago, and all subsequent studies since then showed protection against cardiovascular disease, then this study would have probably been ignored and forgotten. However, since it is recent, then we tend to believe it and reject all the past studies that showed the exact opposite outcome. Nevertheless, one study does not negate many other studies that show opposite results and benefits. So I will log this study on the negative side for testosterone results but it is the only such study on this side. This is in contrast to all the other studies that show benefit of testosterone administration. It is interesting that this study appears now, just after I gave 2 lectures to a medical academy this past weekend in Las Vegas. The two one hour lectures were on all the studies of both estrogen and testosterone protecting against heart attacks and strokes.

These reviews of the world's literature demonstrate all the various mechanisms of benefits of hormones in protecting the heart and brain against heart disease, stroke, dementia, and plaque deposition. The data and literature is overwhelming in favor of a protective effect of estrogen in women and testosterone in men. This recent study, although interesting and intriguing, does not change any of the evidence that I presented in these lectures nor does it change my treatment strategies. Until more studies demonstrate the same, I will continue to follow the scientific literature that demonstrates benefit. As per the suggestion from the authors, they state that more study is needed to evaluate these results. I recommend to patients and physicians that they continue the same treatment with both estrogen in women and testosterone in men based on all prior studies that show benefit in spite of this one negative study. In addition, the FDA recently recommended the same as they are investigating these negative studies but also caution that patients should not stop their current therapy until a conclusion is reached by the FDA.

Certain statements in the discussion section of the study deserve comment. The authors do note that other trials and meta-analyses do not demonstrate adverse cardiovascular outcomes. The trend so far in the literature has been a protective effect as trials demonstrated that testosterone therapy improves a number of intermediate outcomes and cardiac risk factors. This new JAMA study that demonstrates harm should therefore be interpreted carefully in light of all the other studies demonstrating opposite results. In addition, the results of this study differ from a similar retrospective VA study by Shores et al that demonstrated a 39% reduction in mortality risk among patients treated with testosterone which again suggests caution in coming to conclusions only based on the present study. Different confounders and biases might account for the discrepancy. Multiple limitations of this study are noted by the authors that certainly can affect outcomes. All in all, it is an interesting study with unexpected results that are in discordance with all other studies and should not influence current therapy, but one that begs for more study.

For those patients and physicians that are unfamiliar with the current literature on testosterone therapy, I have included 3 attachments that review various categories of hormone replacement. First are studies that review mortality in men treated with testosterone compared to control groups. Studies show improved survival in treated men versus untreated men. There are fewer heart attacks, cancer, and reduced mortality in men treated with testosterone (in contrast to the current study). Other studies go on to prove that low levels of testosterone increase morbidity and mortality in contrast to men with testosterone levels in the higher quartiles. Low levels of testosterone are predictive of an increase in all-cause mortality (CAD, CVD, cancer). So where would you like your levels to be? Other studies show that there was no increased risk of cardiac events in men treated with testosterone (in contrast to the current study).

Journal club

ORIGINAL ARTICLE

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

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Abstract | Article | References | Citing Articles (28) | Letters

BACKGROUND

Current treatment recommendations for patients with polycythemia vera call for maintaining a hematocrit of less than 45%, but this therapeutic strategy has not been tested in a randomized clinical trial.

Full Text of Background...

METHODS

We randomly assigned 365 adults with JAK2-positive polycythemia vera who were being treated with phlebotomy, hydroxyurea, or both to receive either more intensive treatment (target hematocrit, <45%) (low-hematocrit group) or less intensive treatment (target hematocrit, 45 to 50%) (high-hematocrit group). The primary composite end point was the time until death from cardiovascular causes or major thrombotic events. The secondary end points were cardiovascular events, cardiovascular hospitalizations, incidence of cancer, progression to myelofibrosis, myelodysplasia or leukemic transformation, and hemorrhage. An intention-to-treat analysis was performed.

Full Text of Methods...

RESULTS

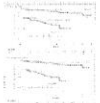
After a median follow-up of 31 months, the primary end point was recorded in 5 of 182 patients in the low-hematocrit group (2.7%) and 18 of 183 patients in the high-hematocrit group (9.8%) (hazard ratio in the high-hematocrit group, 3.91; 95% confidence interval [CI], 1.45 to 10.53; P=0.007). The primary end point plus superficial-vein thrombosis occurred in 4.4% of patients in the low-hematocrit group, as compared with 10.9% in the high-hematocrit group (hazard ratio, 2.69; 95% CI, 1.19 to 6.12; P=0.02). Progression to myelofibrosis, myelodysplasia or leukemic transformation, and bleeding were observed in 6, 2, and 2 patients, respectively, in the low-hematocrit group, as compared with 2, 1, and 5 patients, respectively, in the high-hematocrit group. There was no significant between-group difference in the rate of adverse events.

MEDIA IN THIS ARTICLE

FIGURE 1

Hematocrit (HCT) and White-Cell and Platelet Counts during the Study.

FIGURE 2



Kaplan–Meier Curves for the Primary End Point and Total Cardiovascular Events.

ARTICLE ACTIVITY

29 articles have cited this article

Full Text of Results...

CONCLUSIONS

In patients with polycythemia vera, those with a hematocrit target of less than 45% had a significantly lower rate of cardiovascular death and major thrombosis than did those with a hematocrit target of 45 to 50%. (Funded by the Italian Medicines Agency and others; ClinicalTrials.gov number, NCT01645124, and EudraCT number, 2007–006694-91.)

Full Text of Discussion...

Read the Full Article...

ERYTHROCYTOSIS VS PCV (Polycythemia Vera)

NEAL ROUZIER, M.D.

This is in response to your inquiry about elevated red blood cell counts that are quite common, almost universal, in those who take testosterone. It is more prevalent in those taking injectable testosterone and less so in those using the creams or gels. Most physicians become concerned about this elevation of hemoglobin because they associate this elevation with a blood condition which causes hyperviscosity (thick blood) and potential strokes. However, this is definitely not the case with you or in those that take testosterone and have elevated red blood cell counts. The two conditions are commonly confused with each other, yet they are entirely different in their cause, treatment, and outcomes.

The condition that you have acquired is termed erythrocytosis and is simply an increase in the red blood cells due to increased production of a kidney hormone called erythropoietin. This is the same phenomenon that occurs when cyclists use Epogen or Procrit (erythropoietin) to raise their blood counts to enhance their endurance. This is also the same process that causes people who live at high altitude to have an increase in red blood cell counts. People who live at altitude have the same physiologic increase in red blood cell counts as you and we never worry about them. This is because it is a physiologic (not harmful) increase in only red blood cells, not in any other cells or clotting factors. Treatment is not necessary for anyone with erythrocytosis that lives at altitude as it does not cause any problem whatsoever and it is quite beneficial. Millions of people worldwide live at high altitude and have blood counts higher than yours and no treatment is necessary nor is there ever any harm. In fact athletes train at high altitudes to raise their blood counts to increase their exercise endurance at sea level. It gives them an advantage. People with chronic lung problems (COPD) also have high blood counts and we never treat them as their response is physiologic (normal, expected, and not harmful) in order for the blood to carry more oxygen.

Your physician is confusing your erythrocytosis with a blood disorder called Polycythemia Vera (PCV). This is a harmful blood condition that causes an increase in clotting which leads to strokes and blood clots. The difference is that erythrocytosis only causes increased red blood cells and no harm. PCV causes an increase in platelets which causes increased clotting. More importantly, PCV is associated with a defect in the blood vessel wall which stimulates the clotting cascade of thrombosis in addition to increased platelets. These two entities together cause an increased risk of blood clots and stroke thereby requiring treatment by phlebotomy or blood donation to lower blood counts and prevent the complications of PCV.

PCV is classically defined as an increase in red blood cells, white blood cells, platelets, splenomegaly, and clotting disorders. You do not have this nor are you at risk for this. In addition, the literature clearly demonstrates that testosterone causes erythrocytosis only and not PCV. Testosterone administration has never been associated with any risk of clotting or stroke in any of the studies over the last forty years. Therefore the erythrocytosis requires no treatment. You have the same erythrocytosis that people have who live at altitude and you should receive the same treatment as they do, which is nothing. If your physician is uncomfortable with this, then he can refer you to a hematologist who will hopefully understand this very well. If your physician or you are still concerned, then the treatment is simply to donate blood which is the only necessary treatment for PCV, which you do not have.
Although this explanation was technical, it was intended as such so that you could pass this information along to your physician.

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ed a direct relation between testosterone dosage and the incidence of erythrocytosis. Erythrocytosis occurred in 2.8 percent of men receiving 5 mg per day by nonscrotal patches and in 11.3 percent and 17.9 percent of men treated with gel preparations of 50 mg per day (delivering 5 mg per day) and 100 mg per day (delivering 10 mg per day), respectively.

Although untoward events are unlikely with mild erythrocytosis of relatively short duration, the hematocrit or hemoglobin level should be monitored in men receiving testosterone-replacement therapy so that appropriate measures, such as dosage reduction, the withholding of testosterone, therapeutic phlebotomy, or blood donation, may be instituted if erythrocytosis develops. It is reassuring that as far as we can determine, no testosterone-associated thromboembolic events have been reported to date.

TESTOSTERONE-REPLACEMENT THERAPY AND THE PROSTATE

BENIGN PROSTATIC HYPERPLASIA

It is well recognized that the development of benign prostatic hyperplasia requires the presence of androgens and that the marked reduction in serum testosterone caused by chemical or surgical castration causes reduced prostate volume.[42] However, multiple studies[7,9,11,19,43-46] have failed to demonstrate exacerbation of voiding symptoms attributable to benign prostatic hyperplasia during testosterone supplementation, and complications such as urinary retention have not occurred at higher rates than in controls receiving placebo.

Prostate volume, as determined by ultrasonography, does increase significantly during testosterone-replacement therapy, mainly during the first six months, to a level equivalent to that of men without hypogonadism. However, urine flow rates, postvoiding residual urine volumes, and prostate voiding symptoms did not change significantly in these studies. This apparent paradox is explained by the poor correlation between prostate volume and urinary symptoms. Clinicians should nevertheless be aware that individual men with hypogonadism may occasionally have increased voiding symptoms with testosterone-replacement therapy.

PROSTATE CANCER

More than 60 years ago, Huggins et al.[42] demonstrated that suppression of testosterone levels caused regression of prostate cancer, and it is now commonplace for men with metastatic prostate cancer to undergo treatment designed to lower testosterone levels. If lowering testosterone causes prostate cancer to regress, does elevating testosterone cause prostate cancer to appear? How does one evaluate this risk, given that a high proportion of men harbor microscopic foci of prostate cancer?[47]

Case reports have suggested that testosterone-replacement therapy may convert an occult cancer into a clinically apparent lesion.[48,49] An example is the report of an 85-year-old man in whom prostate cancer was diagnosed because of a rise in the prostate-specific antigen (PSA) level six months after testosterone-replacement therapy was initiated.[49] However, one must be cautious in attributing causality to testosterone in these cases, since over 200,000 men are given a diagnosis of prostate cancer each year in the United States, and most of these cases are first detected by a rise in the PSA level unrelated to testosterone therapy.

To date, prospective studies have demonstrated a low frequency of prostate cancer in association with testosterone-replacement therapy. A compilation of published prospective studies of testosterone-replacement therapy (Table 3)[6-9,11,20,33] revealed only 5 cases of prostate cancer among 461 men (1.1 percent) followed for 6 to 36 months, a prevalence rate similar to that in the general population. These studies were performed in men with hypogonadism of varying causes and degrees, who may or may not have received testosterone treatment before the prospective studies. No follow-up data beyond 36 months are available.

It is of some concern that the underlying prevalence of occult prostate cancer in men with low testosterone levels appears to be substantial, according to our own study[50] in which 77 men with hypogonadism who had normal PSA levels and normal results on digital rectal examinations underwent sextant prostate biopsy before receiving testosterone-replacement therapy. Eleven men (14 percent of the subjects, with a median age of 64 years) had cancer. In a separate, retrospective study of men with known prostate cancer, high-grade prostate cancers were associated with low free testosterone levels.[51] These findings may be explained in part by the observation that the levels of testosterone, luteinizing hormone, and follicle-stimulating hormone all increase after radical prostatectomy, suggesting that prostate cancer itself, or possibly even normal prostate tissue, may have an inhibitory effect on serum androgen levels.[52,53] However, these reports do not address the clinical issue of

RELATED RESOURCE

The Institute for Continuing Healthcare Education

A Panel Discussion on the Importance of Early Diagnosis for Myeloproliferative Neoplasms

http://www.youtube.com/watch?v=qAmywf8w5gU&feature=share

Q & A SESSION

THANK YOU!

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