Male Hormone Restoration

The significance of testosterone for male sexual function is apparent to most Life Extension members. New insights, however, underscore the critical role testosterone plays in maintaining youthful neurological structure, alleviating depression, as well as inducing fat loss in those who are unable to reduce body weight regardless of diet and exercise.

Recent studies have demonstrated that low testosterone in men is strongly associated with metabolic syndrome, type 2 diabetes, cardiovascular disease (Miner and Seftel 2007), and an almost 50% increase in mortality over a seven year period (Malkin et al 2010).

Restoring testosterone to youthful ranges in middle-aged, obese men resulted in an increase in insulin sensitivity as well as a reduction in total cholesterol, fat mass, waist circumference and pro-inflammatory cytokines associated with atherosclerosis, diabetes, and the metabolic syndrome (Kapoor et al 2006, Malkin et al 2004, Heufelder et al 2009). Testosterone therapy also significantly improved erectile function (Fukui 2007) and improved functional capacity, or the ability to perform physical activity without severe duress, in men with heart failure (Malkin et al 2007).

Factors That Affect Testosterone Levels in Men

DHEA: Dehydroepiandrosterone (DHEA) is a hormone produced from cholesterol that then follows one of two pathways, both involving two-step enzymatic conversions, to yield either estrogens or testosterone. Thus, levels of DHEA can have a role in determining levels of estrogen and testosterone, though DHEA alone is seldom enough to sufficiently restore testosterone levels in aging men.

Aromatase: One of the most important factors that affect testosterone levels and the ratio between testosterone and estrogen is the *aromatase* enzyme. Aromatase converts testosterone to estrogen, further depleting free testosterone levels and increasing estrogen levels.

Obesity: Obesity and associated hyperinsulinemia suppress the action of luteinizing hormone (LH) in the testis, which can significantly reduce circulating testosterone levels (Mah and Wittert 2010), even in men under the age of 40 (Goncharov et al 2009). In addition, increased belly fat mass has been correlated with increased aromatase levels (Kalyani and Dobs 2007).

The vicious circle of low testosterone and obesity has been described as the *hypogonadal/obesity cycle*. In this cycle a low testosterone level results in increased abdominal fat, which in turn leads to increased aromatase activity. This enhances the conversion of testosterone to estrogens, which further reduces testosterone and increases the tendency toward abdominal fat (Cohen 1999, Tishova and Kalinchenko 2009).

Sex hormone-binding globulin (**SHBG):** Most testosterone circulating in the bloodstream is bound to either *sex hormone-binding globulin* (SHBG) (60%) or albumin (38%). Only a small fraction (2%) is unbound, or “free”. (Morales et al 2010).

Testosterone binds more tightly to SHBG than to albumin (Henry et al 2002). Consequently, only albumin-bound testosterone and free testosterone constitute the bioavailable forms of testosterone, which are accessible to target tissues and carry out the actions of the essential hormone (Morales et al 2010). Thus the bioavailability of testosterone is influenced by the level of SHBG.

Aging men experience both an increase in aromatase activity and an elevation in SHBG production. The net result is an

increase in the ratio of estrogen to testosterone and a decrease in total and free testosterone levels (Lapauw et al 2008). As will be discussed below, it is crucial that this skewed ratio be balanced.

Liver Function: The liver is responsible for removing excess estrogen and SHBG, and any decrease in liver function could exacerbate hormonal imbalances and compromise healthy testosterone levels. Thus it is important that aging men also strive for optimal liver function.

Effects of Age-Related Decline in Testosterone Levels and Testosterone Therapy

The exact cause of the age-related reduction in testosterone levels is not known; it is probably the result of a combination of factors, including:

- Increasing body fat (especially belly fat, and therefore increasing aromatase activity)
- Oxidative damage to tissues responsible for the production of testosterone
- Reduction in testicular testosterone synthesis
- Declining levels of precursor molecules, such as DHEA
- Nutritional status and liver function

The consequences of declining testosterone levels are striking.

Body Composition and Inflammation: Testosterone affects fat cell metabolism and fat loss in several ways: inhibiting fat storage by blocking a key enzyme called lipoprotein lipase that is necessary for the uptake of fat into the body's fat cells; stimulating fat burning by increasing the number of specific receptors on the fat-cell membrane that release stored fat; increasing insulin sensitivity; enhancing growth of muscle fibers; and decreasing fat deposits. All of these effects promote lean body mass and reduce fat mass (Naharci et al 2007, Saad et al 2007). Placebo-controlled trials have demonstrated both significant increases in lean body mass and decreases in fat mass after varying courses of testosterone treatment in older men. In these studies, the greatest favorable changes in body composition were seen in participants with low baseline testosterone levels who received testosterone therapy for 12 months or longer (Allen et al 2007).

Emergent evidence suggests that maintaining youthful testosterone levels may help aging men avert a variety of inflammation-mediated disease, such as atherosclerosis and arthritis. By powerfully suppressing the activity an enzyme called *5-lipoxygenase*, testosterone calms a fundamental pro-inflammatory pathway involved in the synthesis of signaling molecules known as *leukotrienes* (Pergola 2011). Leukotrienes are derivatives of the pro-inflammatory omega-6 fatty acid *arachadonic acid;* these molecules underlie much of the inflammatory development of asthma and bronchitis, and play a role in the pathology of cardiovascular disease and diabetes as well (Parlapiano 1999; Riccioni 2010).

In a study involving 184 men with low testosterone levels, 18 weeks of testosterone replacement therapy suppressed markers of inflammation including IL-1β, TNF-α, and C-reactive protein. Moreover, when compared to men who received a placebo control, men receiving testosterone replacement exhibited significant decreases in body weight, and BMI, and waist circumference (Kalinchenko 2010). The reduction in waist circumference indicates that testosterone reduces fat accumulation around the trunk of the body; this is particularly important since central fat mass and is strongly associated with increased susceptibility to inflammatory diseases and mortality (Coutinho 2011).

Musculoskeletal system: Bone integrity rests upon a balance between bone formation and bone resorption, which is controlled by multiple factors - including levels of estrogen and testosterone (Tok et al 2004, Valimaki et al 2004). In a clinical trial, testosterone increased bone mineral density in elderly men (Kenny et al 2010). Testosterone supplementation also has a positive effect on muscle metabolism and strength (Herbst 2004). This positive effect is undiminished with age.

Central Nervous System (CNS): Key to aging well is an optimistic outlook on life and the ability to engage in social and physical activity. However, low levels of testosterone have been associated with depression and other psychological

disorders (Almeida et al 2008). To make matters worse for aging men, many conventional antidepressant medications suppress libido. Some experts suggest that testosterone therapy might reduce the need for the antidepressant medications entirely (Morley 2003, Carnhan and Perry 2004). Furthermore, testosterone treatment often increases feelings of well-being (Orengo et al 2004).

Cognition and alertness are also governed, in part, by testosterone's effects on the CNS (Cherrier et al 2004). Low testosterone levels have been shown to correlate with lower scores on various psychometric tests (Moffat et al 2002), and similar effects have been reported in men undergoing androgen (male hormone) -deprivation therapy for prostate cancer (Salminen et al 2004).

Testosterone also acts as an endogenous neuroprotective agent, able to support neuron integrity against a variety of toxic insults, including oxidative stress (Ahlbom et al 2001, Pike et al 2009). In addition, testosterone has been shown to reduce β-amyloid accumulation, an important pathophysiologic factor in Alzheimer's disease (Zhang et al 2004, Rosario and Pike 2008).

Testosterone improves neuron survival in brain regions vulnerable to neurodegenerative disease. This may explain the association of low testosterone levels in men with neurodegenerative diseases (Hogervorst et al 2004, Ready et al 2004). Studies demonstrate testosterone loss occurred 5 to 10 years prior to Alzheimer's disease diagnosis. This suggests low testosterone is an important risk factor for Alzheimer's disease (Moffat et al 2004; Rosario et al 2004). In a clinical study of 36 men recently diagnosed with Alzheimer's disease, intramuscular testosterone treatment with 200mg every two weeks for up to one year was associated with improvement in both overall cognitive ability as well as critical visual-spatial function (Tan and Pu 2003).

Glucose and Lipid Metabolism: Testosterone also has been linked to metabolic function in the body. Specifically, studies have found inverse associations between the severity of metabolic syndrome, a condition characterized by excess abdominal fat, high cholesterol and high blood pressure that predisposes one for cardiovascular disease, and low plasma testosterone (Allan et al 2007, Saad et al 2008). A clinical study demonstrated that men with low testosterone levels are twice as insulin resistant as their counterparts with normal testosterone levels, and 90% met the criteria for the metabolic syndrome (Pitteloud et al 2005).

There also appears to be an inverse relationship between low testosterone levels and diabetes in men (Saad and Gooren 2009). Men with diabetes have lower testosterone levels compared to men without a history of diabetes (Stanworth and Jones 2009). The Third National Health and Nutrition survey of 1,413 men showed that men initially ranked in the lowest one-third with respect to either free or bioavailable testosterone were approximately four times more likely to have prevalent diabetes compared to those ranked in the top one-third, after researchers adjusted the results for age, race/ethnicity, and adiposity (Selvin et al 2007).

Cardiovascular Health: While conventional thought has been that because more men die from heart attacks than women, the disparity must have something to do with testosterone. However, research is pointing out that, in fact, the opposite may be true. Low levels of testosterone appear to be correlated with several cardiovascular risk factors, including atherogenic lipid profiles, insulin resistance, obesity, and a propensity to clot (Jones et al 2005). In addition, recent research is showing a clear relationship between low testosterone levels and increased incidence of cardiovascular disease and mortality in men (Malkin et al 2010).

Prostate health: Compared to younger men, older males have much more estradiol (a potent form of estrogen) than free testosterone circulating in the body. These rising estrogen and declining androgen levels are even more sharply defined in the prostate gland.

Estrogen levels increase significantly in the prostate with age, and estrogen levels in prostate gland tissues rise even higher in men who have BPH (Shibata Y et al 2000; Gann PH et al 1995; Krieg M et al 1993).

An important study indicates that testosterone is beneficial for the prostate gland in the vast majority of cases. In this study researchers looked at multiple parameters, including prostate volume, prostate-specific antigen (PSA) levels, and lower urinary tract symptoms in a group of men with low or low-normal testosterone levels (Pechersky et al 2002). Of the 207 men studied, 187 responded favorably to testosterone treatment.

The Importance of Hormone Testing

Millions of aging men have the dual conditions of low testosterone and high cholesterol. Conventional physicians prescribe cholesterol-lowering drugs to reduce cholesterol, when, in fact, the age-related rise in cholesterol might simply be the body's way of increasing hormone levels by supplying the raw materials necessary to make hormones (Dzugan et al 2002). Researchers at the Life Extension Foundation have successfully treated high cholesterol levels through a program of bioidentical hormone replacement therapy.

Life Extension believes that comprehensive tests, along with a careful physical examination, are essential in detecting hormonal imbalances in aging men.

The so-called "normal" levels of testosterone in older men reflect population averages. The Life Extension Foundation believes that most aging men would prefer not to accept the loss of youthful vigor as normal. Instead, we suggest that a more valid optimal level for all men would be in the upper one-third of the reference range used for men aged 21 to 49 years, and that any supplementation should aim to restore hormone levels to that range. The current Life Extension optimal level of free testosterone is 20-25pg/mL.

When measuring testosterone levels, it is critical to determine the levels of both *free* and *total* testosterone to understand the cause of any observed symptoms of deficiency (Khosla et al 2008).

Because of difficulties with equipment standardization and inter-laboratory variability, it is recommended that physicians consistently use the same local laboratories and gain familiarity with the accuracy, precision and definition of normal values for the assays offered in their communities (Morales et al 2010).

It is also important to remember that blood levels of both free and total testosterone vary widely among individuals, making it difficult to establish a general baseline on which to prescribe a standardized treatment protocol. However, levels are quite consistent within individuals, and thus it is important that men have multiple tests over time to determine trends and individual thresholds for treatment.

Finally, during the initial testing, it is also imperative to test estrogen levels. Many of the unwanted effects of male hormone imbalance are actually caused by an elevated estrogen level relative to low testosterone levels (the estrogen/testosterone ratio). The Life Extension optimal level of estrogen (measured as estradiol) for aging men is 20-30pg/mL.

Estrogen Balance is Critical to Aging Men

A study published in the *Journal of the American Medical Association* (JAMA) measured blood estradiol in 501 men with chronic heart failure. Compared to men in the balanced estrogen quintile, men in the highest quintile (serum estradiol levels of 37.40 pg/mL or greater) were significantly (133%) more likely to die. Those in the lowest estradiol quintile (serum estradiol levels under 12.90 pg/mL) had a 317% increased death rate compared to the balanced group. The men in the *balanced* quintile—with the fewest deaths—had serum estradiol levels between 21.80 and 30.11 pg/mL (Ewa et al 2009). This is the ideal range that *Life Extension* has long recommended male members strive for.

An epidemic problem we at *Life Extension* observe in aging male members is insufficient free testosterone, i.e., less than 20 - 25 pg/mL of serum. When accompanied by excess estradiol (over 30 pg/mL of serum), this can signal excess aromatase enzyme activity.

Testosterone Replacement Therapies

Optimal testosterone treatment usually requires a physician's prescription. Integrative physicians typically prescribe bioidentical testosterone creams (available from compounding pharmacies). Conventional physicians are more likely to prescribe prepackaged, testosterone patches and/or gels from pharmaceutical companies that have sought FDA approval for the mass commercialization of their products.

All forms of bioidentical testosterone have the same molecular structure and will increase free and total testosterone in the blood. The major difference is that prepackaged versions could cost up to 10 times more per dose than compounded versions. Furthermore, prepackaged testosterone gels are sold only in a limited number of doses, whereas compounded testosterone can be formulated at virtually any dose the physician feels is clinically necessary and useful.

Using Hormone Replacement Wisely

If a man opts for testosterone therapy (available orally or as an injection, subcutaneous implant, topical cream, gel, or skin patch), he should keep several facts and precautions in mind (Schaeffer et al 2004, Cunningham and Toma 2010):

- Hormone replacement should not be initiated without comprehensive testing.
- The patterns and trends over time of multiple hormone levels, (for instance free testosterone, total testosterone, and estrogen), determine the specific hormone replacements required.
- It may not be safe to use large amounts of testosterone in any form without also using aromatase-inhibiting supplements or medications.
- Because of the risk of worsening prostate cancer, careful screening, including a digital rectal examination and prostate specific antigen (PSA) screening, must be done before starting any hormone replacement program. However, recent research indicates that low endogenous testosterone levels may present a greater risk for prostate cancer than higher levels (Morgantaler 2006, Rodman et al 2008). If a man already has prostate cancer, however, testosterone replacement should be delayed until the underlying cancer is eradicated.
- A man contemplating hormone replacement, whether through a prescription or supplements, should work closely with a qualified physician to plan a rational treatment approach that includes continued monitoring and screening.
- There is no "one size fits all" treatment. Individuals vary, and hormone replacement can be a simple or complex process and often requires careful attention to signs and symptoms, as well as laboratory testing.

Boost Testosterone and Suppress Estrogen Levels Naturally

For men who choose not to (or are advised not to) use hormone replacement therapy, nutrients can play a vital role in a comprehensive program designed to reduce the impact of aging on sex hormone production and metabolism. The following is a list of nutrients that are part of the Life Extension Foundation's comprehensive male hormone restoration program:

Essential nutrients for optimal testosterone production:

Zinc: This mineral is involved in almost every aspect of male reproduction, including testosterone metabolism, sperm formation, and sperm motility (Ali et al 2005). 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 (Netter et al 1981). The men were given 60 mg of zinc daily for 45-50 days. In the majority of patients, testosterone levels significantly increased and mean sperm count rose from 8 million to 20 million. Some men require higher levels of zinc to adequately suppress aromatase.

DHEA: DHEA is an important hormone that tends to be depleted steadily with age (Basar NM et al 2005). A 2006 study assessing DHEA supplementation in men of average 65 years of age found that the men experienced significant increases in

testosterone and significant decreases in low-density lipoprotein (Martina et al 2006).

Tribulus: *Tribulus terrestris*, also known as puncture vine, contains the active ingredient protodioscin, which is reportedly converted to DHEA in the body (Adimoelja A 2000). This DHEA-boosting activity may account for puncture vine's reputation as an aphrodisiac in its native Europe and Asia. Animal studies appear to confirm the ability of tribulus to improve sexual function (Gauthaman et al 2003; Milasius et al 2009).

Antioxidants: One reason testosterone production may decline with advancing age is oxidative damage in the tissues that produce testosterone. A study examining the role of antioxidants in male hormone imbalance in aging men noted that antioxidant supplements (including vitamins A and E, zinc and selenium) all supported testosterone production (He et al 2005).

Natural products keep aromatase and/or sex hormone-binding globulin (SHBG) in check:

Chrysin: The bioflavonoid chrysin is a natural aromatase inhibitor (Kellis et al 1984). Bodybuilders have used chrysin as a testosterone-boosting supplement, because it minimizes the conversion of testosterone to estrogen. Although chrysin has low oral bioavailability (Walle et al 2001), its bioavailability may be significantly enhanced by co-administration with the black pepper extract, piperine, thus enhancing its actions as an aromatase inhibitor (Srinivasan et al 2007).

Quercetin: One study showed that red wine inhibits aromatase, thus inhibiting the conversion of testosterone to estrogen. The study attributed this effect to the quercetin and other ingredients (Eng et al 2002).

Nettle root: Lignans contained in nettle root extract may help prevent the binding of *sex hormone-binding globulin* to testosterone. This may help ensure that free testosterone is available for promoting male vitality and youthful sexual function (Anon 2007, Chrubasik et al 2007). Nettle root extract is used extensively, either in combination with saw palmetto (Lopatkin 2005) or by itself (Safarinejad 2005) for relief of BPH symptoms.

Fish oil: A study examined how the essential fatty acids EPA and DHA affected SHBG levels in men 43 to 88 years of age (Nagata et al 2000). After controlling for other variables, the researchers concluded that both EPA and DHA decreased levels of SHBG in middle-aged and elderly men.

Protein: While adequate protein consumption is vital to maintaining muscle mass, it is also important in maintaining testosterone levels. A study examined the relationship between diet and SHBG, and found that diets low in protein in men 40-70 years old may lead to elevated SHBG levels and consequently decreased testosterone bioactivity (Longcope et al 2000).

Natural products to support sexual function

Muira Puama: Muira puama, *Ptychopetalum olacoides*, grows in the Amazon region of Brazil. It is considered an aphrodisiac and an effective treatment for impotence. It has been studied by Jacques Waynberg (Waynberg 1990), a prominent medical sexologist at the Institute of Sexology in Paris. In one of his studies, men with loss of libido received 1.5 grams/day of muira puama for 2 weeks. 62% rated the treatment as having a dynamic effect, and 52% with erectile dysfunction rated the treatment as beneficial. In another study, muira puama treatment was given to 100 men, aged 18 years or older, with impotence and/or loss of libido. A significantly increased frequency of intercourse was reported in 66% of the men. Of the 46 men who complained of loss of desire, 70% reported libido intensification. The stability of erection during intercourse was restored in 55% of men, and 66% of men reported a reduction in fatigue. Other reported beneficial effects included improved sleep and morning erections.

Maca: Maca has been used among indigenous people in the Andes region for centuries. It is a reputed aphrodisiac and fertility enhancer. Peruvian researchers conducted a randomized, placebo-controlled double-blind study on a small group of men aged 21-56. Results showed that, versus placebo, maca improved subjective reports of male sexual desire. Subjects

consumed either 1,500 mg or 3,000 mg of maca, or placebo, for three months. After eight weeks, improvements were noted in sexual desire among the subjects who consumed maca (Gonzales et al 2002).

L-Carnitine. L-Carnitine is an amino acid derivative that may be more active than testosterone in aging men who have sexual dysfunction and depression caused by an androgen deficiency (Cavallini G et al 2004). Both testosterone and carnitine improve sexual desire, sexual satisfaction, and nocturnal penile tumescence, but carnitine is more effective than testosterone in improving erectile function, nocturnal penile tumescence, orgasm, and general sexual well-being. L-Carnitine was also more efficacious than testosterone for treating depression (Cavallini G et al 2004).

Natural products to support prostate health

Indole-3-carbinol (I3C): I3C protects against dangerous estrogen metabolites and subsequent prostate cancer. An adequate intake of I3C, through vegetables such as broccoli, Brussels sprouts, and cabbage, or via supplements, may be very helpful for aging men in both keeping undesirable estrogen metabolites such as 16-alphahydroxyestrone in check and decreasing their risk of prostate cancer. Studies have demonstrated that I3C increases the ratio of 2-hydroxyestrone to 16-alpha-hydroxyestrone. For men, this very well might mean a decrease in prostate cancer risk (Sepkovic et al 2001, Bradlow 2008). In a study that examined the association of prostate cancer risk with estrogen metabolism, the authors said, "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" (Muti et al 2002).

Pygeum: A bark extract from the native African cherry tree *Pygeum africanum,* has been used in Europe to treat BPH since 1960, and is currently the most commonly used therapeutic agent for this condition in France (Buck 2004). One theory for the anti-BPH action of pygeum involves the conversion of testosterone to *dihydrotestosterone* (DHT), a potent testosterone metabolite that may exacerbate BPH, via the enzyme 5-a-reductase (Wilt et al 2002). A recent study identified that N-butylbenzene-sulfonamide (NBBS) was isolated from P. africanum as a specific androgen receptor (AR) antagonist. NBBS inhibits AR- and progesterone receptor (PR)- mediated transactivation, as well as endogenous PSA expression and growth of human prostate cancer cells (Papaioannou et al 2009).

Saw Palmetto: In Europe, saw palmetto (*Serenoa repens*) has been used extensively as a drug for reducing symptoms of (BPH). Saw palmetto has multiple mechanisms of action: inhibition of *5-alpha-reductase*; inhibition of DHT binding to the androgen receptor; reduction of the inflammatory component of prostate growth (by inhibiting COX-2 and an enzyme called 5-lipoxygenase); induction of apoptosis and inhibition of prostate cell proliferation (Debruyne 2002; Goldmann et al 2001; Paubert-Braquet et al 1997; Vacherot et al 2000). Its clinical benefits for prostate enlargement include reduced nocturnal urinary urgency (Pavone et al 2010), decreased residual urine volume in the bladder (Giannakopoulos et al 2002), and less discomfort from urination symptoms (Mantovani 2010).

Testosterone and Prostate Cancer: The Myth

For more than 6 decades, the medical establishment erroneously conjectured that testosterone replacement therapy increases one's risk of developing prostate cancer. This fear has made it standard practice for physicians to deprive hypogonadal male patients of testosterone replacement that could otherwise provide them with a world of cardiovascular, musculoskeletal, cognitive, metabolic and other health benefits, as discussed above.

Remarkably, though, it appears that, in most cases, the opposite is true—lower levels of endogenous testosterone present a greater risk of prostate cancer than higher levels (Morgentaler 2009). A review of data from the National Institutes of Health revealed that, in men of advancing age, "*high testosterone levels are not associated with an increased risk of prostate cancer, nor are low testosterone levels protective against prostate cancer"* (Morgentaler 2006).

A collaborative review of 18 prospective studies compared serum concentrations of androgen and estrogen in 3,886 men with prostate cancer with those in 6,438 healthy controls. The results showed *no significant associations between the risk of prostate cancer and sex hormone levels* (Roddam et al 2008).

In more than 500 men diagnosed with prostate cancer (followed over a mean of 8.7 years), high androgen levels were actually associated with a *decreased* risk of aggressive prostate disease, compared with no change in the risk of non-aggressive disease. Overall, levels of any steroid hormones (except estradiol) were not correlated with the risk of aggressive prostate cancer (Severi et al 2006).

Abraham Morgentaler, an associate clinical professor at the Harvard Medical School, in his book *Testosterone for Life,* convincingly makes the case for the benefits and safety of high testosterone vs. the dangers of low testosterone. He also goes back to the original 1941 Nobel Prize-winning research (Huggins et al 1941) about testosterone and shows how these data have been misinterpreted and unquestioned for over 70 years.

What You Need to Know: Optimizing Testosterone Levels in Aging Men

- Testosterone, the chief male hormone, is essential for libido and erectile function, and plays a crucial role in mood, energy, bone health, and body composition.
- Testosterone levels decline with age, usually beginning in a man's mid-30s. Diminishing testosterone levels have been linked with disorders such as depression, fatigue, obesity and cognitive decline.
- Low testosterone in men is strongly associated with metabolic syndrome, and may be a risk factor for type 2 diabetes and cardiovascular disease.
- Restoring testosterone to youthful levels offers men a wealth of health benefits, including benefits for heart health, body composition, mood, and memory.
- Bioidentical testosterone has not been found to have adverse effects on the healthy prostate gland—in fact, it may help improve prostate symptoms in men with low-normal testosterone levels. Testosterone therapy is contraindicated in men with prostate cancer.
- Regular blood testing can help you and your physician decide if testosterone therapy is right for you. Optimizing testosterone levels requires a multi-pronged approach that includes optimal diet, proper nutrition, nutritional supplements, exercise, and bioidentical testosterone.

Life Extension Suggestions

Step One: Testing

It is critical that men undergo comprehensive medical testing before embarking on a hormone modulation program. First, a baseline blood PSA must be taken to rule out existing prostate cancer (for more information, please see the chapter on prostate cancer). Then, free and total testosterone and estradiol tests are needed to make sure that testosterone is not being excessively converted into estrogen. If estrogen levels are too high, the use of aromatase inhibitors can reduce the rate at which testosterone converts to estrogen in the body. Follow-up testing for estrogen, testosterone, and PSA levels are needed to rule out prostate cancer and fine-tune your program. Additional tests that should be considered include:

- Complete blood cell count and chemistry profile, including liver and kidney function, glucose, minerals, lipids and thyroid-stimulating hormone (TSH)
- DHEA
- Luteinizing hormone (LH) (optional)
- SHBG (optional)
- Dihydrotestosterone (optional)

Blood for these tests may be drawn at your physician's office or directly at a laboratory in your area. Information about ordering these tests on your own may be obtained by calling 1-800-208-3444. These tests will yield crucial information that can help you design a program tailored to your unique situation.

Step Two: Interpreting the Results

Free testosterone: The Life Extension Foundation believes that direct testing for free testosterone is the best way to test for testosterone activity, as free testosterone is the active form of the hormone and comprises only about 2% of total testosterone.

The Life Extension Foundation recommends that men strive for a free testosterone level that is in the upper one-third range for men aged 21 to 49 years. The range of free testosterone serum level is 20 to 25 picograms per milliliter (pg/mL), using our current testing methodology.

There are five reasons that free testosterone levels may be low:

1. Too much testosterone is being converted to estrogen through the activity of aromatase.
2. Too much free testosterone is being bound by SHBG. This would be especially apparent if a man's total testosterone level is in the high normal range but his free testosterone level is low.
3. The pituitary gland, which controls testosterone production through the production of luteinizing hormone (LH), is not secreting enough LH to stimulate gonadal production of testosterone. In this case, total testosterone would be low.
4. The testicles (gonads) have lost their ability to produce testosterone, despite adequate amounts of LH. In this case, the level of LH would be high despite a low testosterone level.
5. DHEA level is abnormally low.

Estrogen: Measured as estradiol, should be kept in a range of 20 to 30 pg/ml. If a man's estrogen level is elevated, it could be associated with:

- Increased aromatase activity, often caused by increased abdominal fat.
- The liver is failing to remove excess estrogen, possibly because of heavy alcohol intake. In men, heavy alcohol intake has been shown to boost estrogen levels within the liver (Colantoni et al 2002).

If a man's estradiol level is higher than 30 pg/mL, it should be reduced by using aromatase-inhibiting drugs or nutrients. (Optimal estradiol levels are between 20-30 pg/mL.)

Hormone	**Optimal Range**
DHEA-s:	350-490 µg/dL
Estradiol:	20-30 pg/mL
Total Testosterone:	700-900 ng/dL
Free Testosterone:	20-25 pg/mL

Step Three: Correcting Abnormal Levels

Ultimately, the ideal program will depend on the results of various tests. Below are some common scenarios and solutions to correct hormone imbalances.

Low Free Testosterone, High Estradiol, Mid Total Testosterone: This situation suggests excessive aromatase activity, which converts free testosterone to estrogen. Inhibition of aromatase and reduction in aromatase-containing tissue (fat) is indicated. Suggestions include:

- **Chrysin**: 1500 mg daily
- **Piperine**: 10 mg daily to enhance absorption of chrysin
- **Zinc**: 50 – 90 mg daily

- **Muira puama**: 850 mg daily
- **Quercetin**: 500 – 1000 mg daily
- Lose weight to reduce aromatase activity.
- Reduce or eliminate alcohol intake to enable excess estrogen removal by the liver.
- Review all current medications to see if they might be interfering with healthy liver function. Common medications that affect liver function are nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., naproxen, ibuprofen, and aspirin); the pain relief medication acetaminophen; the statin class of cholesterol-lowering drugs (e.g., simvastatin, atorvastatin); some heart medications; some blood pressure-lowering medications; and some antidepressants. Drugs being prescribed to treat the symptoms of testosterone deficiency (such as the statins and certain antidepressants) may actually aggravate the testosterone deficit, thus making the cholesterol problem or depression worse. However, do not discontinue any prescription medicine without consulting your physician.
- If all of the above fail to increase free testosterone and lower excess estradiol, consider discussing with your physician the use of the aromatase inhibitor anastrozole (Arimidex) at the very low dose of 0.5 mg twice per week.

Low Free Testosterone, Low Estrogen, High Total Testosterone: This situation suggests excessive SHBG levels, making sufficient testosterone unavailable to target tissues. The elevation of SHBG explains why some older men who are on testosterone replacement therapy do not report a long-term beneficial effect, that is, the administered testosterone becomes bound by SHBG and is not bioavailable to cellular receptor sites where it would normally produce an effect. Suggestions include:

- Inhibit aromatase by following some of the recommendations in the previous section, since low testosterone and high estrogen are involved in excess SHBG activity.
- Take the following supplements:
    - **Chrysin**: 1500 mg daily
    - **Nettle root extract**: 240 mg daily
    - **Pygeum extract**: 100 mg daily
    - **Cruciferous vegetable extract (I3C)**: 400 mg daily
    - **Fish oil**: 2000 mg daily (at least 700 mg EPA, 500 mg DHA)
    - **DHEA**: 25 – 75 mg daily, followed by blood tests in 3-6 weeks; consider starting at a lower dose and increase as indicated. For additional information on DHEA, refer to the DHEA Restoration Therapy protocol.

Low Free Testosterone, Low Estrogen, Low Testosterone: This situation suggests low production of testosterone, with resultant low conversion to estrogen. Suggestions include:

- Use testosterone patches or creams. If tests reveal low levels of LH, ask your physician about the possibility of using human chorionic gonadotropin (HCG). HCG functions in a manner similar to that of LH, thus helping to stimulate the leydig cells of the testes to produce more testosterone.
- Take **DHEA**: 25 – 75 mg daily, followed by blood tests in 3-6 weeks; consider starting at a lower dose and increase as indicated. For additional information on DHEA, refer to the DHEA Restoration Therapy protocol.
- **Tribulus fruit extract** (40% saponins): 450 mg daily

General Nutrients to Boost Sexual Function

A number of nutrients have been studied for their ability to boost testosterone and/or treat conditions such as erectile dysfunction and loss of libido. This nutrient group includes antioxidants, which may function by reducing oxidative damage to testosterone-producing tissues.

- **Selenium**: 200 mcg daily
- **Vitamin E**: 400 IU daily with at least 200 mg of gamma-tocopherol
- **Vitamin D** (Wehr et al 2010): 5000 – 10000 IU daily

- **Protein Powder**: 10 – 20 g daily
- **Acetyl-L-carnitine**: 1000 – 2000 mg daily
- **Maca Powdered Extract**: 1500 – 3000 mg daily

In addition, the following blood testing resources may be helpful:

- **Male Comprehensive Hormone Panel**
- **Male Basic Hormone Panel**

Disclaimer and Safety Information

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The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. The publisher has not performed independent verification of the data contained herein, and expressly disclaim responsibility for any error in literature.

Male Hormone Restoration

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