

COVER STORY

Testosterone Attacked by the Media
Life Extension Reveals the Facts...



*On November 12, 2003, the Institute of Medicine, a government-supported nonprofit organization, issued a news release announcing the publication of a book entitled *Testosterone and Aging*.*

The news release stated that after careful evaluation of the pros and cons of conducting a large-scale clinical study of testosterone therapy to treat age-related conditions in men, an expert committee recommended going forward with smaller-scale trials.

Concerns about safety and efficacy were clearly spelled out, as in the following excerpt from the Institute of Medicine news release:

“The committee found no compelling evidence of major adverse side effects resulting from testosterone therapy, but the evidence is inadequate to document safety.”

In response to this news release, the news media attacked the use of testosterone therapy as being dangerous and useless. The following excerpt is from an Associated Press story that was widely circulated throughout the US:

“Tens of thousands of aging men are trying testosterone shots, patches, and gel in hopes of regaining youthful vigor and virility. A new book uncovers little evidence it works— or that the therapy is even safe—but recommends careful study to find out.”

In addition, newspapers and other media organizations around the country ran the following headlines on November 12-13 that blatantly distorted the Institute of Medicine book:

<p>“Hormone Safety doubted—Testosterone Therapy Found ‘Inappropriate’ for Most Men” —<i>The Washington Post</i></p>	<p>“Testosterone Use Grows Despite Risks” —<i>The Boston Globe</i></p>	<p>“Testosterone Not Helpful for Most Men” —<i>Good Housekeeping</i></p>	<p>“Testosterone: Benefits, Risks Unknown” —<i>WebMD.com</i></p>
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The media misrepresented findings about the risks and benefits of testosterone therapy. In this article, Life Extension reviews and critiques the new *Testosterone and Aging* book and the media’s inaccurate portrayal of what the book says.

We have found that a major flaw with these kinds of government-sponsored publications is that they are written by “committees of experts” that appear to lack a comprehensive understanding and the clinical experience of using testosterone to treat age-related disorders. For instance, the committee cites studies where testosterone did not produce long-term benefits. Anti-aging doctors, on the other hand, have long known that most men taking testosterone also need aromatase-inhibitors to block the conversion of testosterone to estrogen. Too much estrogen in a man nullifies the beneficial effects of testosterone. Excess estrogen also contributes to a number of serious disorders ranging from heart disease to prostate cancer.

These committees also fail to realize the critical importance of individualizing a testosterone replacement program. Life Extension’s testosterone protocol, for example, mandates blood testing to ascertain how much testosterone, aromatase inhibitor, and/or 5-alpha reductase blocker are needed based on a person’s individual health profile and needs. The studies reviewed and proposed by the Institute of Medicine give groups of aged men the same amounts of testosterone without factoring in critical individual requirements.

In reviewing safety data, the Institute of Medicine’s committees bring up every side effect that could possibly occur, but overlook the blood-testing protocols used by most anti-aging physicians to guard against these problems. Despite its concern about

possible side effects, the Institute of Medicine recommends initiating clinical trials based on “preliminary evidence” that testosterone therapy may “improve strength, sexual function, cognitive function, and general well-being” in aging men. Left out of the news release is evidence that testosterone therapy also protects against osteoporosis, anemia, and heart disease.

The Institute of Medicine’s proposed initial clinical trials would ascertain the efficacy of testosterone therapy over a one-to two-year period. Once efficacy is established, much longer trials would be needed to ascertain safety.

While the Life Extension Foundation endorses more human clinical trials, the concern is that the study design may be so badly flawed that the results will not reflect the benefits attainable if proper male hormone modulation therapy is administered. Proper testosterone therapy involves the use of drugs to block excess estrogen and DHT (dihydrotestosterone), in addition to individualizing the dose of testosterone. As this will be a government-funded study, the needs of the “individual” are seldom factored in.

It is becoming increasingly clear that government studies are designed for the masses, not for the individual who wants to follow a scientifically designed program to forestall the degenerative effects of aging. In this article, you will see why the government is not the appropriate body to determine the risk-benefit ratio of novel anti-aging therapies, including testosterone replacement.

To fully understand the vital importance of optimal testosterone levels to men of all ages, it is worthwhile to spend a few minutes on the genesis of this quintessential marker of manhood.

Testosterone is a substance that has been intimately tied throughout the ages to a man’s virility and sexuality. While the testicles are the organs in a man’s body that secrete testosterone, production of this vital male hormone actually begins with a cascade of biological events that occur in the brain. Testosterone synthesis begins when the brain’s pituitary gland secretes luteinizing hormone, which then prompts the testicles to produce testosterone via the Leydig cells. It has been estimated that a man begins life with 700 million Leydig cells and begins to lose 6 million of those cells each year after his twentieth birthday.¹

After testosterone is secreted into the bloodstream via the Leydig cells, it can follow several different paths. Some testosterone attaches with another biochemical known as sex hormone binding globulin, or SHBG. Testosterone not bound up with SHBG is known as free testosterone, and it is in this form that testosterone can exert its powerful effects on the human body. Testosterone also can be converted via enzymatic pathways into different hormones. Through the actions of the 5-alpha reductase, an enzyme found in multiple tissues but concentrated in the prostate gland, testosterone can be converted into dihydrotestosterone, or DHT. Testosterone also can be converted to estrogen via the actions of aromatase, an enzyme found in skin, fat, bone, and brain cells.

Estrogen—which is not just one hormone but several related compounds with very similar biological activity—only recently was discovered to be important in many physiological functions in men, including maintenance of bone mass and cognitive function.²

While some estrogen is essential to men’s health, too much of it can be quite harmful, especially when in the form of 16-alpha-hydroxyestrone. This chemical, a breakdown product of estrogen metabolism, has high estrogenic activity and has been implicated for its carcinogenic activity. Another estrogen metabolite, 2-hydroxyestrone, is believed to be much less harmful, and a ratio tilting toward the 2-hydroxyestrone is thought to be beneficial.

Testosterone Decline: Andropause

From the beginning of human record, priests, saints, medicine men, farmers and sultans have been demonstrating how clear-cut, sure, and simple it was to take the vigor of animals and men away. How? By removing their testicles.³

—Paul de Kruif, *The Male Hormone*

Total testosterone levels peak in a man at approximately age 30; by age 40, 5% of men are thought have low testosterone levels, and by age 70, that figure goes up to at least 40-50%.⁴ In addition to the absolute change in total testosterone levels, changes also are seen in the ratio of free testosterone to testosterone bound to SHBG. In many aging men, and certainly in those who are obese, free testosterone levels drop significantly as SHBG levels increase and “bind up” the remaining free testosterone.

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Testosterone is vitally important for both its anabolic properties, including effects on maintaining healthy cholesterol levels, protein synthesis, muscle mass, and bone density, and its androgenic effects, including the development and maintenance of male secondary sex characteristics (deep voice, increase in facial and body hair, muscle development) and sexual functions such as libido and erectile capability.

As men age and testosterone levels decrease, classic signs of testosterone deficiency—andro-pause—frequently appear. These signs include thinning hair, decreasing libido, increasing fat mass and declining muscle mass, and even depression. It is no wonder that in the Institute of Medicine's Testosterone and Aging,⁵ the authors state: *"more than 1.75 million prescriptions for testosterone products were written in 2002, an estimated increase of 30 percent over the approximately 1.35 million prescriptions in 2001, and an increase of 170 percent from the 648,000 prescriptions in 1999."*

Institute of Medicine Report: A Fair Examination?

Because of both the large increase in testosterone use among men and the aging of the estimated 50-70 million members of the baby-boom generation, in 2002 the National Institute on Aging and the National Cancer Institute directed the Institute of Medicine to assess the benefits and risks of testosterone supplementation among older men. The result was a 217-page book released in November 2003. The group of physicians and scientists that authored the book reviewed a significant portion of already published material on testosterone replacement therapy, and offered its own conclusions on whether and how to conduct future studies of testosterone supplementation.

The Institute of Medicine book begins with an introduction that reviews testosterone synthesis and its action on the human body, as well as a short section on testosterone replacement therapy. This introductory section is generally factual and devoid of any overt bias, but also contains some incorrect statements. On p. 23, the authors state:

"Although some older men who have tried testosterone therapy report feeling 'more energetic' or 'younger,' testosterone supplementation remains a scientifically unproven method for preventing or relieving any physical or psychological change that men may experience as they get older."

The following 92 pages of the book, however, detail study after study showing the efficacy of testosterone supplementation therapy in alleviating the multiple symptoms of andropause. Because of this and similar inconsistencies throughout the book, the Institute of Medicine's findings almost certainly will be suspect in the eyes of many anti-aging researchers. This is one of the problems inherent in the authoring of books by "committees of experts."

Testosterone Alleviates Andropause Disorders

The next section of the book, "Testosterone and Health Outcomes," cites various studies showing that testosterone supplementation can play a significant role in alleviating many symptoms of andropause, including the loss of bone and muscle mass, depression, loss of sexual functioning, and heart disease.

This section begins by acknowledging that multiple studies have conclusively proven that testosterone levels significantly decline at a steady rate of 1-2% each year in aging men. Some of the studies cited, such as the Massachusetts Male Aging Study that examined testosterone levels in 1,709 men aged 39 to 70, showed that good health among aging men correlates with higher levels of testosterone.

Following this admission, the authors then spend the next 72 pages on an extensive review of the literature detailing how testosterone supplementation can affect many common symptoms of andropause. In the section on testosterone levels and bone mass, the authors state on p. 45:

"Several studies with large sample sizes that controlled for age and other potential confounding factors found that lower levels of bioavailable testosterone were associated with lower bone density... and "low levels of testosterone have been identified as a risk factor for hip fractures."

This section continues by citing literature detailing testosterone's effect on muscle mass, body composition, and physical function. The Institute of Medicine authors correctly state that the loss of muscle mass (sarcopenia) is a significant cause of



Photomicrograph of human testosterone hormone magnified 130x.

disability in the elderly, thus making the study of supplements such as testosterone all the more important. Although multiple studies show that testosterone supplementation does help aging men regain muscle mass, the Institute of Medicine still hedges on this issue, stating on p. 51 that *“research findings regarding testosterone and various body composition measures have been inconsistent, although many studies find an increase in total or abdominal fat mass with decreased testosterone levels.”*

One such study, which, surprisingly, is not cited by the Institute of Medicine, shows conclusively that testosterone levels are vitally important for overall physical function in aging men. Published in the *Journal of Endocrinology and Metabolism*, this study of 403 healthy men, aged 73 to 94 years, examined decreases in muscle strength, bone mass, and body composition seen in aging males and their relationship to falling testosterone levels.⁶ The researchers measured the men’s hormonal levels and ran multiple tests to gauge their body composition, muscle strength, and bone mass. Their findings were not surprising, at least to physicians well versed in anti-aging medicine—muscle strength and bone mass were at optimal levels in men with the highest levels of free testosterone. According to the authors of this independent study, *“a number of clinical problems present in older men may be related to androgen [testosterone] deficiency, including reduced muscle mass, changes in body composition, and loss of BMD [bone mass density].”*

Low Testosterone Tied to Health Disorders

While optimal testosterone levels are needed to maintain muscle mass and bone strength, testosterone also is needed for cognition, sexual functioning, and even heart health. Multiple studies have confirmed that men who maintain optimal testosterone levels as they age have significantly fewer symptoms of mental senility when compared to men with low levels of testosterone.

The Institute of Medicine book confirms this and cites three widely publicized, randomized, placebo-controlled studies showing that testosterone supplementation improves verbal memory, working memory, and visuospatial performance in elderly men.⁷⁻⁹ Unfortunately, the Institute of Medicine omits a landmark study published in 2002 in which 407 men, aged 50 to 91, were followed for 10 years and had multiple tests to determine their testosterone levels and cognitive functioning.¹⁰ The authors of this independent study concluded:

“Higher FTI [free testosterone levels] was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and a reduced rate of longitudinal decline in visual memory.”

An even more recent study also overlooked by the Institute of Medicine shows that elderly men who suffered from Alzheimer’s disease had lower-than-expected levels of testosterone, which the authors hypothesize may be due to brain degeneration seen in Alzheimer’s sufferers.¹¹ The study authors are now investigating whether low testosterone levels precede cognitive dysfunction in men at risk for Alzheimer’s. If they do, then testosterone replacement therapy could be warranted for men with lower-than-normal testosterone levels to potentially ward off Alzheimer’s disease.



Testosterone supplementation has been shown in multiple studies to improve libido^{12,13} and erectile capability¹⁴ when administered to aging men. Given basic scientific knowledge of how testosterone plays a key role in men’s sexual development during puberty and functioning during adulthood, results such as this should come as no surprise. The Institute of Medicine, however, only grudgingly acknowledges the role that testosterone supplementation can play in improving sexual performance in men, stating on p. 70 that *“overall, there is some suggestion that testosterone therapy may be beneficial [in terms of sexual functioning] to men with low baseline testosterone levels.”*

The Institute of Medicine book includes a brief, three-page section (pp. 77-80) on the possible effects of testosterone and heart health in aging men. With cardiovascular disease being the number-one killer of men in the US and most Western industrialized nations, it is surprising that the Institute of Medicine does not give this very important topic more consideration. As in other sections of the book, the authors overlook studies showing the beneficial effects of testosterone on heart disease, such as the Rotterdam Study, in which researchers examined testosterone levels and cardiac health among 504 men aged 67 to 75. The researchers conclusively showed that men with higher levels of testosterone had lower levels of coronary artery disease.¹⁵ The Rotterdam researchers concluded:

“We found an independent, inverse association between levels of endogenous testosterone and severe aortic atherosclerosis and progression of aortic atherosclerosis in men.”

It is a mystery why the Institute of Medicine would exclude such a well-designed study and state on p. 77 that *“heart and vascular diseases have a complex multifactorial etiology, and the role of testosterone in this mix has yet to be determined.”*

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Does Testosterone Cause Prostate Cancer?

Mainstream medical practitioners often have stated that prostate cancer, which in 2003 was responsible for the deaths of more than 29,000 men in the US, is caused by testosterone. Fortunately, the Institute of Medicine includes some data showing that optimal levels of testosterone do not cause prostate cancer, and in fact may protect against this major killer of elderly men. On p. 90, the authors state:

“population-based studies clearly document the relationship between aging and both increases in prostate cancer incidence rates and decreases in circulating [and free] testosterone levels. While this relationship does not equal causality, the findings do raise intriguing hypotheses regarding the influence of testosterone on inhibiting prostate carcinogenesis.”

Estrogen’s Role in Prostate Cancer

Unfortunately, while the Institute of Medicine spends 11 pages (pp. 87-98) detailing testosterone’s effect on the prostate, it offers no discussion of the possible effects of estrogen on prostate and its role in prostate cancer. The belief that estrogen, rather than testosterone, is one of the prime hormonal initiators of prostate cancer is based on the fact that while testosterone levels are highest in young men, prostate cancer essentially is never seen in this population. It is only in older men, who have lower levels of testosterone but higher levels of estrogen and its breakdown products, that prostate cancer is a significant health threat. Animal studies have shown that male rats treated with testosterone alone showed significantly less prostate growth compared to animals treated with both testosterone and estrogen.¹⁶ A 1993 study showed that men treated with DHT (which cannot convert to estrogen) saw a reduction in the size of their prostate with no sign of prostate cancer.¹⁷ An article published in 2003 in the World Journal of Urology sums up the estrogen-prostate cancer link succinctly: *“Estrogenic stimulation through estrogen receptor alpha in a milieu of decreasing androgens [testosterone] contributes significantly to the genesis of benign prostates hyperplasia, prostate dysplasia, and prostate cancer.”*¹⁸

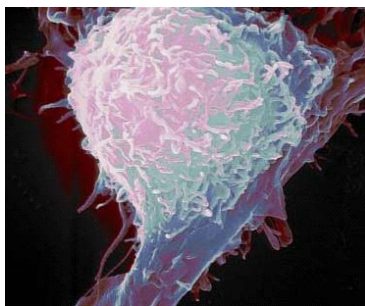
The Institute of Medicine’s Recommendations

With all the positive studies cited by the Institute of Medicine, it would be reasonable to expect the authors to conclude that testosterone supplementation, to even the most conservative-minded researcher, has been shown to be efficacious for a variety of andropause-related symptoms. Unfortunately, that is not the case. In fact, the authors do not even acknowledge that low testosterone contributes to andropause in any way, shape, or form, as seen in the following quote on p. 100:

“Endogenous testosterone levels clearly decline with aging, but it is not clear if lower levels of serum testosterone affect health outcomes in older men.”

Following this remarkable statement, the authors then conclude on p. 100:

“A systematic review of the medical literature on testosterone therapy, particularly placebo-controlled trials in older men, demonstrated that there is not clear evidence for any of the health outcomes examined.”



Given the mind-set exemplified by the previous statement, the Institute of Medicine’s recommendations and conclusions should come as no surprise. On pp. 117-167, the authors detail the committee’s key conclusions, considerations, and recommendations, based on their rather skeptical view of testosterone’s effect on the aging process in men and the use of testosterone supplementation. Their first recommendation is to conduct trials of testosterone supplementation only in older men—those aged 65 and above—and to focus on testosterone supplementation as a therapeutic intervention rather than a preventive measure. The problem here is that it is well established—and even acknowledged by the Institute of Medicine—that in most men, testosterone levels begin falling while they are in their forties. While it is certainly worthwhile to try to treat

New European Study Supports Testosterone Supplementation

A report in The Journal of Clinical Endocrinology and Metabolism (November 2003) sheds more light on the beneficial effects of testosterone supplementation in andropausal men. The study authors conducted a rigorous database search of testosterone’s effect on heart disease in men, and identified multiple studies showing that men with low testosterone levels had higher blood pressure, LDL cholesterol levels, triglyceride levels, and body mass index compared to men with optimal testosterone levels. Discussing the potential side effects of testosterone supplementation in elderly men, the authors noted, **“the scientific basis for these concerns is scarce.”***

** Muller M, van der Schouw YT, Thijssen JH, Grobbee DE. Endogenous sex hormones and cardiovascular disease in men. J Clin Endocrinol Metab. 2003; 88 (11): 5076-86.*

The recommendations continue with the idea of starting research trials with studies to determine whether there is any benefit to testosterone supplementation, and if so, then conducting longer-term trials. The glaring problem with these recommendations is that a significant number of clinical trials already have been conducted—many referenced by the Institute of Medicine—that prove the efficacy of testosterone supplementation for treating a variety of andropause-related symptoms. In addition, longer-term studies of up to three years already have been conducted and have established the usefulness of testosterone supplementation in both middle-aged and elderly men. In the journal *The Aging Male*, researchers recently presented the findings of a three-year study of 122 men, aged 19 to 67, who were treated with testosterone gel.¹⁹ As with numerous earlier studies, the study authors found that long-term treatment with testosterone supplementation causes a statistically significant improvement in bone mineral mass and sexual desire, an increase in muscle mass, and a decrease in fat mass.

The Institute of Medicine's final recommendation concerns the safety of the men participating in the testosterone supplementation trial. To accomplish this, the committee would set up strict exclusion criteria, mandate careful monitoring of markers of prostate function such as PSA (prostate specific antigen) levels, and seek to ascertain whether long-term testosterone supplementation can cause a rise in prostate cancer. While these recommendations are commendable, significant omissions also are obvious, such as failing to include monitoring of SHBG and estrogen levels along with the use of estrogen blockers (aromatase-inhibitors).

It is puzzling, at the very least, why the Institute of Medicine fails to even mention the significant effect of rising estrogen levels on prostate cancer when a substantial amount of well-researched literature has been published on this very subject.

Conclusions of the Institute of Medicine

In the Institute of Medicine book's final pages (pp. 163-7) preceding the appendixes, the authors cast a derisive eye on the myriad reports showing the effectiveness of testosterone supplementation, concluding:

"The trials that have been conducted do not show definitively that there are benefits of testosterone therapy for older men...the committee recommends short-term efficacy trials to determine if there are benefits of testosterone therapy in older men."

Apparently, at the cost of the health and possibly lives of many thousands of middle-aged and elderly men, the Institute of Medicine committee has decided that yet another trial of testosterone supplements should be conducted, a trial that will take years and be funded by taxpayers, while those very same taxpayers are suffering from the very real, and often very debilitating symptoms, of andropause-induced testosterone deficiency.

Instead of reading the Institute of Medicine's book, the media instead chose to malign the multiple benefits of testosterone replacement and exaggerate its potential side effects. *Testosterone and Aging* cites numerous clinical studies showing significant anti-aging effects, but the media reported only the disparaging conclusions made by certain committee members that had little or no basis in fact.

Unlike the mainstream media, we actually read the book, which provides solid scientific evidence that aging men should seek to maintain youthful testosterone levels.

How to Restore Youthful Testosterone Levels

Unlike the Institute of Medicine's dismissive report, Life Extension long ago identified and resolved potential problems associated with testosterone replacement therapy, enabling thousands of aging men to safely enjoy the remarkable rejuvenation effects that can occur when sex hormone levels are restored to youthful ranges.

In 1999, the Life Extension Foundation published an extensive protocol that describes how aging men can restore youthful sex hormone levels. Minor modifications were made to the protocol, which is contained in the fourth edition of *Disease Prevention and Treatment* and also can be accessed at www.lef.org/test.

Low Testosterone = Higher Blood Pressure

In a recent study, Italian researchers compared plasma testosterone levels of 119 elderly men with isolated systolic hypertension to those of 106 nonhypertensive elderly men.* All the study participants were 60 to 79 years old, non-obese, nondiabetic, and nonsmokers. The hypertensive men were found to have 14% lower levels of testosterone compared to the nonhypertensive men. In both the hypertensive and nonhypertensive men, low testosterone levels correlated with higher blood pressure values.

These findings are vastly magnified by the results of another study, which reviewed data to determine how blood pressure affects cardiovascular disease risk.** After reviewing a meta-analysis of data from 61 prospective studies involving almost 1 million participants and 56,000 vascular deaths, the researchers stated: "Persons aged 40 to 69 years had a doubling of risk

of stroke or coronary mortality with every 20-mm Hg increment in [systolic blood pressure] (or 10-mm Hg higher [diastolic blood pressure]) throughout the entire range of [blood pressure].” The researchers’ conclusions were:

“There is overwhelming evidence of a continuous, graded influence of [systolic blood pressure] on [cardiovascular disease] morbidity and mortality at all ages...It is the level of [blood pressure] that kills, not arbitrarily defined hypertension...The importance of what appear to be trivial differences in [blood pressure], even within the high-normal [blood pressure] range, should not be underestimated. The extra effort needed to lower the [blood pressure] down to the recommended goals for avoiding [cardiovascular disease] is worthwhile.”

Taken together, these two studies point to a conclusion that could only escape a committee of government experts: With hypertension linked to impaired testosterone levels, and with higher blood pressure values in turn linked to increased risk of cardiovascular disease in both men and women of all ages, aging men would be well advised to consider taking all measures necessary—including testosterone supplementation—to bring their blood pressure values into the optimal ranges.

The Institute of Medicine researchers note in their report that testosterone’s role in heart and vascular diseases “has yet to be determined”—a conclusion squarely contradicted by many published studies.

* Fogari R, Malacco E, Preti P, et al. Plasma testosterone in isolated systolic hypertension. *Hypertension*. 2003 Oct;42(4). Epub 2003 Sep 15.

** Kannel WB, Vasan RS, Levy D. Is the relation of systolic blood pressure to risk of cardiovascular disease continuous and graded, or are there critical values? *Hypertension*. 2003 Oct;42(4):453-6. Epub 2003 Sep 15.

References

1. Morales A, Tenover JL. Androgen deficiency in the aging male: when, who, and how to investigate and treat. *Urological Clinics North America*. 2002; 29(4):975-82.
2. Nelson LR, Bulun SE. Estrogen production and action. *J Am Acad Dermatol*. 2001 Sep; 45(3):S116-24.
3. de Kruif Paul. *The Male Hormone*. Harcourt, Brace, and Company: New York, 1945.
4. Anawalt BD, Merriam GR. Neuroendocrine aging in men. Andropause and somatopause. *Endocrinol Metab Clin North Am*. 2001 Sep; 30(3):647-69.
5. The Institute of Medicine of the National Academies. *Testosterone and Aging*. National Academies Press; Washington, DC: 2003.
6. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab*. 2000 Sep; 85(9):3276-82.
7. Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older adults. *Behav Neurosci*. 1994 Apr; 108(2):325-32.
8. Cherrier MM, Asthana S, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology*. 2001 Jul 10;57(1):80-88.
9. Janowsky JS, Chavez B, Orwoll E. Sex steroids modify working memory. *J Cogn Neurosci*. 2000 May;12(3):407-14.
10. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab*. 2002 Nov; 87(11):5001-7.
11. Hogervorst E, Combrinck M, Smith AD. Testosterone and gonadotropin levels in men with dementia. *Neuroendocrinol Lett*. 2003 Jun-Aug;24(3-4):203-8.

12. Perry JE, Perry HM 3rd, Kaiser FE, et al. Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geri Soc.* 1993 Feb;41(2):149-52.
13. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement therapy in older hypogonadal males. *J Clin Endo Metab.* 1997 Nov; 82(11): 3793-96.
14. Wang C, Swedloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength and body composition parameters in hypogonadal men. *J Clin Endocrinol. Metab* 2000 Aug; 85(8):2839-53.
15. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: The Rotterdam Study. *J Clin Endocrinol Metab.* 2002 Aug;87(8):3632-9.
16. Suzuki K, Takezawa Y, Suzuki T, Honma S, Yamanaka H. Synergistic effects of estrogen with androgen on the prostate. *Prostate.* 1994 Oct;25(4):169-76.
17. de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause.' *Ann Med.* 1993 Jun;25(3):235-41.
18. Steiner MS, Raghov S. Antiestrogens and selective estrogen receptor modulators reduce prostate cancer risk. *World J Urol.* 2003 May;21(1):31-6.
19. Swedloff RS, Wang C. Three-year follow-up of androgen treatment in hypogonadal men: preliminary report with testosterone gel. *Aging Male.* 2003 Sep;6(3):207-11.
20. Kraemer WJ, Hakkinen K, Newton RU, et al. Effects of heavy-resistance training on hormonal response patterns in younger vs. older men. *J App Physiol.* 1999 Sep;87(3): 982-92.
21. Izquierdo M, Hakkinen K, Ibanez J, et al. Effects of strength training on muscle power and serum hormones in middle-aged and older men. *J App Physiol.* 2001 Apr;90(4): 1497-507.
22. Longcope C, Feldman HA, McKinlay JB, Araujo AB. Diet and sex hormone-binding globulin. *J Clin Endocrinol Metab.* 2000 Jan; 85(1):293-6.
23. Nagata C, Inaba S, Kawakami N, Kakizoe T, Shimizu H. Inverse association of soy product intake with serum androgen and estrogen concentrations in Japanese men. *Nutr Cancer.* 2000;36(1):14-8.
24. Nagata C, Takatsuka N, Kawakami N, Shimizu H. Relationships between types of fat consumed and serum estrogen and androgen concentrations in Japanese men. *Nutr Cancer.* 2000;38(2):163-67.
25. Muti P, Westerlind K, Wu T, et al. Urinary estrogen metabolites and prostate cancer: a case-control study in the United States. *Cancer Causes Control.* 2002 Dec;13(10): 947-55.
26. Tikkiwal M, Ajmera RL, Mathur NK. Effect of zinc administration on seminal zinc and fertility of oligospermic males. *Indian J Physiol Pharmacol.* 1987 Jan-Mar;31(1):30-4.
27. Takihara H, Cosentino MJ, Cockett AT. Zinc sulfate therapy for infertile males with or without varicocele. *Urology.* 1987 Jun; 29(6):638-41.
28. Netter A, Hartoma R, Nahoul K. Effect of zinc administration on plasma testosterone, dihydrotestosterone and sperm count. *Arch Androl.* 1981 Aug;7(1):69-73.
29. Campbell DR, Kurzer MS. Flavonoid inhibition of aromatase enzyme activity in human preadipocytes. *J. Steroid Biochem Mol Biol.* 1993 Sep;46(3):381-8.
30. Hryb DJ, Khan MS, Romas NA, Rosner W. The effect of extracts of the roots of the stinging nettle (*Urtica dioica*) on the interaction of SHBG with its receptor on human prostatic membranes. *Planta Med.* 1995 Feb; 61(1):31-2.
31. Hirano T, Homma M, Oka K. Effects of stinging nettle root extracts and their steroidal components on the Na⁺,K⁺-ATPase of the benign prostatic hyperplasia. *Planta Med.* 1994 Feb;60(1):30-3.
32. Vahlensieck W Jr, Fabricius PG, Hell U. Drug therapy of benign prostatic hyperplasia. *Fortschr Med.* 1996 Nov 10;114

33. Gansser D, Spiteller G. Plant constituents interfering with human sex hormone-binding globulin. Evaluation of a test method and its application to *Urtica dioica* root extracts. *Z Naturforsch. C* 1995 Jan-Feb; 50(1-2):98- 104.
34. Sokeland J. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. *BJU Int.* 2000 Sep;86(4):439-42.
35. Hormonal rejuvenation for men. Replenish testosterone naturally. DHEA treatment for sexual dysfunction. *Life Extension magazine* Jan 2000; 6(1):20-24, 25-30, 34-36.

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Natural Ways to Combat Testosterone Loss



Andropause—caused by a decrease in bioavailable testosterone and rising estrogen—is a potentially troublesome time in a man’s life. In contrast to mainstream medicine’s apparent indifference to the debilitating effects of the aging process, those of us in the anti-aging field know there are numerous ways in which men can combat many of the deleterious aspects of an imbalance in their hormones, especially testosterone and estrogen. While multiple studies have proven that testosterone supplementation can ease or even reverse many symptoms of andropause, some men still may be leery of using testosterone until it is given mainstream medicine’s “stamp of approval.” For those men and others who wish to optimize their testosterone levels as they age, below are some specific recommendations to help maintain optimal testosterone levels, combat the debilitating effects of andropause, and live life to the fullest whether you are 40 or 90 years of age.

1. Physical exercise increases testosterone levels.

Multiple studies have shown that regular, high-intensity exercise keeps a man’s testosterone at optimal levels. A 1999 study examined how the effects of heavy resistance training in both young (23 to 35 years old) and older (58 to 65 years old) men affected their testosterone levels.²⁰ Both groups saw a statistically significant increase in testosterone levels after exercise. A more recent study published in 2001 also showed that strength training in middle-aged (44 to 48 years old) men increased levels of free testosterone.²¹

2. Protein combats SHBG, helps maintain optimal testosterone levels.

While adequate protein consumption is vital to maintaining muscle mass in both men and women, it is also important in maintaining testosterone levels. A study published in 2000 examined the relationship between diet and SHBG, and found that “diets low in protein in elderly men [40-70 years old] may lead to elevated SHBG levels and decreased testosterone availability. The decrease in bioavailable testosterone can then result in declines in sexual function and muscle and red cell mass, and contribute to the loss of bone density.”²²

3. Soy and fish oil keep estrogen and SHBG in check.

Elderly men often see an increase in unhealthy levels of SHBG and estrogen via activity of the aromatase enzyme, which can lead to a net decrease in testosterone levels. Two recent Japanese studies have shown some natural ways in which men can help tilt the ratio back in favor of testosterone. One study of 97 middle-aged to elderly men found that men with high levels of soy intake had lower levels of estradiol (a form of estrogen) compared to men with lower levels of soy intake.²³ The researchers postulated that this beneficial inverse relationship could be due to inhibition of the aromatase enzyme by soy and soy-based food products. Another Japanese study examined how the essential fatty acids EPA and DHA (found in high concentrations in fish) affected SHBG levels in men 43 to 88 years of age.²⁴ After controlling for other variables, the researchers concluded that both EPA and DHA decreased levels of SHBG in middle-aged and elderly men.

4. Indole-3-carbinol protects against high estrogen levels, prostate cancer.

An adequate intake of indole-3-carbinol (I3C), through vegetables such as broccoli, brussels sprouts, and cabbage, or via supplements, may prove to be very helpful for aging men in both keeping estrogen levels in check and decreasing their risk of prostate cancer. Studies have demonstrated that I3C increases the ratio of 2-hydroxyestrone to 16-alpha-hydroxyestrone, thereby causing a decrease in the “bad” estrogen and an increase in the “good” estrogen. For men, this very well might mean a decrease in prostate cancer. In a recent study that examined the association of prostate cancer risk with estrogen metabolism, the authors noted “results of this case-control study suggest that the estrogen metabolic pathway favoring 2-hydroxylation over 16-alpha-hydroxylation may reduce risk of clinically evident prostate cancer.”²⁵

5. Zinc is essential for optimal testosterone production.

One supplement that should be considered absolutely essential for maintaining a man’s testosterone levels is zinc. This busy mineral is involved in almost every aspect of male reproduction, including testosterone metabolism, sperm formation, and sperm motility. Multiple studies have demonstrated the effectiveness of zinc in treating male infertility due to low testosterone levels.^{26,27} A prime example of the usefulness of zinc was illustrated in a study of 37 infertile men with decreased testosterone levels and associated low sperm counts.²⁸ The men were given 60 mg of zinc daily for 45-50 days. In 22 patients, testosterone levels significantly increased and mean sperm count rose from 8 million to 20 million.

6. Chrysin is a natural aromatase inhibitor.

A bioflavonoid called chrysin has shown potential as a natural aromatase inhibitor. Bodybuilders have used chrysin as a testosterone-boosting supplement because by inhibiting the aromatase enzyme, less testosterone is converted into estrogen.

The problem with chrysin is that because of its poor absorption into the bloodstream, it has not produced the testosterone-enhancing effects users expect. Pilot studies have found that when chrysin is combined with piperine, reductions in serum estrogen (estradiol) and increases in total and free testosterone result in 30 days. In a study published in the *Journal of Steroid Biochemical Molecular Biology* (1993), chrysin and 10 other flavonoids were compared to an aromatase-inhibiting drug (aminoglutethimide).²⁹ Chrysin was shown to be the most potent aromatase inhibitor, and was similar in potency and effectiveness to the aromatase-inhibiting drug. Chrysin is not a patentable drug, so do not expect to see a lot of human research documenting its effects. Many FDA-approved drugs (such as Arimidex®) inhibit aromatase, and there is not much financial incentive for finding natural ways to replace these drugs. While prescription aromatase-inhibiting drugs are relatively free of side effects, aging men who are seeking to gain control over their sex hormone levels sometimes prefer natural sources instead of trying to convince a physician to prescribe a drug (such as Arimidex®) that is not approved by the FDA as an anti-aging therapy. (Arimidex® is prescribed to estrogen-dependant breast cancer patients to prevent testosterone and other hormones in the body from converting, i.e., aromatasing, into estrogen.)



7. Nettle root liberates “bound” testosterone.

Testosterone that becomes bound to serum globulin is not available to cell receptor sites and fails to induce a libido effect. When testosterone binds to sex hormone binding globulin (SHBG), it loses its biological activity and becomes bound testosterone, as opposed to the desirable free testosterone. As men age past 45, SHBG’s binding capacity increases dramatically—by an average of 40%—and coincides with age-associated loss of libido and other andropause symptoms. Some studies show that the decline in sexual interest with advancing age is not always due to the amount of testosterone produced, but rather to the increased binding of testosterone to globulin by SHBG. This explains why some older men who are on testosterone replacement therapy do not report a long-term aphrodisiac effect. That is, the artificially

administered testosterone becomes bound by SHBG and is not bioavailable to cellular receptor sites where it would normally produce a libido-enhancing effect. European researchers have identified constituents of nettle root that bind to SHBG in place of testosterone, thus reducing SHBG’s binding of free testosterone.³⁰⁻³⁴ As the authors of one study stated, these constituents of nettle root “may influence the blood level of free, i.e., active, steroid hormones by displacing them from the SHBG binding site.”

8. Human Studies Using Combination Nutrients

To ascertain the safety and efficacy of nutrients that are purported to modulate male hormone levels, the Life Extension Foundation sponsored clinical studies to assess the effects of specific supplements on blood levels of testosterone, estrogen, SHBG, etc.³⁵ Based on the results of these studies, a formula called Super MiraForte was developed that combines chrysin, nettle root, muira puama, piperine, and other nutrients that showed the most potent effects in boosting free testosterone and suppressing estrogen in aging men. For those who would prefer to avoid testosterone-boosting and estrogen-suppressing drugs, four capsules a day of Super MiraForte may be considered. Before embarking on a hormone rejuvenation program, please refer to the Male Hormone Modulation protocol that can be accessed at www.lef.org/test.

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