Last Section Update: 01/2024

Contributor(s): **Shayna Sandhaus**, PhD; **Carrie Decker**, ND, MS

Table of Contents

Start

1 Overview

Summary and Quick Facts for Male Hormone Restoration

- Testosterone levels decline as men age, and other hormones often fall out of optimal balance too. Restoring youthful levels of testosterone and other hormones may help support overall wellbeing and good health.
- Most men know that testosterone is important for health and performance, but many do not know that maintaining healthy levels of other hormones, like estrogen and DHEA, is also important.
- Supplementation with zinc and chrysin may help men maintain healthy hormone balance, while a blend of pomegranate and cacao seed extracts supports healthy free and total testosterone levels.
- This protocol will help you learn about comprehensive hormone restoration and how it can support your health when combined with proper medical care, a healthy diet, adequate sleep, and plenty of exercise.

Why Do Men Need Balanced Hormones?

Maintaining balanced hormone levels is essential to men's overall health. Unfortunately, men's testosterone levels decline as they age. Most men know that testosterone is important for sexual function, but research indicates that normal testosterone levels are associated with preservation of cognitive function,[113] a healthy body weight[114] and metabolic activity,[115] and more. In addition, low testosterone levels have been associated with increased mortality.[116]

Testosterone levels are affected by several other hormones and enzymes, such as dehydroepiandrosterone (DHEA) (a precursor to testosterone and estrogen), aromatase (an enzyme that converts testosterone to estrogen), and sex hormone-binding globulin (SHBG) (a glycoprotein that binds testosterone). Given the complex interplay among various hormones, binding proteins, and several other variables, thorough lab testing is essential before initiating testosterone replacement therapy.

Several natural interventions, such as pomegranate and cacao seed extracts, nettle root, and zinc, may support healthy testosterone levels as well and should be part of a comprehensive hormone balancing regimen for men.

What Can Contribute to Low Testosterone Levels?

- Increasing age
- Increased body fat/obesity
- Chronic disease like diabetes, and acute illness
- Poor nutritional status and liver function
- Oxidative damage
- Declining levels of steroid hormone precursors, such as DHEA
- Certain medications
- Disease of the testes (primary hypogonadism)
- Disease involving the pituitary and/or hypothalamus (secondary hypogonadism)

Why is it Important to Get Hormone Levels Tested?

Comprehensive hormone testing is necessary to obtain an accurate overview of your hormone balance. Both free and total testosterone levels are important, but so is the level of estrogen (estradiol, E2) and ratio of testosterone to estradiol. Other hormones, like DHEA, as well as proteins that influence hormone bioavailability, like SHBG, should be tested as well.

Hormone levels will vary widely between men, so it is important to repeat tests periodically to identify trends over time. Consideration should also be given to other symptoms or disease conditions one is experiencing. Only after comprehensive testing and thorough clinical evaluation can one decide whether hormone replacement therapy is a good choice. Testosterone replacement therapy should be embarked upon with the guidance of a qualified healthcare professional experienced in men's hormone restoration and balance.

Do High Testosterone Levels Increase the Risk of Prostate Cancer?

No. As of the time of this writing, the scientific literature does not support an association between high testosterone levels and an increased risk of prostate cancer. However, the use of testosterone restoration by men at high risk for, or who have or have had, prostate cancer remains very controversial. All men should discuss the risks and benefits of testosterone restoration with a qualified healthcare provider before initiating testosterone treatment, including with respect to prostate health.

What are Natural Ways to Boost Testosterone Levels?

Aside from hormone replacement therapy and diet and lifestyle changes to promote metabolic health and a healthy body weight, there are natural approaches to support testosterone levels and healthy male hormone balance:

- **Pomegranate and cacao seed**. A blend of pomegranate and cacao seed extracts has been shown to promote testosterone production in clinical and laboratory studies, also improving testosterone-related parameters such as grip strength.
- **Zinc**. Zinc is essential for many aspects of male reproductive function, from testosterone metabolism to sperm motility.

- **DHEA**. As a precursor to testosterone, adequate DHEA levels are required for healthy testosterone production. DHEA levels tend to decline with age.
- **Tribulus**. Protodioscin, an active ingredient in *Tribulus terrestris* (or puncture vine), may convert to DHEA in the body. It has a reputation as an aphrodisiac, and animal studies seem to confirm its ability to boost sexual function.
- **Chrysin**. This bioflavonoid naturally inhibits aromatase, and thus may help reduce the conversion of testosterone to estrogen. Its bioavailability may be boosted by taking with **piperine** (black pepper extract).
- **Luteolin**. Luteolin, a flavonoid with protective antioxidant effects, has been shown to be a natural inhibitor of aromatase and also promote testosterone production by additional mechanisms.
- **Nettle root**. Lignans in nettle root may prevent SHBG from binding testosterone, which may boost free testosterone levels. Nettle root is often used to relieve benign prostatic hyperplasia (BPH) symptoms.
- **Muira puama**. Muira puama may improve sexual performance in men who have loss of libido.

2 Introduction

The **significance of testosterone for male sexual function** is well known. Substantial research has clarified the critical role testosterone plays not only in maintaining youthful sexual vitality, but also neurological health, bone health, depression, metabolic disease, as well as inducing fat loss in those who are unable to reduce body weight with diet and exercise alone.

Observational studies have demonstrated that low testosterone in men is associated with metabolic syndrome, type 2 diabetes, and cardiovascular disease.[117-120] Moreover, low total testosterone has been associated with a substantial increase in mortality.[116,121] Similarly, a low testosterone to estradiol ratio has been associated with increased cardiovascular mortality.[121] Other studies have shown that testosterone treatment in men with low testosterone levels is associated with reduced mortality.[122] Ongoing clinical trials will provide further evidence as to the effects of testosterone therapy in men with low testosterone levels with respect to hard clinical outcomes, such as time to major adverse cardiovascular events. One such ongoing trial is the larger TRAVERSE trial, which is examining the effects of testosterone therapy versus placebo in 6,000 men with low testosterone levels. This trial is expected to be completed in June 2022.[123]

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.[3-5] However, because a bi-directional relationship exists between low testosterone and metabolic disease, such as diabetes and obesity, it is imperative that these conditions be addressed as well.[117-119] In men with low levels of testosterone, testosterone therapy also significantly improves erectile function.[6,124]

3 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, although DHEA alone is seldom enough to sufficiently restore testosterone levels in aging men, and may also promote an increase in estrogen.[125,126]

Aromatase

One of the most important factors that affect testosterone levels and the ratio between testosterone and estrogen is the *aromatase* enzyme. Aromatase is produced in many locations in the body including adipose tissue, the gonads, breast tissue, brain, skin, and bone.[127] Aromatase converts testosterone to estrogen, further depleting free testosterone levels and increasing estrogen levels. Increased aromatase activity has been shown in aging, obesity, hyperthyroidism, and with various malignancies.[127]

Sex Hormone-Binding Globulin

Sex hormone binding globulin (SHBG) is a protein produced in the liver that binds both testosterone and estrogen and regulates hormone bioavailability.[128] Most testosterone circulating in the bloodstream is bound to either SHBG (60%) or albumin (38%). Only a small fraction (2%) is unbound, or "free."[13]

Testosterone binds more tightly to SHBG than to albumin.[14] 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.[13] Thus, the bioavailability of testosterone is influenced by the level of SHBG; however, low levels of SHBG may contribute to low total testosterone measurements in obesity and diabetes.[129] Excess liver adiposity related to metabolic disease, known as non-alcoholic fatty liver disease, commonly occurs in conjunction with both obesity and diabetes and has been shown to play a role in the lower levels of SHBG seen in these conditions.[128]

Aging men experience both an elevation in SHBG production and an increase in aromatase activity.[130,131] The net result is a decrease in total and free testosterone levels and an increase in the ratio of estrogen to testosterone.[15] As will be discussed below, it is crucial that this skewed ratio be balanced.

Obesity & the Benefits of Weight Loss

The vicious circle of low testosterone and obesity has been described as the ***hypogonadal/obesity cycle***.[129] Obesity is also associated with a decrease in luteinizing hormone levels.[132,133] Luteinizing hormone promotes the production of testosterone in the testis. Low testosterone levels contribute to increased abdominal fat, which in turn leads to increased aromatase activity.[10] This enhances the conversion of testosterone to estrogens, which further reduces testosterone and increases the tendency toward abdominal fat.[11,12] Certain genetics also may play a role in the development of low testosterone levels in overweight/obese men.[133-135]

Research has shown that various interventions with the intended goal of weight loss in obese individuals also increase testosterone levels. Specifically, in obese men with type 2 diabetes, five years after having bariatric surgery, free testosterone levels increased by 48% in men who had surgery compared with a decrease of 2% in men having medical therapy without surgery.[136] Increases in total testosterone have also been observed in obese men six months after bariatric surgery.[137] Simply losing weight by following a low-calorie diet, and maintaining the weight loss, also has been shown to increase free testosterone levels in obese men, with the increases maintained up to a year later.[138]

Diabetes

Much like obesity, diabetes has been shown to have a bi-directional relationship with low testosterone levels: hypogonadism is more commonly found in those with the disease, while treatment of hypogonadism with testosterone helps prevent progression of pre-diabetes to diabetes.[119,139] In a population of 103 diabetic men, one-third were found to have low testosterone levels. Both free and total testosterone have been shown to be lower in men with diabetes.[140]

Medication/Drug Use

Use of certain medications, including glucocorticoids,[141] opioids,[142] gonadotropin-releasing hormone (GnRH) agonists (commonly used for the treatment of prostate cancer),[143] and androgens for performance enhancement, can lead to reduced testosterone levels by interrupting pathways critical to testosterone production.[144] Low testosterone levels have been shown to persist for up to two years or more after cessation of anabolic steroid misuse.

Illness

Critical and chronic illness can lead to low testosterone levels. This includes acute events such as head trauma, a heart attack, or surgery, or chronic illnesses such as chronic kidney or lung disease, and cirrhosis of the liver.[145-148] The liver produces SHBG and albumin, converts androgens to estrogen and other testosterone metabolites, and inactivates and removes estrogen among other activities related to hormone metabolism.[148] Decreases in liver function, including liver fat accumulation or liver cancer, may exacerbate hormonal imbalances and compromise healthy testosterone levels.[149,150]

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

The exact cause of the age-related reduction in testosterone levels is not entirely known; it is probably the result of a **combination of factors**, including[151]:

- 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
- Elevation in SHBG production
- Nutritional status and liver function

The consequences of declining testosterone levels are striking, and a factor in many of the degenerative changes and chronic diseases that are seen with increasing age.

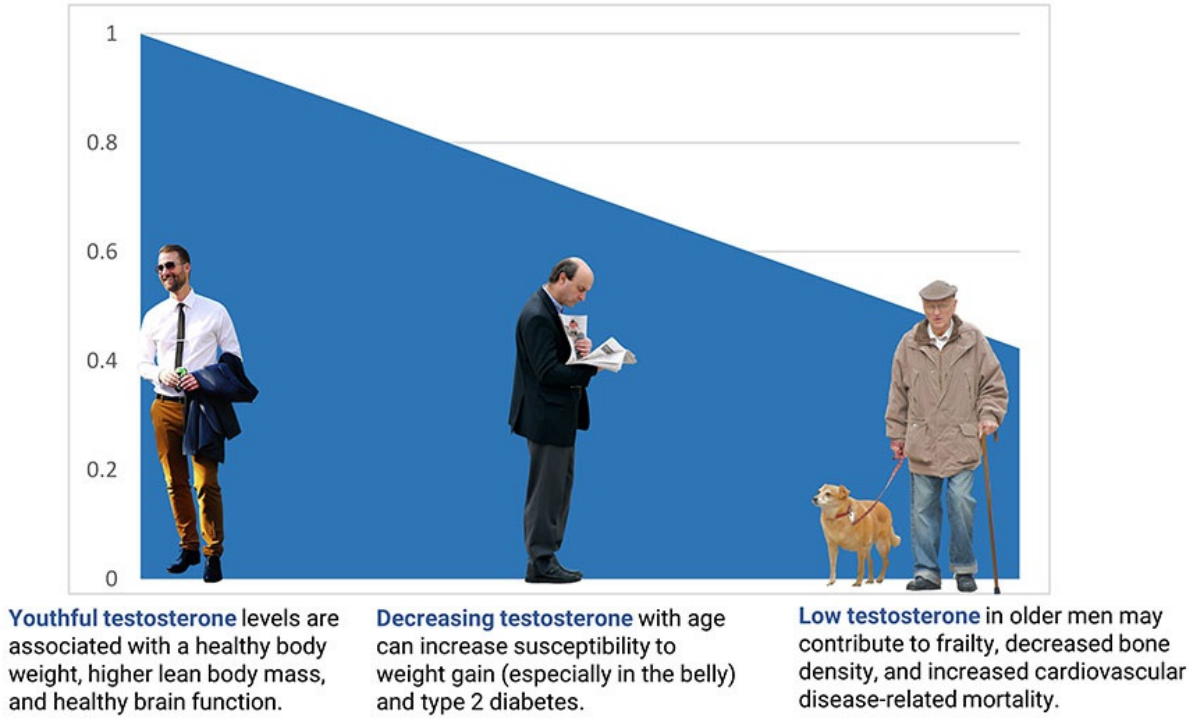

Figure 1: Relative decrease in salivary testosterone with increasing age in U.S. men. Plot made using data from Ellison PT, et al. Population variation in age-related decline in male salivary testosterone. Hum Reprod. 2002 Dec;17(12):3251-3.

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 releases 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.[16,17] 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.[18]

Emergent evidence suggests that maintaining youthful testosterone levels may help aging men avert a variety of inflammation-mediated diseases, 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*.[19] Leukotrienes are derivatives of the pro-inflammatory

omega-6 fatty acid *arachidonic acid*; these molecules underlie much of the inflammatory development of asthma and bronchitis, and they play a role in the pathology of cardiovascular disease and diabetes as well.[20,21]

In a study involving 184 men with low testosterone levels, 18 weeks of testosterone replacement therapy suppressed markers of inflammation including interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and C-reactive protein. Moreover, when compared with men who received a placebo, men receiving testosterone replacement exhibited significant decreases in body weight, body mass index (BMI), and waist circumference.[22] 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 is strongly associated with increased susceptibility to inflammatory diseases and mortality.[23]

Testosterone therapy has been shown to decrease weight and improve measures of health in men with low testosterone levels. In a non-randomized registry study of 471 obese men with hypogonadism, patients elected to receive either testosterone undecanoate injections (1,000 mg every 12 weeks) or no therapy (control group). After up to 11 years, weight decreased an average of 23 kg (51 lb, or about 20% of body weight) in the testosterone group versus a 6 kg (13 lb, or about 6% of body weight) increase in the control group. Testosterone treatment was also associated with a decrease in waist circumference of 13.3 cm compared with an increase of 6.7 cm in the control group. Finally, testosterone may have had positive effects on other health outcomes. In the control group, heart attacks occurred in 28% and stroke in 27% of men; no heart attacks or strokes were reported in the testosterone group. Deaths were also reported at a significantly lower rate in those who received testosterone compared with those who did not (8% vs. 32%).[99] Importantly, the findings of this study had not yet been published in a peer-reviewed journal at the time of this writing and could change following peer review; the findings were presented at the 2020 virtual *European and International Congress on Obesity*.

Musculoskeletal System

Bone integrity rests upon a balance between bone formation and resorption, which is controlled by multiple factors—including levels of estrogen and testosterone.[24,25] In a clinical trial, testosterone increased bone mineral density in elderly men.[26] Low testosterone levels also may contribute to the development of **sarcopenia**, the loss of muscle mass and strength which is commonly seen with increasing age and in chronic kidney or liver disease.[152-154] Sarcopenia contributes to physical disability, mortality, and morbidity. Testosterone supplementation has been shown to have a positive effect on muscle metabolism and strength and increase lean body mass in older men.[27,155] Further studies are needed to determine the role low testosterone levels and its restoration play in sarcopenia and age-related frailty.[156]

Central Nervous System (CNS)

Keys 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.[28] 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.[29,30] Furthermore, testosterone treatment often increases feelings of well-being.[31]

Cognition and alertness are also governed, in part, by testosterone's effects on the CNS.[32] Low testosterone levels have been shown to correlate with lower scores on various psychometric tests,[33] and similar effects have been reported in men undergoing androgen (male hormone)-deprivation therapy for prostate cancer.[34]

Testosterone also acts as an endogenous neuroprotective agent, able to support neuron integrity against a variety of toxic insults, including oxidative stress.[35,36] In addition, testosterone has been shown to reduce β-amyloid accumulation, a pathophysiologic factor in Alzheimer disease.[37,38]

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.[39,40] Studies demonstrate testosterone loss occurred 5–10 years prior to Alzheimer disease diagnosis, suggesting low testosterone is an important risk factor for Alzheimer disease.[41,42] In a clinical study of 36 men recently diagnosed with Alzheimer disease, intramuscular testosterone treatment with 200 mg every two weeks for up to one year was associated with improvement in both overall cognitive ability as well as critical visual-spatial function.[43]

Glucose and Lipid Metabolism

Testosterone also has been linked to metabolic function. Specifically, studies have found that low testosterone in men correlates with increased risk of metabolic syndrome (ie, a state of metabolic dysregulation characterized by excess abdominal fat, high blood sugar and cholesterol, and high blood pressure that increases risk of cardiovascular disease).[157,18] One clinical study found that men with low testosterone levels were twice as insulin resistant as their counterparts with normal testosterone levels, and 90% met the criteria for metabolic syndrome—3-fold higher than those with normal testosterone levels.[45]

There also appears to be an inverse relationship between low testosterone levels and diabetes in men.[157,46] Men with diabetes have lower testosterone levels compared with men without a history of diabetes.[47] 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 diabetes compared with those ranked in the top one-third after researchers adjusted the results for age, race/ethnicity, and adiposity.[48]

Several interventional studies have found that testosterone therapy can improve body composition, ameliorate abnormal glucose and insulin metabolism, and lower total cholesterol levels. Among men with metabolic syndrome and low testosterone levels, testosterone therapy has been reported to reduce waist circumference and improve glucose and insulin metabolism.[157] In men with type 2 diabetes and low testosterone levels, similar metabolic benefits have been observed with testosterone therapy.[157] However, these improvements may not manifest in men with metabolic syndrome and/or diabetes who do not have low testosterone levels. Moreover, it is difficult to disentangle the origins of these metabolic improvements in response to testosterone therapy. These responses may be indirect: weight loss and improvements in body composition that result from increased well-being and motivation following testosterone restoration may contribute to the observed metabolic improvements. Regardless, men who have low testosterone levels and/or type 2 diabetes may stand to benefit from testosterone restoration.

Importantly, a 2016 meta-analysis of data from 32 studies reported that the metabolic benefits of testosterone restoration may be time-dependent. This analysis found that metabolic benefits apparent after two years of testosterone treatment were less pronounced after only one year. In other words, men may need to adhere to testosterone therapy for two years or more to realize marked improvements in metabolic parameters.[157,158]

Cardiovascular Health

Observational research has provided evidence for an association between low testosterone levels and increased risk of cardiovascular disease and mortality.[116,159] Administration of testosterone appears to be correlated with improvement in several cardiovascular risk factors, including atherogenic lipid profiles, insulin resistance, obesity, and propensity to clot.[49] A 2018 meta-analysis of 37 observational studies including over 43,000 men, followed for an average of 6.4 years, found that low endogenous testosterone levels predicted overall and cardiovascular mortality and cardiovascular morbidity.[160] In addition, research has identified an association between low testosterone levels and increased incidence of cardiovascular events in men with existing cardiovascular disease. For instance, in a longitudinal study of 930 consecutive men with coronary heart disease referred for diagnostic angiography, those with low testosterone levels had almost double the absolute rate of all-cause mortality over a seven-year period.[2] Additionally, in men with atherosclerotic cardiovascular disease, low testosterone levels were associated with a higher risk of cardiovascular disease-related hospitalization and adverse outcomes,[161] while in men with heart failure, low testosterone was associated with increased all-cause mortality, myocardial damage, and lower exercise capacity.[162]

Although data available as of late 2021 suggest an association between low testosterone levels and cardiovascular disease, these types of correlations are prone to residual confounding. Additionally, there is research that has not shown this relationship.[163] Large, prospective, interventional trials are still needed to clarify whether testosterone therapy in men with low testosterone levels will improve outcomes. One such study in a population of U.S. male veterans with low testosterone and multiple comorbidities found that over a mean follow up of 4.3 years, use of transdermal or intramuscular testosterone was not associated with risk of the composite cardiovascular outcome (myocardial infarction, ischemic stroke, or venous thromboembolism) in men without

existing cardiovascular disease; however in those with existing cardiovascular disease, trasndermal testosterone treatment was associated with lower risk.[164] The **TRAVERSE trial** is assessing the efficacy of topically applied testosterone gel (Androgel) compared with placebo in 6,000 hypogonadal men. This trial's primary endpoint is time to major adverse cardiovascular events, including heart attack, stroke, or death due to a cardiovascular cause. The study's estimated completion timeline is June 2022.[123]

Prostate Health

Androgens are essential for the proper growth and development of the prostate. Later in life, androgen signaling, in particular activation of the androgen receptor by the potent androgen dihydrotestosterone (DHT), influences prostate cell proliferation and function of the prostate gland.[165] In addition, aromatization of androgens to estrogens locally in prostate tissue may contribute to prostate growth.[166] These findings, which are undergoing continued refinement in active research, suggest that the balance between testosterone and estrogens may be important for maintaining prostate health. Life Extension suggests that most men strive to maintain a total testosterone to estradiol ratio of about 23 – 40.

5 The Importance of Hormone Testing

Comprehensive testing, along with a thorough assessment of signs, symptoms, and overall metabolic health, are essential in **detecting hormonal imbalances in aging men**.

The so-called "normal" levels of testosterone in older men reflect population averages. Life Extension believes that most aging men would prefer not to accept the loss of youthful vigor as normal. Instead, we suggest that an optimal level for all men would approximate the upper one-third of the reference range used for younger men, and that testosterone replacement therapy should aim to restore hormone levels to that range. To this end, Life Extension suggests optimal hormone levels for most men as follows:

- Free testosterone: 15–25 pg/mL
- Total testosterone: 600 – 900 ng/dL
- Estradiol: 20 – 40 pg/mL

When measuring testosterone levels, it is critical to determine the levels of both free and total testosterone to understand the underlying biological phenomena that may be contributing to androgen deficiency symptoms. [55] 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. Consideration should also be given to other symptoms or disease conditions one is experiencing.

During the initial testing, it is also imperative to test estrogen levels. Many of the unwanted effects of male hormone imbalance may be caused by an elevated estrogen level relative to low testosterone levels (the testosterone:estrogen ratio). The Life Extension optimal level of estrogen (measured as estradiol) for aging men is 20–40 pg/mL.

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.[13]

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 with 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 risk 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.[56] This is within the ideal range that *Life Extension* suggests.

A study published in 2021 evaluated levels of testosterone, estradiol, and their ratio in over 1,109 men in the United States. The men were then categorized into quartiles based on their levels of the aforementioned hormonal variables. Men whose testosterone was in the lowest quartile had about 1.7 times greater death risk than those whose testosterone was in the upper quartile. Similarly, men with a testosterone to estradiol ratio of less than 10 had about 1.3 times greater risk of dying from cardiovascular disease than men with higher testosterone:estradiol ratios.[121] Life Extension suggests that most men strive to maintain a ratio between 23 and 40.

An epidemic problem we at *Life Extension* observe in aging males is insufficient free testosterone, that is less than 15–25 pg/mL in serum. When accompanied by excess estradiol (over 40 pg/mL of serum), this can signal excess aromatase enzyme activity.

6 Testosterone Replacement Therapies

Testosterone replacement therapy can counteract the effects of testosterone deficiency on bone and muscle mass, mood, sexual function, and libido.[176,177] Some research also indicates testosterone replacement therapy may improve insulin sensitivity and metabolic health in older men with low testosterone levels.[178] Intramuscular injections, transdermal (topical) gels and patches, oral capsules, subdermal implants, and nasal formulations of testosterone are available.[177]

Importantly, there is no "one-size-fits-all" approach to testosterone replacement therapy. Individuals vary, and hormone replacement requires careful attention to signs and symptoms as well as periodic laboratory testing. The choice to initiate testosterone replacement and the mode of therapy should be made in consultation with a qualified healthcare provider versed in testosterone replacement and based on an individuals' hormone levels and signs and symptoms.[176]

For men whose estradiol levels rise above 40 pg/mL during testosterone therapy, nutrients with aromatase-inhibiting properties (eg, chrysin[179,180] and luteolin[181]) may help bring estradiol levels back down to a range of 20 – 40 pg/mL. If an initial trial with nutrients does not adequately reduce estradiol levels, then a trial of an aromatase-inhibiting prescription drug may be warranted but should be discussed with a qualified healthcare provider.[182]

Routes of Administration

Injections. The historical method for administering testosterone is by intramuscular injection. Injections may be needed every one to three weeks to maintain adequate levels. Testosterone enanthate (Delatestryl, Xyosted), testosterone cypionate (Depo-Testosterone), and testosterone undecanoate (Andriol, Aveed) are examples of injectable forms of testosterone and are typically used at a dosage of 75–100 mg weekly or 150–200 mg every two weeks.[176] Testosterone injections have been shown to rapidly restore normal hormone levels, as well as increase bone mineral density and lean body mass, decrease body weight and waist circumference, lower some cardiovascular risk markers, improve urinary and erectile function, and raise self-reported quality of life.[176,177]

Some side effects have been attributed to testosterone injection therapy. These include pain at the injection site, increased levels of prostate-specific antigen (PSA), and high hemoglobin and red blood cell levels.[176] These effects are most often seen at higher dosages of testosterone, thus monitoring testosterone levels is important throughout its use.

Transdermal approaches. Transdermal testosterone therapy allows for more consistent testosterone levels to be sustained. Androgel and Axiron are examples of alcohol-based bioidentical testosterone gels, typically used in doses of 50–100 mg (5–10 grams of 1% testosterone gel) applied once daily.[176] The location of application depends on the product; for example, Androgel is applied to the upper arms and shoulders, while Axiron is applied to the armpit.[183] Alternatively, a patch known as Androderm that provides either 2 mg or 4 mg of testosterone, or a combination of both for 6 mg, may be used nightly.[177] It is difficult to compare doses between gels and patches, since gels are only absorbed at a rate of 9–14%, and although the testosterone in Androderm is absorbed at a rate of about 20%, it is labelled according to the absorbable amount rather than the amount actually present in the patch (ie, the 2 mg patch is manufactured with 9.7 mg and the 4 mg patch with 19.5 mg of testosterone).[184,185]

Transdermal testosterone has been shown to normalize hormone levels over a period of a few days.[184] It can also

improve bone density, increase lean body mass, and decrease fat mass, but its effects on body composition are less substantial than with injections. On the other hand, the effects of transdermal testosterone on mood and sexual function appear to be at least as robust as with injection.[176]

Adverse side effects associated with transdermal use of testosterone include skin irritation, which is more common with patches than with gels. Transdermal testosterone can also cause a rise in PSA levels that depends on the dose being used. Importantly, residual testosterone gel on the skin or clothing of the person using transdermal testosterone can be transferred by direct contact with others, and has been reported to cause problems such as precocious puberty (ie, abnormally early onset of puberty) in children.[176]

Oral preparations. Until recently, oral testosterone therapy was hampered by low bioavailability due to extensive transformation in the liver after absorption through the gastrointestinal tract, as well as potential liver toxicity.[177] Testosterone undecanoate is a testosterone ester that has been found to have sufficient oral bioavailability to normalize low androgen levels without damaging liver cells or adversely affecting liver function.[186,187] The first oral testosterone undecanoate capsule (Jatenzo) was approved for use in 2019, and another (Kyzatrex) was approved in 2022.[188,189] Because its absorption is still inconsistent and half-life is short, it is generally taken in divided doses, totaling 120–240 mg per day, with high-fat meals to optimize its effects.[176,177] In addition to restoring normal hormone levels, oral testosterone has been shown to improve bone mineral density and body composition similarly to transdermal testosterone, and has positive effects on sexual function, mood, cognition, and quality of life.[176]

Oral testosterone has been reported to cause dose-related adverse side effects such as digestive upset, increased hematocrit, worsening of high blood pressure, and decreased HDL-cholesterol levels. However, in contrast to other forms of testosterone therapy, several clinical trials lasting as long as one year have found oral testosterone undecanoate, at doses of 160 mg to 240 mg per day, did not increase PSA levels or prostate volume in older men being treated for symptoms of low testosterone levels.[53,190-193] Even men treated with oral testosterone undecanoate for two years were recently reported to have no significant PSA level elevation.[186]

Subdermal implants. Testosterone pellets (Testopel) are implanted under the skin in a fatty area (eg, near the hip) and can provide consistent long-term therapy in men with testosterone deficiency. Typical dosing is 150–450 mg every three to six months, but higher doses such as 900 mg and 1,200 mg are sometimes used. Testosterone pellets have been reported to normalize testosterone levels and improve mood and sexual function. While subdermal testosterone pellets have the advantages of requiring infrequent clinic visits and having no risk of testosterone transfer, implantation is a minimally invasive procedure. Furthermore, side effects can occur at the implant site, such as extrusion (breaking through the skin surface) and, rarely, infection, bleeding, and scarring can occur. Testosterone pellets have also been associated with increased hematocrit and red blood cell numbers, though often this is from too high a dose given.[177] Subdermally implanted testosterone pellets are uncommonly used to treat age-related low testosterone levels.

Nasal formulations. Testosterone can be efficiently absorbed across mucous membranes, such as with Natesto which is administered intranasally.

Natesto is a testosterone gel for nasal use that was approved in 2014 for use in men with low testosterone levels. Nasal testosterone is applied at a dose of 11 mg three times daily and quickly achieves target testosterone levels. One study examining the effects of nasal testosterone found improved bone mineral density, body composition, mood, and sexual function 90 days after the beginning of therapy. Because of its very short duration of action, nasal testosterone appears to have the advantage of not suppressing the hypothalamic-pituitary-testicular axis and therefore not inhibiting sperm production and thus preserving fertility in men of reproductive age with low testosterone levels; however, its effectiveness in aging men has not been well studied.[177]

"Bioidentical" Testosterone

Bioidentical hormones are chemically identical to those that occur naturally in the body. Some synthetic hormonally active drugs that are not bioidentical appear to have disadvantages compared with bioidentical hormones. For example, non-bioidentical estrogen and progesterone combinations have been associated with an increased blood clot risk relative to bioidentical combinations.[194]

In the case of testosterone, bioidentical options are the norm. For example, injectable testosterone undecanoate, cypionate, and enanthate are testosterone esters that are broken down to release bioidentical testosterone into circulation. Similarly, oral testosterone undecanoate is a source of bioidentical testosterone. Testosterone gels, patches, and pellets are also made with bioidentical testosterone, each specially formulated with other agents or materials that modulate testosterone absorption or release in ways that lead to different patterns of testosterone level fluctuations. In addition, nasal testosterone preparations contain bioidentical testosterone that raise testosterone levels by being absorbed into the bloodstream.[195]

Sometimes the term "bioidentical" is confused with the term "compounded." Compounding allows pharmacists to prepare non-standard formulations and doses of drugs, including bioidentical hormones. Flexible dosing or avoidance of allergenic materials in compounded hormone products may pose advantages for some patients. It is important to keep in mind compounded medications are considered less reliable than FDA-approved formulations,[196] although evidence from trials in women suggest they have similar efficacy and safety.[197]

Table 1: Forms of Testosterone Used in Testosterone Replacement Therapy[176,177,198]*

Mode of Therapy	Typical Dose Range	Advantages	Disadvantages
Intramuscular Injection			
Testosterone cypionate or enanthate	75–100 mg weekly or 150–200 mg every two weeks	Highly effective Relatively long action	Injection site pain Requires administration by a healthcare professional Levels diminish between injections
Testosterone undecanoate	750–1,000 mg every 10–14 weeks	Highly effective Relatively long action Less fluctuation in blood levels	Injection site pain Requires administration by a healthcare professional Prolonged withdrawal if adverse side effects occur
Transdermal			
Testosterone 1%, 1.6%, or 2% gel	10–120 mg applied once daily to non-scrotal skin	Convenience Stable testosterone levels	Possibility of transfer to others through contact with skin or clothing Can irritate skin Not as effective as intramuscular injections
Testosterone patch	2–6 mg in total, applied one to three times daily on non-scrotal skin, rotating sites of application in ≥7-day cycles	Convenience Low possibility of transfer to others	More likely to irritate skin than transdermal gels Not as effective as intramuscular

Table 1: Forms of Testosterone Used in Testosterone Replacement Therapy			
Mode of Therapy	**Typical Dose Range**	**Advantages**	**Disadvantages**
Testosterone cream	Custom	Individualized dosing	Requires compounding pharmacist Possibility of transfer to others through contact with skin or clothing Efficacy and safety have not been established in comparison trials
Oral Testosterone undecanoate	120–240 mg daily, taken in divided doses with high-fat foods	Convenience No risk of injection site issues or transfer of testosterone to others through contact May be less likely to raise PSA levels or increase prostate volume	Short half-life requiring multiple daily doses Unreliable absorption may result in fluctuating levels Not as effective as intramuscular injections May increase levels of cardiovascular risk markers
Troche (lozenge)	Custom	Individualized dosing	Requires compounding pharmacist Efficacy and safety have not been established in comparison trials
Subdermal Testosterone pellets	150–1,200 mg implanted every three to six months under the skin	Infrequent need for replacement	Invasive Risk of extrusion Rare local skin problems Use in older men is uncommon
Nasal Testosterone nasal	11 mg three times daily	Rapidly increases	Little known about its

injections or transdermal gels

gel		testosterone levels	use in older men

Table 1: Forms of Testosterone Used in Testosterone Replacement Therapy*

Mode of Therapy	Typical Dose Range	Advantages	Disadvantages
		May not increase infertility	

*Modified table from Barbonetti A, D'Andrea S, Francavilla S. Testosterone replacement therapy. *Andrology*. Nov 2020;8(6):1551-1566.

Human Chorionic Gonadotropin – Potential Alternative or Complement to Testosterone

Human chorionic gonadotropin (hCG) is made by the placenta during pregnancy and plays an important role in fetal reproductive system development. In adult males, hCG therapy stimulates testosterone release and sperm production and is used to treat male infertility. In addition, it is sometimes used as an alternative to, or in combination with, testosterone therapy in men with low testosterone levels who want to preserve their fertility.[199]

In younger men with low testosterone levels being treated with testosterone therapy, the addition of 500 IU of hCG by injection every two days was associated with preserved fertility.[200] Several clinical trials have also shown hCG therapy can raise total testosterone levels and improve androgen deficiency in aging men.[201] In a randomized controlled trial that included 282 men with low testosterone levels who wished to preserve their fertility, 5,000 IU hCG injections, given twice weekly, improved total testosterone levels and improved symptoms of androgen deficiency.[202] In a placebo-controlled trial in 40 men over age 60, 5,000 IU hCG twice weekly for three months raised free and total testosterone levels.[203]

hCG therapy has also been reported to improve sexual function in men with symptoms of low testosterone but whose testosterone levels were not overtly low. In addition, hCG therapy in these men did not increase hematocrit, hemoglobin, or PSA levels during monitoring for almost three months to more than two years.[204,205] Furthermore, it appears hCG therapy has beneficial effects on body composition and metabolism similar to those seen with testosterone therapy.[206]

The main disadvantages of hCG therapy are its high cost and the need for frequent injections.[207]

Safety Considerations with Testosterone Replacement Therapy

The long-term safety of testosterone replacement therapy in older men has yet to be clearly established.[208] It is important to note testosterone replacement therapy can trigger the growth of existing metastatic prostate cancer. In addition, it has been associated with increased red blood cell numbers, especially when administered as intramuscular injections and in higher doses.[177,208] Having excess red blood cells in circulation could theoretically increase blood clot risk, leading to higher likelihood of venous thrombosis and pulmonary embolism, as well as arterial thrombosis resulting in heart attack or stroke.[209] In one observational study that compared testosterone use in 19,215 men with venous thromboembolism (venous thrombosis and pulmonary embolism) and 909,530 men in the general population, venous thromboembolism was found to be 63% more likely during the first six months of testosterone use, but the correlation disappeared after six months.[210] Nevertheless, meta-analyses of data from controlled trials have not found an increased risk of blood clot-related outcomes in men treated with testosterone.[211-213]

Some evidence suggests testosterone therapy may worsen obstructive sleep apnea, but this effect, if seen at all, appears to be short-lived.[177,208] Furthermore, there is conflicting evidence linking testosterone replacement therapy to risks of developing prostate cancer and cardiovascular disease.[208] Despite the lack of clarity around whether testosterone therapy increases or decreases cardiovascular and prostate risks, men with low testosterone levels generally undergo an evaluation of their prostate and cardiovascular health prior to considering testosterone replacement therapy, and ongoing therapy is accompanied by regular monitoring of hormone levels, as well as hematocrit and markers of prostate and cardiovascular risk.[177,208]

The American Urological Association has indicated testosterone therapy is contraindicated in the following conditions[177]:

- high hematocrit

- high hematocrit
- locally advanced or metastatic prostate cancer
- for three months following a cardiovascular event (eg, heart attack or stroke)
- reproductive aged men currently trying to conceive

Other guidelines suggest men with breast cancer, severe lower urinary tract symptoms (ie, due to severe BPH), and obstructive sleep apnea should avoid testosterone therapy due to the possibility of worsening these conditions. On the other hand, testosterone replacement therapy can be considered for men with mild-to-moderate BPH and men who have been treated for prostate cancer and without current evidence of active disease.[177]

7 Nutrients to Support Healthy Testosterone and Estrogen Levels

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 Life Extension's comprehensive male hormone restoration program.

Essential Nutrients for Optimal Testosterone Production

Ashwagandha. Ashwagandha is an herb that helps the body adapt to stress and as such is described as an "adaptogen." Emerging research suggests that ashwagandha may also increase testosterone levels in men.[214]

The effect of a standardized ashwagandha extract called Shoden (std. to 35% withanolide glycosides) was assessed in a 16-week crossover trial in 50 healthy men aged 40–70 years who reported mild-to-moderate fatigue or reduced vitality. Participants had a BMI between 25 and 35, and their mean salivary testosterone levels were not below normal. They were randomized to take 30 mg of the ashwagandha extract or placebo twice daily for eight weeks then crossover to the other treatment for another eight weeks. During the ashwagandha intake period, subjects' mean salivary testosterone was 14.7% higher than during the placebo period. Also during the ashwagandha period, levels of DHEA-sulfate (DHEA-S), which is the most stable form of DHEA measured in the blood, were 18% higher than during the placebo period and DHEA-S levels fell significantly after subjects switched from ashwagandha to placebo. There were no significant changes in participants' estradiol or cortisol levels.[215] A separate randomized controlled trial examined the effect of supplementing with 240 mg ashwagandha (Shoden) daily for 60 days in 60 healthy adults. Ashwagandha intake resulted in greater reductions in cortisol and DHEA-S compared with placebo in both men and women; testosterone levels increased in males over time, but the change was not significant compared with the placebo.[216]

Perhaps in part by increasing testosterone, ashwagandha may also lead to increased muscle growth from strength training. In an eight-week, randomized, controlled trial, 57 male subjects aged 18–50 years engaged in regular resistance training and supplemented twice daily with a placebo or 300 mg of a standardized ashwagandha extract known as KSM-66 (std. to 5% withanolides). Compared to the placebo group, the group receiving KSM-66 had a significantly greater increase in strength as assessed by bench press performance, arm muscle size, a greater reduction in exercise-induced muscle damage, and significantly greater increase in serum testosterone.[217] In an eight-week, randomized, controlled trial including 50 adult men, 300 mg of KSM-66 ashwagandha twice daily was associated with a 17% increase in testosterone compared with a 2% increase observed in the placebo group.[218]

The mechanism by which ashwagandha might increase testosterone levels is not completely understood. However, ashwagandha has been shown to reduce levels of the "stress hormone," cortisol, and elevated cortisol levels tend to correlate with lower testosterone concentrations.[219,220] More research is needed to firmly establish the potential utility of ashwagandha to promote healthy testosterone levels in men.

Some evidence suggests ashwagandha may also support male fertility. A meta-analysis was conducted on four observational studies and one randomized controlled trial that evaluated the effect of ashwagandha supplementation on males with infertility. Systemically reviewed data revealed that, compared with baseline, ashwagandha supplementation led to the following increases: 167% in sperm concentration, 59% in semen

volume, 57% in sperm motility, 17% in serum testosterone, and 34% in luteinizing hormone after 90 days of treatment.[221]

Pomegranate extract. Pomegranate (*Punica granatum*) and pomegranate extracts have shown positive effects on testosterone levels in men. A controlled cross-sectional repeated measure study on 60 volunteers (22 males and 38 females) examined salivary levels of testosterone three times daily (AM, noon, and PM) and at the end of two weeks of pomegranate juice intake (500 mL daily). Salivary testosterone levels were significantly increased (24% on average) after one and two weeks of pomegranate juice consumption in both men and women compared with baseline.[100] Pomegranates are also a rich source of ellagitannins, which are metabolized into various products upon consumption. Preclinical studies identified that the ellagitannin-derived compound urolithin B acts as a strong inhibitor of aromatase, the enzyme that converts testosterone into estrogen, which may help improve the efficacy of testosterone supplementation.[101,102] In a randomized, double-blind, placebo-controlled study of 120 healthy young males aged 21–35, once daily supplementation with 200 or 400 mg of a novel composition of extracts derived from pomegranate peel and cacao seed significantly increased serum levels of total testosterone after 56 days; significant increases in total testosterone were seen in the 400 mg dose group. A second clinical study with 120 males aged 36–55 taking 200 or 400 mg of the blend also showed a significant improvement in total testosterone levels by seven days and free testosterone levels by 56 days.[103,104]

***Theobroma cacao* seed extract.** *Theobroma cacao*, commonly called the cacao tree, produces cocoa bean seeds rich in polyphenols such as epicatechin; these seeds can also be processed into chocolate. Preclinical studies have identified that the major polyphenols found in the cacao seeds can increase the production of testosterone and nitric oxide.[105,106] Nitric oxide can increase testosterone levels by acting on neurons involved in the release of gonadotropin-releasing hormone that increase levels of luteinizing hormone, the hormone responsible for testosterone production in the testes.[107]

Zinc. This mineral is involved in almost every aspect of male reproduction, including testosterone metabolism, sperm formation, and sperm motility.[61] 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.[62] 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 decrease steadily with age.[63] 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.[64] A 2020 meta-analysis of 42 publications found that DHEA administration significantly increased testosterone levels, and the effects were more pronounced with increased dose and duration of treatment.[125]

Tribulus. *Tribulus terrestris,* also known as puncture vine, contains the active ingredient protodioscin, which is reportedly converted to DHEA in the body.[65] This DHEA-boosting activity may account for puncture vine's reputation as an aphrodisiac in its native Europe and Asia. Animal studies support the ability of tribulus to improve sexual function.[66,67]

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.[68]

Trimethylglycine. Trimethylglycine (TMG), also known as betaine, is an endogenous compound that plays several important roles in the body, contributing to various aspects of health. It is a methyl donor in biological methylation reactions, including conversion of homocysteine to methionine. TMG also helps cells maintain proper hydration status and volume; that is, it is an osmolyte.[222,223]

Some research suggests TMG may have exercise performance-enhancing effects.[224,225] However, several of the studies that have evaluated the effects of TMG supplementation in the context of exercise have enrolled teenagers under 18,[226-228] so it is unclear whether these effects will replicate in adults. The mechanism(s) by which TMG may enhance exercise performance are not completely understood, but may involve increasing testosterone signaling

and modulating muscle protein synthesis.[229]

In a randomized, controlled, crossover trial published in 2023, 43 CrossFit practitioners (mean age 34 years) received either placebo or TMG at a dosage of either 2.5 or 5 grams daily. Each treatment period lasted three weeks with a three-week washout period in between. Supplementation with TMG was associated with a 29 ng/dL (7%) increase in mean total testosterone, irrespective of the dose and there was no significant improvement during the placebo phase. Insulin-like growth factor 1 and cortisol levels did not change in any group.[228]

β-hydroxy β-methylbutyrate (HMB). HMB, a bioactive metabolite of the branched chain amino acid leucine, may enhance recovery and improve skeletal muscle function during high-volume and high-intensity exercises. It has been suggested that HMB may increase testosterone by converting to HMG-CoA (a precursor to cholesterol) in the cytosol of the liver and muscle. Cholesterol is the substrate precursor for all steroid hormones, one of which is testosterone.[230] Randomized controlled studies evaluating the effect of HMB supplementation on testosterone concentrations have yielded mixed results.[231]

A meta-analysis of seven randomized controlled trials that enrolled a total of 235 trained athletes, aged 16–25, evaluated the effects of HMB with exercise on testosterone and cortisol response. All studies included in the meta-analysis enrolled healthy subjects receiving oral HMB supplementation before and after exercise (totaling 3 grams per day) and included one outcome measure of cortisol and testosterone. The meta-analysis generally did not show any effects of HMB on cortisol and testosterone concentrations compared with controls. However, a subgroup analysis based on exercise type showed a significant decrease in cortisol concentrations in the group that received HMB combined with resistance training exercises. In addition, there was a significant increase in testosterone concentration in the subgroup of sports that combined aerobic and anaerobic activity. Studies that lasted for six weeks or more showed greater increase in testosterone concentration.[231]

Natural Products to Keep Aromatase and/or Sex Hormone-Binding Globulin (SHBG) in Check

Luteolin. Luteolin is a flavonoid found in various fruits and vegetables such as celery, parsley, cabbage, and apples. Preclinical studies suggest luteolin can decrease the activity and expression of aromatase, the main enzyme responsible for converting testosterone into estrogen, both *in vitro* and *in vivo*.[109,110] In rat Leydig cells (the cells responsible for producing androgens in the testes), luteolin upregulated the expression of steroidogenic acute regulatory protein (StAR), which controls the transport of cholesterol into the mitochondria and enhances the conversion of cholesterol to the testosterone precursor pregnenolone.[111] Luteolin also effectively increased cAMP-dependent accumulation of progesterone, a precursor to testosterone, in mouse Leydig cells.[112] Together, these effects may work synergistically to help maintain healthy testosterone levels.

Chrysin. The bioflavonoid chrysin is a natural aromatase inhibitor.[69] Bodybuilders have used chrysin as a testosterone-boosting supplement, because it minimizes the conversion of testosterone to estrogen. Although chrysin has low oral bioavailability,[70] its bioavailability may be significantly enhanced by co-administration with the black pepper extract, piperine, thus enhancing its actions as an aromatase inhibitor.[71]

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.[72] In rats exposed to bisphenol A (BPA), a common environmental toxin that contributes to testicular dysfunction, treatment with quercetin increased testosterone and decreased estrogen levels.[170] Other animal models have also shown quercetin is protective against testicular damage from environmental toxicant exposure.[171,172]

Nettle root. Lignans contained in nettle root extract may help prevent the binding of SHBG to testosterone. This may help ensure that free testosterone is available for promoting male vitality and youthful sexual function.[73,74] Nettle root extract is used extensively, either in combination with saw palmetto[75] or by itself[76] 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.[77] 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.[78]

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,[79] 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 two weeks. Sixty-two percent 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 with the treatment. 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.[80]

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. In one clinical study, both testosterone and carnitine improved sexual desire, sexual satisfaction, and nocturnal penile tumescence, but carnitine was 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. Carnitine was not shown to increase free or total testosterone levels however, suggesting different mechanisms were at play.[81]

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-alpha-hydroxyestrone 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 may translate to a decrease in prostate cancer risk.[82,83] 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."[84] Multiple mechanisms by which I3C may help prevent oncogenic changes have been shown in preclinical research.[173]

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.[85] One theory for the anti-BPH action of pygeum involves the reduced conversion of testosterone to *dihydrotestosterone* (DHT), a potent testosterone metabolite that may exacerbate BPH, via the enzyme 5-alpha-reductase.[86] 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.[87]

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.[88-91] Its clinical benefits related to prostate enlargement include reduced nocturnal urinary urgency,[92] decreased residual urine volume in the bladder,[93] and less discomfort from urination symptoms.[94]

8 Testosterone and Prostate Cancer

Historically, testosterone was believed to promote prostate cancer. This view changed beginning around 2000 when evidence accumulated showing that testosterone levels were not consistently associated with prostate cancer. Subsequently, the "saturation" model emerged. This view suggests that, beyond near-castration levels, testosterone has little effect on prostate cancer growth. Meta-analyses of randomized controlled trials revealed either null effects or small protective effects of testosterone therapy on prostate cancer risk.[168]

A review of data from 18 prospective studies compared serum concentrations of androgens and estrogens in 3,886 men with prostate cancer to 6,438 healthy controls. The results showed no significant associations between risk of prostate cancer and sex hormone levels.[60] A large cohort study published in 2020 supported the safety of testosterone therapy. Analysis of nearly 70,000 patients with a history of non-metastatic prostate cancer treated with radiation or surgery found that those who subsequently underwent testosterone treatment did not have an increased risk of cancer recurrence or mortality.[98]

In more than 500 men diagnosed with prostate cancer who were followed for over a mean of 8.7 years, high androgen levels were associated with a decreased risk of aggressive prostate disease compared with no change in risk of non-aggressive disease. Overall, levels of any steroid hormones (except estradiol) were not correlated with risk of aggressive prostate cancer.[96]

Observational studies and small case series reported that testosterone therapy did not increase risk of progression in men who had been treated for low-risk prostate cancer. Larger observational studies of testosterone therapy in men who had been treated for predominately low-risk prostate cancer did not associate testosterone treatment with poor outcomes. Further studies showed that low testosterone levels in fact appear to be associated with higher-grade prostate cancer.[168]

Thus, the totality of the evidence available as of late 2021 does not suggest that high testosterone levels or testosterone therapy increase prostate cancer risk per se. In fact, researchers are actively exploring the risks and benefits of testosterone replacement therapy among men who have been treated for low-risk prostate cancer.[168] Some men who have symptoms related to low testosterone levels and have been successfully treated for low-risk prostate cancer may be candidates for testosterone therapy. However, consultation with a physician with experience in this area is essential before men in this situation begin testosterone therapy.[174] Increased monitoring of PSA levels may be recommended in this setting.

One active area of research focuses on the concept known as "bipolar androgen therapy" for prostate cancer. This approach entails using intermittent testosterone therapy to cause men's testosterone levels to oscillate between castration levels and high, supraphysiological levels as a means of modulating androgen receptor sensitivity. The aim of this approach is to prevent prostate cancer cells' ability to adapt to very low testosterone conditions.[175] This is an active area of research, and more studies are needed before clear conclusions as to the utility of this approach can be drawn.

Despite considerable advances in our understanding of the influence of testosterone on prostate cancer risk and pathophysiology, the use of testosterone therapy in the context of prostate cancer remains very controversial. Data remain sparse in the context of men with low-grade disease who have yet to undergo active treatment for prostate cancer. Therefore, men at high risk for, or who have or have had, prostate cancer should not undertake testosterone therapy without first consulting with a qualified healthcare provide who is intimately familiar with the latest literature on this complex topic.

Update History

many of the therapies discussed. The reader assumes the risk of any injuries. The authors and publishers, their affiliates and assigns are not liable for any injury and/or damage to persons arising from this protocol and expressly disclaim responsibility for any adverse effects resulting from the use of the information contained herein.

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

References