Testosterone as a Marker of Disease Risk

Alan P. Mintz, M.D.

We have previously discussed the importance of testosterone in relation to male and female sexual response. Now I want to focus more on the role of testosterone as a marker of disease risk and discuss some other organ specific roles testosterone plays in maintaining optimum health. There is also a component of “self defense” here, as the information and links may be useful when describing testosterone treatment rationales and outcome measurements.

General Testosterone Physiology

Testosterone exerts its main effect on cells by affecting DNA transcription. Testosterone can freely enter the cytoplasm of a cell, where it binds to androgen receptor proteins. Once bound, androgen receptor/androgen complexes are formed which change the conformation of the androgen receptor, and the complex enters the cell’s nucleus. Once in the nucleus the complex can bind DNA receptor sites and act as a promoter for specific gene transcription. Testosterone can be converted intra- or extra-cellularly by 5-alpha-reductase to become dihydrotestosterone (DHT) and bind the androgen receptor in that form as well. DHT is the more biologically active form of testosterone. Once bound by either molecule, the net effect is pro-transcriptional and moves a cell toward positive, or anabolic, nitrogen balance and protein synthesis. This effect is not limited to the sex organs, and, in fact, plays an important role in maintaining general physiologic function.

Testosterone and Cardiovascular Disease

The organ with the highest concentration of testosterone receptors is not the one that may first come to mind. The heart has the highest concentration of testosterone receptors, and there is an abundant body of literature supporting its contribution to maintenance of healthy cardiac status and the risk associated with the lack of adequate testosterone levels.

Testosterone is associated with several effects on cardiac health. It has been shown to be associated with reducing risk of coronary artery disease (CAD) and hypertension, as well as being associated with improving cardiac function in patients with pre-existing heart disease.

Since our institute’s main focus of care is on disease prevention, I will begin there. Multiple studies have shown the association between sub-optimal testosterone levels and elevated risk for CAD.

In 1988, Webb demonstrated a fivefold reduction in CAD risk associated with the highest vs. lowest quartile of testosterone levels. These findings were unchanged by risk factor control.


Muller, M., Endogenous Sex Hormones and Cardiovascular Disease in Men: JCEM, November 2003, was a landmark meta-analysis of the relationship between testosterone and subsequent risk for cardiovascular disease. While there had been some conflicting data in previous observational studies, this group analyzed the data from studies that included adjustments for concurrent risk factors so that testosterone was the only identifiable difference between otherwise matched groups. Their review included 8,150 men from 11 studies. The data analysis revealed that in 10 of 11 studies, higher testosterone levels were associated with lower cardiovascular disease risk (including aortic and carotid disease.) In the link, you will see that the 66th percentile for testosterone levels was associated with a significant reduction in disease risk.

The following link offers a PDF of the full article.


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Other studies have examined CAD risk and also the findings associated with CAD risk, such as blood pressure, lipid profiles, waist to hip ratio, and insulin levels and have also shown risk to be associated with lower rather than higher testosterone levels.

Khaw, 1988, reported in a review of 1132 men, ages 30-79, that systolic and diastolic BP correlated inversely with testosterone levels. Found for all BP ranges, and across all age groups in study. He additionally noted a progressive decrease in blood pressure values for each higher quartile of testosterone level.
Khaw, 1992, in a prospective study with a 12-year follow-up of 511 men showed low testosterone associated with increased central adiposity. These findings were obtained before onset of findings.

Marin, 1992, in two separate studies, showed that normalization of testosterone levels produced decreases in waist/hip ratio, insulin resistance, total cholesterol and diastolic BP. He also described similar associated results in studies on females. His second study showed similar findings, repeating his previous findings showing decreased glucose clearance times after insulin clamping – concluding that testosterone replacement was associated with improvement in insulin sensitivity.

Tenover, 1992, JCEM, treated male subjects between the ages of 57 and 76 years with intramuscular testosterone replacement therapy. Her data revealed increases in lean body mass, depression of urinary hydroxyproline excretion (a marker of bone turnover that is elevated when net bone loss is occurring), a significant increase in hematocrit, a decline in total cholesterol and a decline in low-density lipoprotein cholesterol.

The full text of the linked reference is available at mdconsult.com or can sometimes be accessed free of charge at the Journal of Clinical Endocrinology and Metabolism website.

Zmuda, 1992, published a 13-year longitudinal study of men ages 41 to 61 years at the time of enrollment. This was a “normal” population sample, with and average total testosterone of 751 ng/Dl at the study’s start, with a fall in testosterone levels over that 13-year period of 41 ng/Dl. This relatively small drop in testosterone (small in terms of the treatment levels we see and what our goals of therapy are) was associated with a rise in triglycerides and drop in HDL that was present after correction for body habitus and lifestyle parameters, but did note an association between “Type A” behavior and smoking as magnifiers of decline in testosterone and unfavorable changes in cardiac risk parameters.

Wu and Weng, 1993, studied and examined a group of 62 men with CAD. The group had lower testosterone levels than non-CAD control subjects, and demonstrated a significant improvement in angina symptoms, improvement in ST changes during ETT electrocardiography, and improvement in ambulatory ST segment readings during Holter monitoring in 68.8 and 75% of the study patients, respectively. They also noted that testosterone levels were inversely associated with the extent of coronary artery occlusion on angiographic imaging.

In a 1999 study, similar findings by Webb were reported, with patients with CAD showing a 20% prolongation in time to ST segment depression on exercise testing.

English, 2000, found that men with CAD had lower testosterone levels than age matched non-CAD subjects. Lower testosterone was seen in subjects unaware of, and without previous symptoms of, CAD.

A follow-up study by the same author demonstrated reduction in exercise-induced myocardial ischemia in men with CAD, and the lower the baseline testosterone, the greater the degree of improvement.

Following are additional references and literature links examining testosterone and CAD risk:

1. Malkin, Journal of Endocrinology. You will note the highlighted area points out the association with low testosterone levels and risk for coronary artery disease.
2. Bhasin, Clinics of Infectious Disease. This article acknowledges the widespread belief that Testosterone supplementation increases the risk of atherosclerosis, but points out the fact that actual evidence of this premise is lacking. This author points out that in epidemiologic studies, testosterone levels have actually been inversely correlated to risk for heart disease and other factors that predispose to heart disease.

3. Eckardstein, 2003, is overall neutral with regard to testosterone replacement therapy, showing that they could find neither increase nor decrease risk, but it is interesting to note in this article’s discussion that they provide a good description of why the negative articles regarding testosterone that look only at HDL miss important points with regard to cardiac risk. In this case, we see that no associated risk is also a positive outcome when looking at testosterone therapy. No harm is a fine result.

4. Sieminskn, 2003, found that men with coronary artery disease had significantly lower levels of free testosterone than did men without CAD.

5. Barud, 2002, showed a significant inverse correlation between testosterone level and antibodies to oxidized LDL, and that only testosterone levels were actually associated with lowering this risk factor for heart disease.

6. Kabakci, Cardiology, 1999, found that testosterone levels in men with heart disease were comparable to those in men without heart disease, and that the two groups shared similar lipid profiles. Again, a neutral study is actually a positive outcome when we are talking about whether or not a given intervention increases risk for heart disease.

7. Wassef, 1998, points out that only a very few items affect Lipoprotein(a) in a positive fashion. Lipoprotein(a) is a significant heart disease risk factor. The author points out that Niacin compounds, moderate doses of alcohol, Neomycin and Androgens are associated with lowering Lp(a).

8. Zhao, International Journal of Cardiology, 1998, found that testosterone levels in patients with heart disease were significantly lower than in healthy subjects, and pointed out that low total testosterone levels, statistically, are associated with increased risk for diagnosis of heart disease.

9. Phillips, 1994, showed that testosterone levels correlated negatively with risk factors for heart disease including Fibrinogen, Plasminogen, Activator Inhibitor 1, and insulin, and concluded that in men, low testosterone levels maybe a risk factor for heart disease.

10. Hauner, 1991, again is a neutral study finding no significant differences in serum concentrations of testosterone between men with and without heart disease. Their conclusion was that there was no significant role of sex hormones in risk for coronary artery disease. Again, a neutral finding, but pointing out the lack of evidence for Testosterone as a risk factor for heart disease.

11. Contoreggi, 1990, was another neutral study finding no significant differences in testosterone when comparing groups of men with heart disease and without.
12. Sewdarsen, Atherosclerosis, 1990, found that in their total patient population of men who had had myocardial infarction (heart attacks) between age 30-60, it was found that their testosterone concentration was significantly lower than in men without a cardiac history.


13. Srzednicki, 1990, again found testosterone concentrations in unstable coronary artery disease were significantly lower than in men with stable coronary artery disease, and lower still than found in healthy controls. Again, this points out an inverse correlation between Testosterone and coronary artery disease risk.


14. Chute, American Medical Journal, 1987, found significantly lower testosterone levels were observed among men with heart disease compared with control groups. His epidemiologic analysis demonstrated a 5-fold decrease in risk for severe heart disease between the lowest and highest quartile of total testosterone. This study is interesting because even within the range of what we call normal testosterone, it was the men with the lowest testosterone levels that were at the greatest risk, even within normal populations, and the highest testosterone levels were correlated with the lowest risk.


15. Cauley, American Journal of Cardiology, 1987, again as a neutral study, saying that they cannot support any relation between sex hormone levels and risk of heart attack among men.


16. Sewdarsen, Atherosclerosis, 1986, found statistically that low testosterone levels were a risk factor for myocardial infarction.


I have also included a copy of the Rotterdam study published in 2003 in the Journal of Clinical Endocrinology and Metabolism, showing men in the upper third for testosterone level were at 1/5 the Atherosclerosis risk, as men in the lower 1/3.

Testosterone and the Prostate:

At some point in most physicians’ training, they must have met the same spectral urologist who traveled from training program to training program, walking the hallways proclaiming that testosterone is associated with prostate cancer risk. Then, these same physicians in training must have been hypnotized by this urologist and their post-hypnotic suggestion has been to never go to the literature and look this topic up for themselves. On one level, the mythical urologist was correct, testosterone is associated with prostate cancer risk, but in the exact opposite relationship that he proclaimed. Following is a review of testosterone and prostate cancer risk.

There is a repeated lack of association between testosterone and cancer risk, with the studies either yielding a null result or demonstrating an inverse relationship between testosterone and prostate cancer risk.

1. Cooper, Journal of Urology, showed that Testosterone replacement therapy was not associated with any rise in PSA or prostate volume.


2. Hoffman, Journal of Urology, 2000 reported that patients with prostate cancer and low free testosterone had more extensive disease. In addition, all men with a biopsy Gleason score of 8 or greater had a low serum free testosterone. His conclusion was that low testosterone levels maybe a marker for aggressive prostate disease.


3. Asbell, Journal of the National Medical Association, found no correlation between PSA and Androgen levels in a study of prostate cancer patients.

4. Rhoden, New England Journal of Medicine, 2004, a comprehensive review of 72 prior studies concluded that there was no evidence supporting a causal link between testosterone replacement therapy and an increase in prostate cancer risk.


5. Carter, Journal Prostate, 1995, again found no correlation between Testosterone and prostate cancer risk in patients followed as long as 15 years before any diagnosis of prostate pathology was noted. His conclusion was that his data point out that there is no measurable difference in testosterone levels among men who are destined to develop prostate cancer in those without disease.


7. Gustafsson, British Journal of Urology, also failed to demonstrate a connection between testosterone levels and prostate cancer risk.


8. Zhang, Journal Prostate, 2002, found that patients with prostate cancer were found to have low Androgen levels.


9. Massengill, Journal of Urology, May 2003, showed that low testosterone levels were predictive of pathological stage in patients with prostate cancer.


10. Rhoden, Journal of Urology, December 2003, evaluated patients with prostatic intraepithelial neoplasia, which is commonly regarded as a pre-malignant change in the prostate, showed no change in PSA or their tissue status when given Testosterone replacement therapy over a one year period.


11. Chen, Journal of Cancer Epidemiology Biomarkers and Prevention, also found that testosterone levels were unrelated to prostate pathology.


12. Carter, Journal Prostate, found the same thing.


13. Hoffman, Journal of Urology, 2000, again found that low testosterone levels were a marker of prostate disease rather than high.


14. Stattin, International Journal of Cancer, did a pool to prospective study and found that there was no evidence to conclude that there was a connection between high testosterone levels and increased prostate cancer risk.


15. Gann, Journal of the National Cancer Institute, 1996, found that it was not testosterone levels that related to prostate cancer risk, but rather low levels of Sex Hormone-Binding Globulin in conjunction with high testosterone levels.

16. Hsing, Journal of the National Cancer Institute, 2003, found a connection between insulin-resistance and the effect of high insulin levels on prostate cancer risk being a positive association. 

17. Slater, Drugs and Aging, 2000, again points out the lack of prostate cancer risk and testosterone levels. 

18. Cooper (J Urol.) No changes in PSA or prostate volume with TRT at doses up to 500 mg/week.


20. *Vermeulen, A (JCEM) meta analysis: hypogonadal men treated for decades with TRT show p-Vol and p-ca risk to be the same as population with normal levels.


23. After 1 year of TRT men with PIN do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN. These results indicate that TRT is not contraindicated in men with a history of PIN.

24. Slater, S. Drugs and Aging , 2000. Reviewed 34 studies. No data to support higher risk for prostate CA with elevated testosterone levels vs. controls.


26. Zhang, Prostate, 2002; Gustafsson, Br J Uro, 1996. Inverse relationship between testosterone levels and prostate cancer risk,

27. Testosterone levels and prostate cancer survival

Testosterone and the Brain

28. The brain is second only to the heart in terms of abundance of testosterone receptors.


30. Hogervorst, Int J Ger Psy, 2003, Patients with the APO-E4 allele are at high risk for development of future AD, and have been shown to demonstrate a concurrent decrease in testosterone compared to normal controls, even in the absence of any other demonstrable finding. This link will also provide a link to the full text article from Pub med.

31. Schmidt (Front. Neuroendo.), Compaganone (FN), Rupprecht (Trends in Neurosci.), Teyle (Science): demonstrated specific neurotransmitter sites for testosterone and increased hippocampal activity with testosterone supplementation.

32. Moffat SD et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 27-JAN-2004; 62(2): 188-93. nAssociated inversely with Free Testosterone Index (FTI) by itself associated inversely with FTI after adjustments for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplement. Increases in FTI 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 calculated free testosterone concentrations lower in men who developed Alzheimer disease difference occurred before diagnosis.


33. Gouras GK, Xu H, Gross RS, et al. Testosterone reduces neuronal secretion of Alzheimer’s ?-amyloid peptides. Proc Natl Acad Sci USA 2000; 97: 1202–1205. This link will take you to the abstract, where a full text link is offered.


34. Papasozomenos demonstrated that testosterone decreases the change of Tao protein phosphorilation seen in AD plaques.


35. Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia. Gillett MJ, Martins RN, Clarnette RM, Chubb SA, Bruce DG, Yeap BB.


Testosterone and Total Mortality:

37. Testosterone and HBA1C and diabetes:


38. Not a very clean study, examining CEE replacement therapy and the addition of testosterone demonstrated an associated reduction in plasma viscosity in the testosterone treated group vs. the CEE alone group. There was an accompanying decrease in Total Cholesterol, HDL, and Triglycerides. Testosterone did not moderate the rise in fibrinogen associated with CEE.


39. Study by……..shows associated reduction in carotid intimal thickness associated with maintained testosterone levels in women, with the lowest intimal thickness seen in women in the highest tertile of testosterone levels.


Summary:

Part of age management medicine, or any specialty for that matter, requires literature in defense of one’s clinical position. What I’ve tried to get started here is a rudimentary “article armamentarium” for use in keeping discussions about the merits of testosterone replacement in the realm of using it as a dispassionate marker of disease risk, and show that modulation of testosterone is associated with decreases in these established and well accepted markers and a diminishment in interval mortality during aging.

Alan P. Mintz, M.D., is Chief Medical Officer, Chief Executive Officer, and co-founder, Cenegenics® Medical Institute. Dr. Mintz has completed the AMA/PRA Level 4 Classification, Parts 1 & 2, Tutorial Training in Age Management Medicine jointly sponsored by the Cenegenics Medical Institute and The Foundation for Care Management. A University of Chicago graduate, Dr. Mintz earned the Degree of Doctor of Medicine from the University of Illinois - School of Medicine. He went on to serve as a physician with the United States Navy, prior to postgraduate training in radiology. Dr. Mintz is a Diplomate of the American Board of Radiology, including nuclear medicine and radiation therapy. Dr. Mintz was appointed chairman of the Department of Radiology for several Chicago-area hospitals and remains an adjunct professor for the Center for
Cardiovascular Research, at Northeastern Illinois University. He previously held the positions of chief executive officer, president and co-founder at the world’s largest radiology management company. Thanks to his professional expertise and guidance, Cenegenics Medical Institute (with the joint sponsorship of Foundation for Care Management) has been recognized by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education to physicians.