Testosterone and Male Sexual Function

Logan B. Galansky, MD[a,*], Jason A. Levy, DO, MS[b], Arthur L. Burnett, MD, MBA[c,d]

KEYWORDS

• Testosterone • Male sexual function • Erectile dysfunction • Ejaculatory dysfunction • Low libido

KEY POINTS

- Testosterone is the driving hormone of male sexual development and function. It has functions in the central nervous system, peripheral nervous system, and end organs.
- The male sexual response cycle is complex and the exact role of testosterone in mediating libido, arousal, erection, ejaculation, and orgasm is multifactorial.
- For men presenting with sexual dysfunction, it is important for clinicians to understand the signs and symptoms and appropriate work-up for low testosterone.

INTRODUCTION

Male sexual function involves a complex interplay between hormonal, anatomic, and neuropsychologic functions and mediators. At the basis of any discussion surrounding normal and abnormal male sexual function is the "male sexual hormone," testosterone (T). Hypogonadism, defined broadly as testicular failure with androgen deficiency, can disrupt the male sexual response cycle as well as normal systemic physiology. The resulting signs and symptoms can include decreased libido, erectile dysfunction, ejaculatory dysfunction, infertility, fatigue, decreased bone density, decreased lean body mass, increased body fat, and sleep disturbances.[1]

The most widely accepted model of the human sexual response cycle was developed by Masters and Johnson in 1996. They described a four-stage linear process through the phases of arousal, plateau, orgasm, and resolution.[1] Some frameworks, such as that proposed by Singer Kaplan, also include a desire phase which precedes the arousal phase.[2]

For men, the corresponding physiologic processes to the sexual response cycle are libido and sexual desire, arousal and erection, and ejaculation and orgasm. These physiologic functions are mediated by central and peripheral nervous system pathways, end-organ motor and sensory mechanisms, and molecular signaling pathways of the vascular system.

Basics of Testosterone

T is the main bioavailable androgen circulating in men. Most of the circulating T is produced by Leydig cells in the testis, with a smaller amount synthesized by the adrenal glands.[3] Testicular synthesis of T is dependent on a functional hypothalamic–pituitary–gonadal (HPG) axis. Beginning in the hypothalamus, gonadotropin-releasing hormone (GnRH) is secreted, stimulating the production of luteinizing hormone (LH) in the gonadotropic basophil cells of the anterior pituitary gland.[4] LH then acts on the Leydig cells in the testis to stimulate the production of T. T, and its metabolite estradiol (E2), then act to inhibit

[a] Johns Hopkins School of Medicine Brady Urological Institute, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287, USA; [b] Johns Hopkins School of Medicine Brady Urological Institute, The Johns Hopkins Hospital, 600 North Wolfe Street Park 2, Baltimore, MD 21287, USA; [c] Oncology Center, Johns Hopkins School of Medicine Brady Urological Institute, The Johns Hopkins Hospital, 600 North Wolfe Street, Marburg 407, Baltimore, MD 21287, USA; [d] Johns Hopkins Clinical Research Network, 1830 Monument Street, Suite 328, Baltimore, MD 21205, USA
* Corresponding author.
E-mail address: lgalans1@jhmi.edu
Twitter: @LoganGalanskyMD (L.B.G.)

Urol Clin N Am 49 (2022) 627–635
https://doi.org/10.1016/j.ucl.2022.07.006
0094-0143/22/Published by Elsevier Inc.

GnRH and LH secretion at the hypothalamus and pituitary gland as well as downstream T secretion by Leydig cells in a standard negative feedback loop.[4]

Once produced by the Leydig cells, T can circulate freely, become bound to carrier molecules, or undergo conversion to its main metabolites, dihydrotestosterone (DHT) and E2. T is converted to DHT by the enzyme 5-alpha reductase and to estradiol by the enzyme aromatase in various tissues throughout the body, including the prostate, liver, skin, testis, adipose tissue, and brain, respectively. It is then that T, DHT, and E2 can act directly on target tissues, primarily by binding to the androgen receptor. Free T accounts for 1–2% of circulating T that is unbound. Of the remaining circulating T, approximately 60% is bound to sex hormone binding globulin (SHBG), with the remaining bound to albumin and other serum proteins. Only circulating T that is free or albumin-bound is biochemically available to act on target tissues.[5]

T and its metabolites act throughout the body on multiple organ systems, including muscle, bone, skin, brain, and peripheral nerves. It is also essential for the development of the male phenotype, male puberty, male sexual function, and spermatogenesis.

Role of Testosterone in Male Sexual Anatomy Development

Male sexual anatomy development is influenced by T as early as the eighth week in utero.[5] During this time, Leydig cells differentiate from genital ridge cells and begin to produce T. Serum and testicular T levels continue to rise between the 8th and 13th week to maintain the Wolffian duct system and stimulate the development of the male external genitalia, male accessory sexual tissues (seminal vesicles, prostate, bulbourethral glands), male reproductive tract tissues (testes, epididymides, vas deferens, ejaculatory ducts), and pelvic floor structures (pelvic diaphragm muscles). After 13 weeks gestation, T levels begin to decline.[5]

Studies have shown that T regulates the differentiation of penile stem cells to the smooth muscle phenotype that is necessary to form the functional and structural anatomy for penile erection.[6] In developmental and adult rodent castration models, penile architecture is compromised as demonstrated by lower intracorporal peak pressures following cavernous nerve stimulation compared with noncastrate animals.[7]

In prepubertal men, T levels remain low at less than 30 ng/dL.[8] During adolescence, puberty and further development of male secondary sex characteristics are triggered by pulsatile hypothalamic GnRH, with respondent increases in T levels to 100–300 ng/dL during puberty and levels greater than 300 ng/dL as an adult.[9]

The sympathetic and parasympathetic nerves that supply the urogenital organs form the major pelvic ganglia. These autonomic nerves arise from the spinal preganglionic neurons of the lumbar and sacral spinal cord and control erection, ejaculation, and detumescence.[9] During late gestation and in the early postnatal period, T contributes to proper pelvic ganglia formation, and thereby sexual reflexes.[8,10]

MALE SEXUAL FUNCTION PHYSIOLOGY: ROLE OF TESTOSTERONE

Physiologic Mechanisms

Despite numerous studies investigating the physiology of the male sexual response cycle, the exact role of T in mediating the steps of the process remains incompletely known. However, the literature suggests that T is key in coordinating the processing of sexual libido, the mechanics of erections, and ejaculatory function.

The first stage of the sexual response cycle involves sexual desire and libido. Sexual desire is influenced by many factors, including psychosocial, cultural, and situational, whereas libido is a biologic response directly related to T levels. Mediation of libido by T occurs in the central nervous system. Studies have shown expression of the androgen receptor in key brain areas, including the amygdala, preoptic area, and paraventricular nucleus of the hypothalamus.[10]

It has also been demonstrated that T is involved in the physiology of erections, most likely through its influence on molecular mediators of erectile function, formation of penile architecture, and activity of smooth muscle pathways.[8] T has been shown to influence enzymatic activity in the corpora cavernosa that is responsible for both erection and detumescence.[8] In hypogonadal animal models, T regulates the formation of molecules involved with erection, namely nitric oxide (NO), RhoA-ROCK, and PDE5.[8] Castration models have also demonstrated the downregulation of the NO/cyclic guanosine monophosphate(cGMP) pathway in conjunction with other T-dependent biologic effects, causing smooth muscle and endothelial apoptosis and lipofibrosis of the penile corpora cavernosa that results in corporal veno-occlusive dysfunction.[11]

The neural networks involved in ejaculation include both peripheral pelvic and genital nerves as well as galaninergic neurons in the central spinal cord.[12] It has been suggested that the formation of

galaninergic neurons is at least partially androgen-mediated, as studies of female and male cadavers show a greater density of galaninergic neurons in the L3–L4 segments of male spinal cords.[13] Lesions to these structures have been associated with ejaculatory failure despite penile stimulation.[13] The ejaculatory reflex is coordinated by neuromuscular mediators in the hypothalamic nuclei, specifically serotoninergic and dopaminergic neurons, responsible for inhibition and promotion, respectively.[14] In the peripheral nervous system, emission and expulsion are then controlled by sympathetic and parasympathetic pathways.[15] In rat models and some human studies examining ejaculatory dysfunction, T deficiency has been associated with decreased dopaminergic response, leading to a delay in orgasmic function, as dopaminergic neurons facilitate the central ejaculatory reflex.[13] It has been hypothesized that low T is associated with increased inhibitory tone in male genital smooth muscle cells, which subsequently contributes to delayed ejaculation.[16]

MALE SEXUAL DYSFUNCTION PATHOPHYSIOLOGY: ROLE OF TESTOSTERONE

Libido Dysfunction (Symptomatic Hypogonadism)

Libido plays a critical role in initiating the male sexual response cycle. Low libido is characterized by a persistent deficient desire for sexual activity. This can be experienced in isolation, as with hypoactive sexual desire disorder, or as one symptom among a cluster of problems, as in symptomatic hypogonadism. Prevalence of low libido in men is variable with studies reporting between 5 and 17% of men endorsing problems with libido and other aspects of sexual desire, and further diminishing libido with increasing age.[15]

The American Urologic Association (AUA) defines T deficiency as < 300 ng/dL.[17] In men with T deficiency, diminished libido is a common sexual symptom. Although the exact mechanism of T's effect on libido remains unknown, studies have shown that in men undergoing androgen deprivation therapy (ADT), libido is severely impacted with only 5% of men maintaining a high level of sexual interest.[18] Moreover, many human and animal castration studies have demonstrated the connection between hypogonadism and decreased libido.[8] A study on T and hypogonadism found that as T drops below a threshold of 15 nmol/L (433 ng/dL), men can start experiencing loss of libido. Interestingly, libido seems to be one of the early signs of hypogonadism as other symptoms, such as changes in sleep, concentration and mood, obesity and diabetes, and erectile dysfunction, are not observed until T levels drop below 8–12 nmol/L (231–346 ng/dL).[19] Thus, T has been linked to sexual behaviors and connecting these behaviors when an appropriate stimulus is present. As such, in men diagnosed with hypogonadism, treatment with T supplementation has been shown to improve libido along with other sexual symptoms.[17] Interestingly, in eugonadal men with low libido, over-supplementation with exogenous T was not shown to improve sexual drive, suggesting that there are multiple factors underlying male hypoactive sexual desire.[17]

Erectile Dysfunction

Erectile dysfunction (ED) is defined as, "an impairment in the arousal phase of [the male] sexual response" with "consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance."[20]

The prevalence of ED has been widely reported by a variety of sources. Approximately 20 percent of adult men are reported to have ED.[21]

ED is typically classified as psychogenic or organic.[22] The pathogenesis of ED is multifactorial and can involve multiple underlying disturbances, including vasculogenic, neurogenic, hormonal, and/or medication-induced.

Although most men with ED do not have hypogonadism, ED has been shown to be related to low T levels in some cases. It has been postulated that T may exert local effects to mediate erections based on studies demonstrating fluctuations in serum and corporal T levels during erection.[23] Studies have shown that once T drops below a threshold of roughly 230 ng/dL, men can begin to experience ED.[21] This is particularly relevant for men undergoing ADT, for whom ED is a well-established potential side effect. Further research is being undertaken to better understand the mechanisms by which hypogonadism affects erectile function.

Ejaculatory Dysfunction

Disorders of ejaculation arise when a man does not have control of ejaculation and if there is distress by the man or sexual partner related to ejaculation.[24] Based on when and if ejaculation occurs it can be classified as retrograde ejaculation, premature ejaculation, delayed ejaculation, or failure of ejaculation/anejaculation.

The AUA and Sexual Medicine Society of North America (SMSNA) 2020 guideline on disorders of ejaculation primarily details premature and

delayed ejaculation. It defines premature ejaculation (PE) as, "poor ejaculatory control, associated bother, and ejaculation within about 2 minutes of the initiation of penetrative sex that has been present since sexual debut."[24]

The epidemiology of PE has been challenging to capture due to the confounding factors of perceived PE and normal ejaculation latency time. Thus, although 30% of men have self-reported PE, most men have ejaculation latency times greater than two minutes.[25] In turn, the actual prevalence of PE for those having distress is likely around 5%, but this does not discount that men with PE experience substantial distress.[25] The exact pathophysiology of PE is not known. However, similar to ED, the hypothesized risk factors can be psychologic, neurologic, hormonal, and medication-related.

The understanding of the effect of T on ejaculatory response is limited, but some studies have shown that higher T levels are correlated with premature ejaculation while lower levels are associated with delayed ejaculation in humans.[26] A randomized controlled trial of testosterone replacement therapy (TRT) in hypogonadal men found improvements in ejaculatory function, although perceived bother remained unchanged.[27] Additionally, there is evidence to suggest that T may act on peripheral and central pathways that impact ejaculatory response time by increasing arousal, regulating CNS effects, and changing seminal fluid volume.[8]

In contrast to PE, some men may experience delayed ejaculation (DE), defined as, "lifelong, consistent, bothersome inability to achieve ejaculation, or excessive latency of ejaculation, despite adequate sexual stimulation and desire to ejaculate."[25]

The epidemiology of DE is similarly difficult to capture as DE often exists concurrently with low libido or ED and is therefore underreported. According to the Global Survey of Sexual Attitudes and Beliefs, approximately 14% of men aged 40–80 years old reported difficulty attaining orgasm.[25]

The pathophysiology of DE can be related to problems with sexual stimulation resulting in complications with emission and expulsion. Risk factors that contribute to DE are increasing age, medications, drugs, or neurologic suppression of the normal CNS arousal responses that produce sexual climax, ED, lower urinary tract symptoms, hypothyroidism, and low serum T. In one systematic review, low T levels were significantly associated with mild to moderate DE and a history of hypogonadism doubled a man's relative risk for DE.[28]

CLINICAL EVALUATION OF LOW TESTOSTERONE

Men presenting with issues related to sexual function should undergo a comprehensive evaluation, including medical, surgical, and social history, medication reconciliation, physical examination, and laboratory/adjunct studies as indicated.

History

A focused patient history should be the first step in evaluation. Assessing for T deficiency should include questions related to both sexual and nonsexual symptoms. As described above, low libido, ED, and problems with ejaculation are often commonly attributed to low T. Other symptoms, such as decreased energy, irritability or depression, and weight gain may also be signs of T deficiency.

Validated questionnaires can be useful in further elucidating sexual history. For example, the International Index of Erectile Function (IIEF), Sexual Health Inventory for Men (SHIM), and Erection Hardness Score (EHS) are frequently used in the assessment of ED. Importantly, when discussing a patient's sexual history, it is imperative to understand any psychological or interpersonal factors that may be contributing to the patient's symptoms before any additional work-up.

There are questionnaires focusing on screening for low T in general, though they should not be used to determine if patients are candidates for TRT per AUA guidelines. Common hypogonadism questionnaires include the androgen deficiency in the aging male (ADAM) questionnaire, the Aging Male's Symptoms (AMS) scale, and the New England Research Institute (NERI) Hypogonadism Screener.[29] Notably, while these screening tools have relatively strong sensitivity, ranging from 59 to 97%, the specificity differs widely from 19 to 59%, resulting in varying degrees of success in predicting hypogonadism.[30] Consequently, a quantitatively-proven low T level continues to be the first line for diagnosing hypogonadism.[30]

Social history should involve discussion of any recreational drug or alcohol use, current or prior use of anabolic steroids, and any occupational exposures as certain substances can influence T levels.

Surgical history should focus on both procedures involving the pelvis and testicles (e.g., prostatectomy, orchiectomy, pelvic radiation, and so forth) as well as the brain (e.g., intracranial surgery or radiation, pituitary surgery). It is also useful to discuss the relevant history of any trauma to the testicles or genitals, as this can affect sexual function.

A general overview of the patient's other chronic health conditions, or common signs of undiagnosed conditions associated with sexual dysfunction (e.g. claudication for peripheral vascular disease), should be undertaken.

Reviewing the patient's current medication list is important as certain medications can affect sexual function and T synthesis, particularly corticosteroids, selective serotonin reuptake inhibitors, opioids, chemotherapeutics, and aldosterone receptor antagonists, among others (**Box 1**).

Physical Examination

As with any physical exam, vital signs should be evaluated. Deviations in secondary male sexual characteristics, such as lack of facial and pubic hair, decreased muscle distribution, and gynecomastia, can suggest possible T deficiency. If there is a concern for ED, palpation of peripheral pulses, abdominal exam for abdominal aortic aneurysm, and neurologic exam for neuropathy should be performed as ED can be a harbinger of cardiovascular or neurologic disease.

Although a physical exam can be normal in men with T deficiency, a comprehensive genital exam should be performed. The penis should be thoroughly examined with careful palpation of the shaft to evaluate for any deformities or plaques consistent with Peyronie's disease. The penis should also be examined for any skin lesions or urethral meatus abnormalities. The scrotal exam should include the assessment of testicular size, consistency, and location, as well as the evaluation for the presence of any testicular masses or other abnormalities, such as varicocele. In men reporting lower urinary tract symptoms or who are being considered for possible TRT, a digital rectal exam to evaluate the prostate for any abnormalities can be performed.

Box 1
Medications associated with hypogonadism

- Corticosteroids (e.g., dexamethasone)
- Psychotropic medications (e.g., paroxetine, amitriptyline)
- Opioids (e.g., oxycodone)
- Alkylating agents (e.g., cisplatin)
- Aldosterone receptor antagonists (e.g., spironolactone)
- H_2-receptor antagonists (e.g., cimetidine)
- Antifungals (e.g., ketoconazole)
- Substance use (e.g., marijuana, nicotine, anabolic steroids)

Laboratory Tests

Current AUA guidelines recommend obtaining 2 morning serum total T levels on separate occasions as the initial screening for T deficiency.[15] If the total T level is < 300 ng/dL and the patient is experiencing signs and/or symptoms of low T, this is consistent with a diagnosis of T deficiency.[15] Moreover, in men presenting with ED, total T concentration can be useful in detecting underlying hypogonadism and informing treatment options.

There is some debate regarding testing for free T levels in the setting of normal total T concentrations. As total T concentrations can be affected by SHBG levels, some experts advocate for measuring free T when clinical suspicion for T deficiency is high, despite normal total T levels. Free T can be measured directly by radioimmunoassay (RIA), liquid chromatography, equilibrium dialysis, or calculated indirectly using total T and SHBG concentrations. There can be significant variability in free T reference ranges, but in general, RIA free T levels < 1.0–1.5 ng/dL and calculated free T levels < 80–100 pg/mL are consistent with T deficiency in symptomatic men.[31] It is important to note that current AUA guidelines do not recommend treatment for T deficiency based on low free T levels alone and clinical judgment should be used based on symptoms and patient-specific risks and benefits of trialing TRT.

In evaluating for T deficiency, additional tests can be considered to help differentiate between primary, secondary, and compensated T deficiency. These can include LH, prolactin, FSH, estradiol, thyroid function studies (TSH, T3, T4), and hematocrit.[32] In men over the age of 40 years old who may be started on TRT, prostate-specific antigen (PSA) screening should be considered to establish a baseline.[33] In men desiring fertility, semen analysis can also be considered before starting TRT to determine semen quality, as exogenous T use can suppress spermatogenesis.[34]

As noted above, T deficiency can have deleterious effects on many organ systems and ED can be a preceding symptom of other undiagnosed medical comorbidities. As a result, it is reasonable for clinicians to also obtain a complete blood count, basic metabolic panel, serum glucose, hemoglobin A1c, and lipid panel. While any derangements in these studies may not change the treatment options for T deficiency or ED, they can help identify related medical conditions that may require attention.

Similarly, in asymptomatic men presenting with unexplained medical conditions, such as anemia, bone density loss, HIV/AIDS, male infertility, or diabetes, or who have known risk factors for T

deficiency, such as history of chemotherapy, pelvic/testicular radiation, chronic opioid use, or chronic steroid use, it may be prudent to obtain labs to investigate for T deficiency.

Other Studies

For patients with T deficiency, additional testing is based on laboratory and exam findings. For instance, pituitary MRI should be obtained if low T levels are found concurrently with abnormal prolactin, FSH, or LH levels. Karyotype studies can be considered if men have small firm testes and other phenotypic changes suggestive of Klinefelter syndrome on examination. For patients presenting with ED, adjunct neurologic or vascular testing may be warranted.

TREATMENT OPTIONS FOR MALE SEXUAL DYSFUNCTION

Interest in TRT has increased dramatically over the past decade and has been a topic of much debate among the FDA, general practitioners, and the urologic community. In general, the AUA/SMSNA guidelines state that TRT can be safely used for adult-onset hypogonadism with careful monitoring of treatment efficacy and side effects.[33]

Low Libido

Meta-analyses investigating the effect of TRT on male sexual function have demonstrated variable improvements in libido. In these studies, TRT led to reported improvements specifically in hypogonadal men, with no change in libido for eugonadal men.[32] Furthermore, the benefits of TRT were found to be greater in men with lower baseline levels of T (< 288 ng/dL).[35] Although the literature suggests that TRT can improve libido in hypogonadal men, some studies have shown no significant difference in sexual satisfaction after TRT.[36]

Erectile Dysfunction

In hypogonadal men, TRT has been shown to improve responses to PDE5 inhibitors (PDE5i) for ED.[37] Several randomized controlled trials and systematic reviews of hypogonadal men with ED have shown that PDE5i therapy in conjunction with TRT is more effective in improving ED than PDE5i therapy or TRT alone.[24,28] Therefore, the AUA recommends that urologists inform hypogonadal men with ED that PDE5i therapy may be augmented by TRT.[24]

While TRT in hypogonadal men may optimize the efficacy of other ED treatments by restoring normal T levels, there is not adequate data to support combining TRT with other ED treatments. Similarly, TRT is not recommended as a monotherapy for ED.[30]

Ejaculatory Disorders

Some studies have shown the benefits of TRT on ejaculatory function in hypogonadal men.[38] AUA/SMSNA guidelines on ejaculatory disorders state that clinicians can offer TRT in men with DE and T deficiency.[39]

It is important to note that there is no evidence-based target T level for hypogonadal men with DE, but a T level at or above the 50th percentile (>500–550 ng/dL) is recommended unless symptoms improve at lower T levels. If TRT is to help with DE symptoms, clinical improvements are typically observed within 90 days of achieving eugonadal T levels. TRT is not indicated in eugonadal men with DE per AUA/SMSNA guidelines.[40]

CONSIDERATIONS FOR SPECIAL POPULATIONS

While the clinical evaluation will be largely the same for any man presenting with sexual dysfunction, it is prudent to consider several specific circumstances that may alter the clinician's approach to evaluating concerns of low T.

Men with Medical Chronic Health Conditions

Adult-onset hypogonadism (AOH) occurs more frequently in men who have a history of chronic disease.[41] In particular, metabolic syndrome, obesity, and renal failure are some of the most common conditions associated with AOH.[3,41]

Metabolic syndrome is a collection of risk factors for heart disease, stroke, and type 2 diabetes, defined as high blood pressure, increased fasting glucose, central obesity, and dyslipidemia.[42] In the United States, the incidence of metabolic syndrome has steadily increased with over 34% of adults diagnosed with the disorder and a 38% incidence of obesity among American men.[43] Metabolic syndrome can cause secondary hypogonadism for a variety of reasons. For obese men, in particular, aromatization of T in adipose cells leads to higher physiologic levels of estrogen and resultant low libido, ED, and ejaculatory dysfunction in these men.[41]

Renal failure has a similar effect on the hypothalamic–pituitary–gonadal axis. While hypogonadism in renal failure is again multifactorial, it has been demonstrated that renal failure causes decreased production of LH and decreased prolactin clearance, both of which hinder T production.[44] Studies have shown that hypogonadism is associated with increased morbidity and mortality

in men with renal failure, due to systemic effects of low T such as anemia, reduced bone density and muscle mass, and premature cardiovascular disease.[35] Although the risk–benefit ratio is controversial, in appropriately selected patients with renal failure, TRT has been shown to help normalize hormonal parameters, decrease medical morbidity, and improve sexual dysfunction.[45]

Men After Radical Prostatectomy

Pelvic surgery, and specifically radical prostatectomy, can impact erectile function, ejaculatory function, and orgasmic function to varying degrees depending on the patient's preoperative baseline as well as the surgical approach.

In treating men who present with low T after radical prostatectomy, it is important to understand the theoretical risk of TRT on prostate cancer recurrence. Presently, both the AUA and European Association of Urology (EAU) have posited that the current literature does not demonstrate clear evidence connecting T to the development of prostate cancer.[17,40] That being said, current practice guidelines recommend considering TRT postprostatectomy only in those men with favorable pathology (ie. negative margins, negative seminal vesicle involvement, negative lymph nodes) who have undetectable postoperative PSA levels.[15] This is based on a series of studies demonstrating that in patients started on TRT who had undergone radical prostatectomy with undetectable postoperative PSA levels, there was no rise in PSA or recurrence of prostate cancer.[36,46,47] For men on active surveillance, the literature suggests that TRT is not associated with the progression of prostate cancer in men with low volume and low-to-moderate grade cancer when used for a limited amount of time.[48] TRT may be harmful in men with advanced diseases who are on active surveillance protocols.[49]

Overall, it is essential that the clinician engages in shared-decision making with the patient the risks and benefits of TRT when treating symptomatic hypogonadal men with a history of prostate cancer.

Transgender Patients

Transgender patients pose unique work-up and treatment considerations as the hormonal milieu has been medically and/or surgically altered depending on the patient's stage of transition.

For transgender men (female-to-male transition), the goal of gender affirmation hormonal therapy is to increase serum T levels to a male-appropriate range and suppress estrogen levels. This is accomplished with both medical TRT (target physiologic T level of 300–1000 ng/dL) and surgical estrogen suppression (ie. bilateral oophorectomy). TRT can be delivered parenterally or transdermally, using testosterone cypionate, testosterone undecanoate, or testosterone gel or patch, with regular laboratory monitoring.[50]

As with cisgender men undergoing TRT, transgender men experience phenotypic and neuropsychiatric changes. In regards to sexual function, TRT most notably can cause increased libido and irreversible clitoral hypertrophy (in patients who have not yet undergone masculinizing genital gender affirmation surgery). Erectile function is dependent on the creation of a neophallus and implantation of an implantable penile prosthesis.

For transgender women (male-to-female transition), hormonal therapy involves androgen deprivation and estrogen supplementation. Androgen deprivation is achieved medically with GnRH analogs, spironolactone, or cyproterone acetate and surgically with bilateral orchiectomy.[43] Estrogen is typically administered transdermally to minimize the cardiovascular risks associated with oral estrogen therapy.

It is important to note that removal of the prostate and seminal vesicles is not a standard procedure in feminizing genital gender affirmation surgery. As a result, transgender women can still be at risk for prostate cancer. For urologists taking care of these patients, the World Professional Association for Transgender Health (WPATH) recommends using current prostate cancer screening guidelines for cisgender men regarding age and risk stratification when counseling transgender women.[51] Importantly, WPATH recommends that the PSA upper threshold of normal in transgender women should be set at 1 ng/mL.[46] This recommendation was established based on evidence that a biopsy positive for prostate cancer despite a low PSA value is more common in the setting of T deficiency, which is akin to the hormonal status of transgender women.[46] Finally, WPATH advises transvaginal prostate palpation over DRE in patients who have undergone gender affirmation surgery given the altered anatomy.[46]

CLINICS CARE POINTS

- Work-up for men with sexual dysfunction should include a thorough history and physical examination, with particular focus on signs and symptoms of low T, common medical comorbidities, and physical exam findings suggestive of hormonal imbalance.

- Low T can present with sexual and nonsexual symptoms. In patients presenting with signs and symptoms of low T, clinicians should obtain two-morning serum total T levels, with values < 300 ng/dL indicative of low T.
- AUA/SMSNA guidelines state that TRT may improve low libido, ED (when paired with PDE5i therapy), and DE in hypogonadal men, but is not recommended in eugonadal men.
- Certain special patient populations, including men with metabolic syndrome, men who have undergone radical prostatectomy, and transgender patients may require additional assessment and testing.
- Our understanding of the complex role of T in the male sexual response cycle and the pathophysiology of sexual dysfunction is evolving and can help inform clinicians on current and future treatments for patients.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Masters WH, Johnson VE. Human sexual response. Boston: Little, Brown; 1966.
2. Kaplan HS. The new sex therapy: active treatment of sexual dysfunctions. London: Routledge; 1974.
3. Alex Tatem MD. Testosterone deficiency: physiology, epidemiology, pathophysiology, and evaluation - Sexual Medicine and andrology: Urology core curriculum. Available at: https://university.auanet.org/core/sexual-medicine-andrology/testosterone-deficiency-physiology-epidemiology-pathophysiology-and-evaluation/index.cfm. Accessed January 24, 2022.
4. Matsumoto AM, Bremner WJ. Testicular disorders. In: Melmed S, Polansky KS, Larsen PR, et al, editors. Williams textbook of endocrinology. New York: Elsevier; 2016. p. 688–777.
5. Ceccarelli F. The embryology of the genitalia. AUA Update Ser 1982;1(26):2–6.
6. Corona G, Maggi M. The role of testosterone in erectile dysfunction. Nature News. 2009. Available at: https://www.nature.com/articles/nrurol.2009.235. Accessed January 24, 2022.
7. Podlasek CA, Mulhall J, Burnett AL, et al. Translational perspective on the role of testosterone in sexual function and dysfunction. J Sex Med 2016. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5333763/. Accessed January 24, 2022.
8. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2010;95(6):2356–9.
9. Keast JR. Plasticity of pelvic autonomic ganglia and urogenital innervation. Int Rev Cytol 2006;248:141–208.
10. Swaab DF. Sexual differentiation of the brain and behavior. Best Pract Res Clin Endocrinol Metab 2007;21:431–44.
11. Kovanecz I, Ferrini MG, Vernet D, et al. Pioglitazone prevents corporal veno-occlusive dysfunction in a rat model of type 2 diabetes mellitus. BJU Int 2006;98:116–24.
12. Chehensse C, Facchinetti P, Bahrami S, et al. Human spinal ejaculation generator. Ann Neurol 2017;81:35.
13. Sato Y, Shibuya A, Adachi H, et al. Restoration of sexual behavior and dopaminergic neurotransmission by long term exogenous testosterone replacement in aged male rats. J Urol 1998;160:1572–5.
14. Ralph DJ, Wylie KR. Ejaculatory disorders and sexual function. BJU Int 2005;95(9):1181–6.
15. Hypoactive sexual desire disorder. Mestonlabcom. Available at: https://labs.la.utexas.edu/mestonlab/hypoactive-sexual-desire-disorder/#:~:text=Prevalence%20rates%20typically%20decrease%20when,%2C%20%26%20Moreira%2C%202009)). Accessed January 24, 2022.
16. Corona G. Psychobiological correlates of delayed ejaculation in male patients with sexual dysfunctions. J Androl 2006;27(3):453–8.
17. Testosterone deficiency guideline - american urological association. Available at: https://www.auanet.org/guidelines/guidelines/testosterone-deficiency-guideline. Accessed January 24, 2022.
18. Potosky A, Knopf K, Clegg L, et al. Quality of life outcomes after primary androgen deprivation therapy: results from the prostate cancer outcomes study. J Clin Oncol 2001;19:3750–7.
19. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006;91(11):4335–43.
20. Erectile dysfunction (ED) guideline - american urological association. Available at: https://www.auanet.org/guidelines/guidelines/erectile-dysfunction-(ed)-guideline. Accessed January 24, 2022.
21. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007;120(2):151–7.
22. MacDonald SM, Burnett AL. Physiology of erection and pathophysiology of erectile dysfunction. Surg Clin North Am 2021;48(4):513–25.
23. Becker AJ, Ückert S, Stief CG, et al. Cavernous and systemic testosterone levels in different phases of human penile erection. Urology 2000;56(1):125–9.

24. Guideline statements. Disorders of ejaculation: an AUA/SMSNA guideline - american urological association. Available at: https://www.auanet.org/guidelines/guidelines/disorders-of-ejaculation. Accessed January 24, 2022.
25. Nicolosi A, Buvat J, Glasser DB, et al. Sexual behaviour, sexual dysfunctions and related help seeking patterns in middle-aged and elderly Europeans: the global study of sexual attitudes and behaviors. World J Urol 2006;24:423.
26. Corona G, Jannini EA, Lotti F, et al. Premature and delayed ejaculation: two ends of a single continuum influenced by hormonal milieu. Int J Androl 2010;34:41–8.
27. Maggi M, Heiselman D, Knorr J, et al. Impact of testosterone solution 2% on ejaculatory dysfunction in hypogonadal men. J Sex Med 2016;13(8):1220–6. https://doi.org/10.1016/j.jsxm.2016.05.012.
28. Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction. Ann Intern Med 2012;157(10):681.
29. Sterling J, Bernie AM, Ramasamy R. Hypogonadism: easy to define, hard to diagnose, and controversial to treat, 2015 treat. Can Urol Assoc J 2015;9(1–2):65–8.
30. Boloña ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007;82(1):20–8.
31. Morgentaler A. Commentary: guideline for male testosterone therapy: a clinician's perspective. J Clin Endocrinol Metab 2007;92:416–7.
32. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol 2005;63(4):381–94.
33. Khera M, Broderick GA, Carson CC, et al. Adult-onset hypogonadism. Mayo Clin Proc 2016;91(7):908–26.
34. Tatem AJ, Beilan J, Kovac JR, et al. Management of anabolic steroid-induced infertility: novel strategies for Fertility Maintenance and recovery. World J Men's Health 2020;38(2):141.
35. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374(7):611–24.
36. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. J Urol 2005;173:533.
37. Buvat J, Montorsi F, Maggi M, et al. Hypogonadal men nonresponders to the PDE5 inhibitor Tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med 2011;8(1):284–93.
38. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med 2014;11:1577–92.
39. Disorders of ejaculation guideline – american urological association. Available at: https://www.auanet.org/guidelines/guidelines/disorders-of-ejaculation. Accessed January 24, 2022.
40. Salonia A, Bettocchi C, Boeri L, et al. European association of urology guidelines on sexual and reproductive health—2021 update: Male sexual dysfunction. Eur Urol 2021;80(3):333–57.
41. Freedland SJ, Aronson WJ. Examining the relationship between obesity and prostate cancer. Rev Urol 2004;6(2):73–81.
42. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. Circulation 2009;120(16):1640–5.
43. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. Centers Dis Control Prev 2017. Available at: https://www.cdc.gov/pcd/issues/2017/16_0287.htm. Accessed January 24, 2022.
44. Snyder G, Shoskes DA. Hypogonadism and testosterone replacement therapy in end-stage renal disease (ESRD) and transplant patients. Transl Androl Urol 2016;5(6):885–9.
45. Thirumavalavan N, Wilken NA, Ramasamy R. Hypogonadism and renal failure: an update. Indian J Urol 2015;31(2):89–93.
46. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol 2004;172:920.
47. Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. J Sex Med 2009;6:1165.
48. Morgentaler A, Lipshultz LI, Bennett R, et al. Testosterone therapy in men with untreated prostate cancer. J Urol 2011;185:1256.
49. Kim M, Byun SS, Hong SK. Testosterone replacement therapy in men with untreated or treated prostate cancer: do we have enough evidences? World J Mens Health 2021;39(4):705–23.
50. UCSF Transgender Care, D.o.F.a.C.M., University of California San Francisco. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People; 2nd edition. Deutsch MB, ed. June 2016, transcare.ucsf.edu/guidelines.
51. Standards of care - WPATH world professional association. Available at: https://www.wpath.org/media/cms/Documents/SOC%20v7/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf?_t=1605186324. Accessed January 24, 2022.