Testosterone Therapy in Older Men: 
*Updated Guideline Recommendations*

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Introduction:
Testosterone serves several purposes in the body, including maintenance of lean muscle mass, muscle size, muscle strength, and bone mass. Libido, fat distribution, and the production of red blood cells and sperm are also affected by testosterone. Low levels of free testosterone (FT) and total testosterone (TT), which occur as the ability of the testicles to produce testosterone diminishes, can lead to a variety of symptoms in men. The exact symptoms can vary depending on age of onset of hypogonadism, presence of other health conditions, length of testosterone deficiency, level of sensitivity to androgens, and any previous testosterone therapies. The Endocrine Society recently updated their clinical practice guidelines on the use of testosterone therapy in men with hypogonadism. These guidelines, which introduce new evidence and recommendations from the previous update in 2010, were cosponsored by the European Society of Endocrinology and endorsed by the European Academy of Andrology. The guidelines explain appropriate testing and monitoring of patients on testosterone therapy and describe which patients may qualify for testosterone therapy along with the benefits and risks associated with testosterone use. How testosterone should be used for patients and what advantages and disadvantages clinicians might anticipate from testosterone use in patients with low testosterone, with an emphasis on testosterone therapy in older adults, will be discussed below.

*How can a clinician be confident that a patient has hypogonadism and should be treated with testosterone?*
First, it is important to be aware that levels of testosterone in the body can vary throughout the day and can be affected by external factors. Blood levels follow a daily rhythm, with levels that are highest in the morning and wane throughout the day. This means that patients, especially those aged 65-80 years, with low testosterone levels in the afternoon may have normal testosterone levels in the morning. When drawing labs for testosterone levels, it is important that the sample is collected in a fasting state and in the morning. It is also recommended to evaluate two separate testosterone measurements in order to diagnose low testosterone with certainty. Other factors which may influence testosterone levels are acute illness, nutritional deficiency, certain medications (i.e., opioids and glucocorticoids), age, obesity, diabetes, sleep disorders, and overall health status.

When it has been determined that a patient has hypogonadism, the next step is to differentiate its etiology, as this will help plan a treatment regimen or verify that patients are on an appropriate treatment regimen. There are two categories: primary and secondary hypogonadism. Primary hypogonadism indicates there is an issue with the testes and can be caused by cryptorchidism, some cancer chemotherapies, trauma, testicular torsion, HIV infection, and myotonic dystrophy. Secondary hypogonadism indicates that there is dysfunction of the
pituitary-hypothalamic axis and requires additional testing of luteinizing hormone and follicle stimulating hormone levels to diagnose. This can be caused by hyperprolactinemia, severe obesity, use of opioids/glucocorticoids/androgen-deprivation therapy with gonadotropin-releasing hormone agonists, androgenic-anabolic steroid withdrawal, idiopathic hypogonadotropic hypogonadism, head trauma, pituitary surgery or radiation, and hypothalamic/pituitary tumors. Both primary and secondary hypogonadism will result in low testosterone and impairment of spermatogenesis, but primary hypogonadism will result in elevated gonadotropin levels, while secondary hypogonadism will result in low or inappropriately normal gonadotropin levels. It is necessary to measure FT in men that are at an increased risk for alterations in their levels of sex hormone binding globulin (SHBG). If patients are obese, have type 2 diabetes, or previous use of androgens, they are predisposed to presenting with low SHBG, while advanced age, some anticonvulsants, or HIV infection may predispose a patient to present with higher SHBG.

What do the guidelines say about using testosterone therapy in older men?

The guidelines recommend using testosterone for induction and maintenance of secondary sex characteristics and to relieve symptoms associated with hypogonadism. Testosterone should not be routinely prescribed for all men greater than 65 years old with low testosterone concentrations, but should be offered only on an individualized basis to patients which complain of symptoms and have consistently low morning testosterone concentrations. As evident by the Testosterone Trials, testosterone treatment in men 65 years of age or older demonstrated reasonable improvements in sexual function and minute improvements in walking distance, mood, anemia, bone mineral density (BMD), and depressive symptoms. However, no improvements in vitality or cognitive function resulted from testosterone therapy in this age group. By not treating all men with low testosterone resulting from advanced age, recommendations are more closely linked to the avoidance of unknown long-term risks, especially since long-term benefits regarding disability, fractures, and progression to diabetes or dementia are currently unknown. The guidelines note that there is still considerable disagreement among practitioners about the appropriateness of testosterone therapy in older men, primarily due to limited or incomplete evidence.

The efficacy of testosterone therapy may vary between patients, but patients can expect an impact on various body systems. Possible anticipated benefits and risks of testosterone therapy, with an emphasis on the impact of these outcomes in older males, follow.

What are the benefits of testosterone therapy?

Bone mineral density (BMD):

For hypogonadal men with few other comorbidities, an improvement in BMD has been observed in several patients receiving testosterone therapy. These improvements were primarily seen in the vertebral and femoral regions, although no study has shown a reduction in fracture risk. Therefore, testosterone is not an approved or recommended treatment for osteoporosis in men with normal testosterone levels, nor should it be the sole agent used to treat osteoporosis in men with low testosterone levels. Osteoporosis should be managed with appropriate vitamin D and calcium supplementation, along with an approved osteoporosis therapy. If hypogonadal men are started on testosterone therapy and are at a low risk for fracture, it may be decided to delay treatment of additional osteoporosis therapy until the effects of testosterone are evaluated by conducting repeat BMD tests of the lumbar spine, femoral neck, and hip after 1-2 years on testosterone therapy.
Depression:
While testosterone does not improve depressive symptoms in men with clinical depression, there is some evidence that testosterone may generally improve positive aspects of mood and reduce negative aspects, but the degree of the effect is small. Some studies have shown that testosterone may provide positive results in the resolution of depression symptoms for middle-aged and elderly men, as long as those men had late-onset, low-grade, persistent depressive disorder and low testosterone.

Muscle mass:
An additional benefit of testosterone therapy is an increase in muscle mass and strength, with a reduction in fat throughout the body when used in healthy men with hypogonadism. The effect on muscle mass is directly proportional to the dose of testosterone. Furthermore, when older men with good health and mobility were evaluated, several studies observed that there was a greater magnitude of muscle mass, maximum voluntary strength, muscle power, and some performance-based measures of physical function in men taking testosterone versus placebo. Something to consider regarding these positive results is that the study analysis did not show any significant difference in mobility, gait speed, or measure of disability, or significant improvements in memory or other aspects of cognitive function in patients using testosterone. These are all key factors related to risk of falls and ability to complete activities of daily living in older patients.

Sexual function:
Patients are likely to see maintenance of secondary sexual characteristics and a significant improvement in sexual function with testosterone therapy. This may be a desired effect or goal for the patient, but other health conditions, such as cardiovascular health, should also be monitored.

What risks are associated with testosterone therapy?
Not all effects of testosterone therapy are beneficial; as with other medications, there are risks and adverse effects associated with this therapy. The most common adverse effects of testosterone include acne, oiliness of the skin, and breast tenderness. Other side effects which have been associated with testosterone therapy include erythrocytosis, detection of subclinical prostate cancer, growth of metastatic prostate cancer, and reduced sperm production and fertility. More rare events which may occur include gynecomastia, male pattern balding, growth of breast cancer, and induction or worsening of obstructive sleep apnea, although these events are not very well-linked to the use of testosterone.

The most concerning adverse events are related to thrombotic, cardiovascular, and prostate risk. Administration of testosterone increases the levels of hemoglobin and hematocrit and can even lead to erythrocytosis (hematocrit >54%) in some men. These risks are higher in older men than in younger men. To mitigate these risks, it is recommended that men who develop erythrocytosis stop taking testosterone until hematocrit levels return to normal and then resume therapy at a smaller dose. The other adverse effect that may be cause for concern is cardiovascular risk associated with testosterone use. Multiple retrospective studies and meta-analyses have been performed to investigate whether there is a relationship between testosterone replacement therapy and the risk of major adverse cardiovascular events, but these studies have shown
inconsistent results and contained several limitations which impact their validity in identifying a causal relationship. But while there is insufficient evidence to directly link adverse cardiovascular events and testosterone use, the FDA has placed a Boxed Warning on testosterone products indicating there may be potential association between the two. There are also little data to support a relationship between testosterone use and an increased risk of venous thromboembolism (VTE). Some case reports have demonstrated a possible link, as they have shown VTE when patients are in a hypercoagulable state without a rise in hematocrit, particularly in the 6 months following initiation of testosterone therapy.

There are a few considerations to note regarding prostate risk for patients on testosterone therapy. First, providers should be aware that an increase in prostate specific antigen (PSA) may occur while taking testosterone, so PSA should be monitored more closely in patients using testosterone. Secondly, many eugonadal men have subclinical prostate cancer which may or not develop into clinical cancer throughout their life. Testosterone supplementation may cause these subclinical cancers to grow and develop more quickly and maturely than without the presence of additional testosterone therapy. Therefore, men treated with testosterone therapy are more likely to be closely monitored for prostate cancer risk. Thirdly, due to an increase in PSA and increased monitoring of hypogonadal men using testosterone therapy, preclinical tumors will be identified earlier, and these patients are more likely to undergo prostate biopsies, putting them at an increased risk of adverse effects including pain, fever, bleeding, infection, risk of false positives, transient urinary difficulties, and over diagnosis. Not to imply that men on testosterone should not be adequately monitored for prostate cancer, but clinicians should be aware of this link between early identification of preclinical cancers and possible unnecessary treatment of these tumors.

Clinicians should conduct a baseline evaluation in men being considered for testosterone therapy in order to exclude patients with a high risk of prostate cancer or family history of prostate cancer. For men 55-69 years old, clinicians should screen all hypogonadal patients if they are considering testosterone therapy, in excellent health, and have a life expectancy > 10 years. Screening should start at age 40 for men with a high risk of prostate cancer, while men younger than 40 do not require prostate monitoring. Prostate monitoring is not necessary in men 70 years of age and older who are receiving testosterone treatment due to the fact that a diagnosis of prostate cancer at this age rarely leads to prostate-cancer related death.

**Bottom Line**

Per the updated guidelines, testosterone should not be routinely prescribed for all men greater than 65 years old with low testosterone concentrations. Instead, it should be offered on an individualized basis to patients which complain of symptoms and have consistently low morning testosterone concentrations. As stated previously, testosterone treatment comes with some risks. However, clinical evidence has not consistently demonstrated a significant increase in the risk for prostate cancer, thrombotic events, or major cardiovascular adverse outcomes with testosterone therapy. Ultimately, discussing the potential benefits and risks associated with testosterone therapy should be at the forefront of communication between patients and providers, as well as between patients and pharmacists, when testosterone replacement therapy is being considered.
References:


