Chapter 52
Is there an andropause, more appropriately named Late Onset Hypogonadism, and if so, what tissues are affected and how?

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Even thousands of years before isolating the compound, which we now call testosterone, scholars across the globe understood that some component of the testes was important for the health and vitality of men. There is documented evidence that traces back to Roman times, of utilizing animal testicular tissues to improve the declining virility of aging men, demonstrating the collective understanding of the intimate link between gonadal failure and common symptoms of old age.

Today, it is understood that testosterone is a hormone produced in the Leydig cells of the testes and this hormone is responsible for male sexual differentiation and development; these cells are regulated by the hypothalamic-pituitary-gonadal axis (Chapter 2). Testosterone affects the entire body regulating many functions including fertility, sex drive, erectile function, bone density, fat distribution, and lean muscle mass. While it is no surprise that men with low testosterone will show impairment in these functions, a decrease in testosterone can also present symptoms of reduced energy, diminished physical performance, visual field changes, anosmia, depression, decreased concentration, and impaired memory.

Aging is associated with gender-specific hormonal changes that progressively lead to gonadal insufficiency. While all women can expect to experience menopause as they age with dramatic decline in circulating estradiol and progesterone, men do not experience a similar rapid decline in steroid production. Rather, aging men experience a decline in circulating testosterone over several decades; this is termed late onset hypogonadism (LOH), previously inappropriately referred to as andropause. LOH is associated with advanced age and characterized by symptoms of deficiency in serum testosterone. Serum testosterone levels decline gradually with age

at an approximate rate of 1% per year after the third decade of life; however, only 20% of men aged 65 years or more have testosterone levels below the normal range for young men.

LOH was first coined in 2002 and defined as a disease entity. Several societies including the American Society of Andrology, the American Urological Association (AUA), and the European Academy of Andrology have endorsed recommendations for further investigation into this clinical and biochemical syndrome. The efforts of these societies led to guidelines that accurately diagnose LOH, which were then updated and adopted by other societies, including the Canadian Society of Urology, the European Menopause and Andropause Society, and the Endocrine Society.

It is worth noting that not all academic entities have adopted the term LOH to describe this condition. The AUA and the Testosterone Panel were also committed to creating a guideline that ensures that men in need of testosterone therapy (TT) are treated effectively and safely. The Panel chose to cease the use of the term hypogonadism as it has recently been used interchangeably with the idea of low testosterone production alone. To capture the full clinical picture, the AUA has adopted the term testosterone deficiency (TD) in place of LOH, as it better describes the signs and symptoms associated with low total testosterone in addition to the state of low testosterone production itself. Thus, a patient diagnosed with TD is a candidate for TT only when he meets both criteria.

While there is consensus in the guidelines of various societies that TD is based on the presence of both abnormal laboratory measurements and clinical signs and symptoms, there is variation in the exact laboratory cut off value of testosterone concentration that they use. This discrepancy is likely due to various symptoms of TD correlating to different testosterone threshold levels. In other words, professional societies view different symptoms as the priority point to start TT. Hence, a reliable cut-off value for testosterone level is critical to accurately diagnose TD in aging men given the correlations that have been observed between TD and several more life-threatening issues.

Approximately 1-4% of total testosterone circulates in the body as free form and the rest is bound to sex hormone binding globulin (SHBG) or albumin. Since testosterone binds to albumin with low affinity, albumin-bound testosterone provides most of the bioavailable testosterone that is physiologically active. SHBG binds testosterone with high affinity, and its concentration increases with age, thereby further decreasing bioavailable testosterone. In addition, aging is also

associated with a decline in the ability of Leydig cells to synthesize testosterone, and an increase in the sensitivity of the hypothalamic-pituitary axis to be inhibited by circulating testosterone.

The 2018 AUA testosterone guidelines defined the clinical diagnosis of TD as having total testosterone concentrations below 300ng/dL recorded on two separate mornings, using the same assay from the same laboratory. This must be combined with patient interviews and physical symptoms to assess symptoms and/or signs associated with low testosterone levels, and counseling to evaluate potential risk factors. If the testosterone levels are consistently low, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be measured to determine if the hypogonadism is primary or secondary (Chapter 32). Secondary hypogonadism with other possible hormonal deficiencies warrants further testing for prolactin levels and magnetic resonance imaging (MRI) of the *Sella Turcica* region. The Endocrine Society has adopted these guidelines and recommends an evidence-based, individualized approach to TT in older men with TD (Fig. 1).

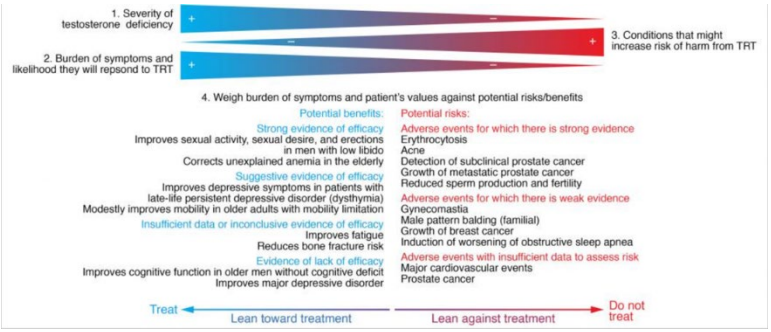

Figure 1. An evidence-based, individualized approach to testosterone therapy (TT) in older men with testosterone deficiency (TD). Bhasin S. Testosterone replacement in aging men: an evidence-based patient-centric perspective. J Clin Invest. 2021 Feb 15;131(4):e146607.

Testosterone is a steroid hormone that exerts its biological action through binding to androgen receptors located in target cells of various tissues (Chapter 3). Target tissues include sexual organs, as well as the brain, liver, muscle, skin, and bone. Commonly reported presentations of TD in aging men include diminished sexual desire, reduced semen volume, delayed ejaculation, and

erectile dysfunction with reduced morning and nocturnal erections. Affected men express decreased sense of vitality, with mood changes, decreased intellectual activity, decreased spatial orientation, depression, and anger.

Age-related TD leads to increased loss of skeletal muscle volume in conjunction with an increase in fat mass. Loss of muscle mass combined with decreases in bone mineral density, predisposes aging men to osteoporosis and subsequent fractures. TD has also been associated with metabolic syndrome in men due to increased insulin resistance and accumulation of visceral adipose tissue. Through this effect, TD may additionally contribute to the development of non-alcoholic fatty liver disease in men. Since testosterone has a stimulatory effect on erythropoiesis, TD is associated with anemias of known cause (iron deficiency) and unknown cause. Gynecomastia may also be clinically observed as both TD and increased fat lead to more unopposed estrogen that can result in a stimulation of breast tissue growth. Lastly, TD may play a role in skin alterations in aging men such as decreased epidermal skin moisture and hair concentration, skin thickness, and elasticity. However, it should be noted that these symptoms can also be manifestations of other co-morbid conditions prevalent with aging; thus, it is imperative that clinicians can exclude other diseases first before making the diagnosis of TD and begin TT.

In order to improve age-related risks for adverse health outcomes, the question of restoring the diminishing testosterone level has garnered much interest and has inevitably set the stage to develop various formulations of TT to treat TD. TT has been approved in the United States since the 1950s and over the years, various options have been developed, including formulations in topical patches and gels, nasal gel and buccal tablets, oral pills and capsules, and injections and implants. Table 1 shows TT approved by the Food and Drug Administration (USA) as of 2021.

All these options, when used according to recommendations, can restore the testosterone concentration to normal physiological range of 450-600ng/dL and relieve symptoms in most hypogonadal men. However, it is important to note that while the FDA can approve a drug for its intended use when submitted with substantial evidence of clinical benefits, the FDA does not regulate any off-label use of a drug. Clinicians are expected to make the best judgment with adherence to the guidelines to optimize the benefit-to-risk ratio of TT for each patient.

Delivery System/Drug	Brand Name	Recommended Dose Regimen	Available Format
Topical/Transdermal			
Testosterone patch	Androderm	2 or 4 mg patch/day	4 mg starting dose Do not apply the patch to the same area within 7 days Apply to back, abdomen, upper arms
Testosterone gel	AndroGel	1% gel – 50 to 100 mg of testosterone per day 1.62% gel – 40.5 to 81 mg of testosterone per day	25 or 50 mg testosterone packets Apply to shoulders and upper arms 20.25 mg testosterone, one pump actuation or a 20.25 mg packet 40.5 mg testosterone, two pump actuation or a 40.5 packet Apply to shoulders and upper arms
Testosterone gel	Testim	1% gel – 50 mg of testosterone/tube	50 mg/day starting dose Apply to shoulder and upper arms
Testosterone gel	Fortesta	2% gel 10 mg/0.5 g per pump actuation	40 mg (4 pump actuations)/day starting dose Apply to inner thighs
Testosterone gel	Vogelxo Testosterone Gel	1% gel 50 or 100 mg per tube or packet, 12.5 mg per actuation for pump 1.62% gel similar to AndroGel (1.62%)	Generic testosterone gel Generic, same as AndroGel 1.62%
Testosterone lotion	Axiron	2% lotion 30 mg/pump actuation	Start with 60 mg Apply to axilla Discontinued
Buccal/Nasal			
Buccal tablets	Striant	30 mg twice/day	Apply to gum Dislodging of tablets Discontinued
Nasal gel	Natesto	11 mg gel intranasal three times per day	Start with one actuation (5.5 mg) into each nostril total 11 mg Apply to nose three times per day

Suggested reading

Bhasin S. Testosterone replacement in aging men: an evidence-based patient-centric perspective. J Clin Invest. 2021;131(4).

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