Testosterone Deficiency: Epidemiology, Pathophysiology, and Evaluation

Editors:

Alexander J. Tatem, MD

Authors:

Matthew Pollard, MD

Last Updated:

Thursday, February 23, 2023

Keywords

Testosterone; Free testosterone; Sex-hormone binding globulin; Androgen; Hypogonadism; Pituitary; Physiology; Assays

Key Points

Upon the completion of this module, readers should achieve**:**

1. A basic understanding of the physiology, pathophysiology, and epidemiology of testosterone deficiency (TD).
2. The optimal evaluation of men suspected to possess TD.
3. The educational foundation required to best comprehend subsequent treatment and monitoring, which will be discussed in the following module.

1. Introduction

The biological actions of the “male” hormone testosterone (T) require an intact hypothalamic-pituitary-gonadal axis to produce the hormone itself in addition to appropriate interactions of the T ligand with both binding proteins and the androgen receptor. Repletion of serum T in carefully selected patients can have profound effects on well-being due to the significant effects of this hormone on numerous biological processes. The diagnosis of Testosterone Deficiency (TD) requires the presence of characteristic signs and symptoms along with low T serum concentrations. The definition of “deficient” in the context of T remains controversial but a cut-off for total T of less than 300 ng/dL has been endorsed by the recent **American Urological Association (AUA) Guidelines on Testosterone Therapy**.[1,2] Accurate measurement of serum T is complicated by the lack of standardization of assays, intra-individual variation, and marked heterogeneity in laboratory supplied reference ranges. Clinical judgement and shared decision making are essential for the appropriate utilization of T therapy in clinical practice.

2. Testosterone Physiology

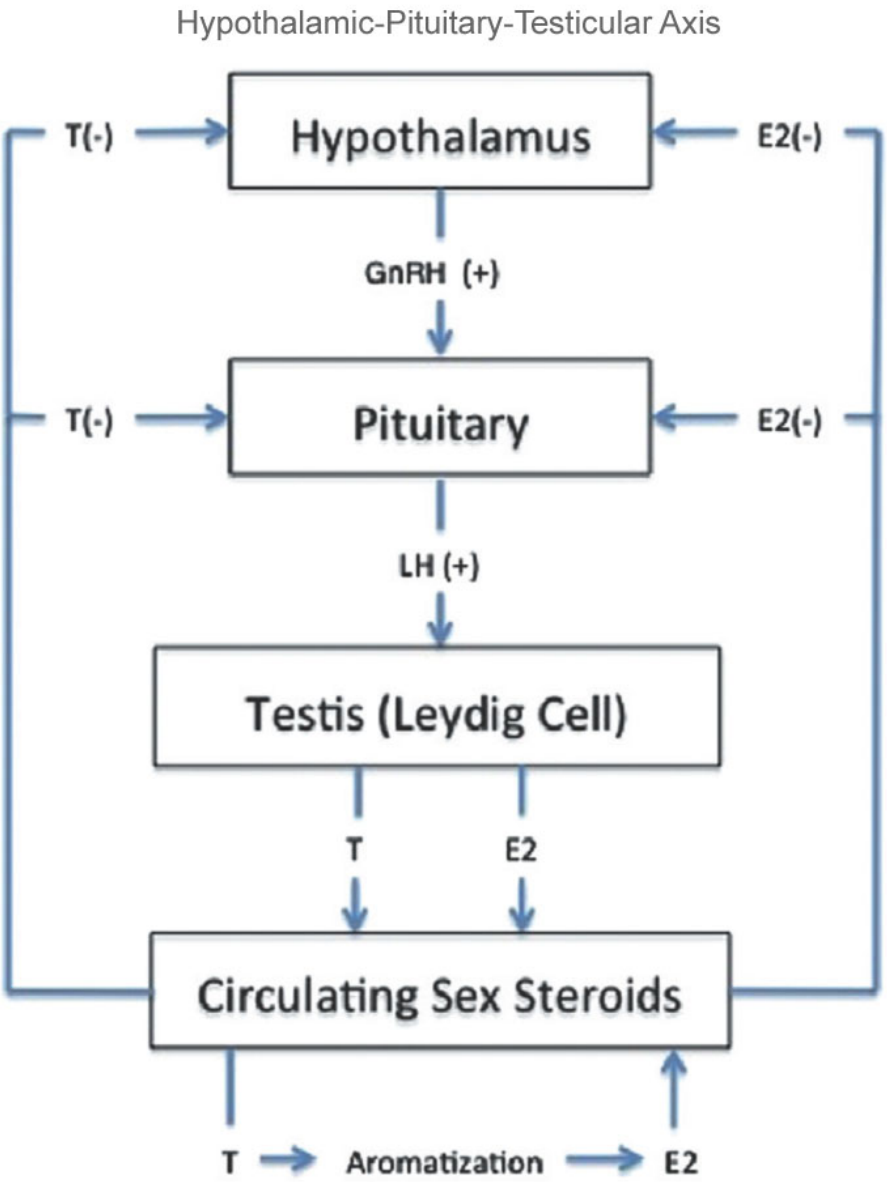

Figure 1: Hypothalamic-Pituitary-Testicular Axis

2.1 Testosterone Production and Regulation

T is the principal circulating androgen in males.[3] In men, **90% of circulating T is synthesized from Leydig cells in the testis with roughly 10% coming from the adrenal glands**. (See also Core Curriculum section **Anatomy and Physiology: Testis, Epididymis and Vas Deferens**). Testicular synthesis of T is stimulated by **luteinizing hormone** (**LH**), which is produced in the **anterior pituitary gland** by **the gonadotropic basophil** cells. LH production is, in turn, stimulated by secretion of gonadotropin-releasing- hormone (GnRH) from the hypothalamus. T, as well as its metabolite estradiol, inhibit GnRH and LH secretion via **negative feedback** at the level of both the hypothalamus and the pituitary.[3] (see **Figure 1**)

2.2 Testosterone Actions

T acts directly or via its **primary metabolites, dihydrotestosterone (DHT) and estradiol (E2)**. It is converted to **DHT via the enzyme 5-alpha reductase**, and to **estradiol via the enzyme aromatase**. T is critical for development of the male phenotype and drives male puberty. T and/or its metabolites have important normal physiological contributions to muscle, bone, skin, spermatogenesis, sexual function, brain, peripheral nerves, and hematopoesis. Deficiency of T has been associated with abnormalities in all of these organ systems. [3]

2.3 Androgen Receptor

T acts primarily via binding to the **androgen receptor** (**AR**)**.** The AR binds both T and DHT, but has greater affinity for DHT. The androgen-AR complex then enters the nucleus and stimulates **transcription** via binding to androgen response elements.[3]

Previous studies have demonstrated that polymorphisms in the number of CAG repeats on Exon 1 of the AR gene can have a significant effect on T activity. Increased numbers of CAG repeats have been correlated with decreased transcriptional activity, decreased androgenicity of endogenous T, and decreased symptomatic response to T therapy. [4,5]

The relationship between CAG repeats and physiological effects remains complex and incompletely understood; however, presence of this polymorphism may contribute to the marked variability noted in T-related symptoms between men with similar serum T levels. While no assay for CAG repeats is available for clinical use at present, assessment of CAG repeats may be used to individualize T supplementation in the future. [6]

2.4 Free and Bioavailable Testosterone

Approximately 98% of circulating T is bound to carrier molecules; roughly 60% to sex hormone binding globulin (SHBG), and the remainder to albumin and other serum proteins. **Approximately 1-2% of circulating T is unbound**, and is termed **free T**.

The portion of T bound to SHBG is not biologically available due to tight binding to this globulin. **Bioavailable T** refers to albumin-bound T and free T portions. Although free T only represents a small fraction of total T, some authorities consider it the most useful indicator of a man's T status due to its lack of significant interaction with SHBG. [7] A 2017 study indicated that low free T was significantly associated with greater likelihood of sexual symptoms regardless of total T level, even after adjustment for age, comorbidities, and body mass index. [8] However, as no major guidelines advocate for preferential use of free T over total T in the diagnosis of TD. While free T may be a better estimate of actual androgen levels, there are no validated threshold for free T making is clinically utility debatable. Still, free T is a useful adjunct that may be used by clinicians to aid in decision-making when required.

2.5 Effect of Aging on Testosterone

In young healthy men serum total T levels demonstrate significant diurnal variation, with **peak levels observed during the early morning hours of 7-9 am**.[9] This diurnal variation is substantially blunted

in men over 45 years of age.[9] Cross-sectional data in older men (45-50 years of age) has shown minimal change in mean serum T between the hours of 6am through 2pm, with a subsequent 13% decline noted from 2p-6p.[9]

As men age, **total T declines by approximately 1% per year after the age of 40 years, whereas free T declines even more rapidly**. The increased SHBG that occurs with aging tends to make total T appear more normal, even though free T may be depressed.[7,10,11] More rapid declines in T have been associated with increased all-cause mortality. A 10-year longitudinal Danish study examining 1,167 men found that men with the most pronounced decline in serum T (bottom 10th percentile) had a significantly increased risk of mortality compared to men in the 10th to 90th percentile (HR for mortality 1.60, 95% CI 1.08-2.36). Causality cannot be determined from these data but further investigation is warranted.[12]

3. Epidemiology

3.1 Definition

The term TD has become preferred over the traditional term hypogonadism due to its clarity, specificity, and simplicity. Technically, hypogonadism refers to a global deficiency of testicular function which includes both T production and spermatogenesis. Comparatively, TD refers only to the deficiency of T and subsequent clinical symptoms. Additional terms that may be used to refer to TD include andropause and late onset hypogonadism (LOH). The **diagnosis of TD requires the combination of both characteristic symptoms** (see ***Section 4.1***) **and/or signs together in conjunction with abnormally low serum T concentrations.**[1] At this point in time neither symptoms alone, nor low biochemical T concentrations without symptoms/signs, are considered an indication for T therapy.[1]

3.2 Prevalence

Estimates of TD prevalence in adult men vary widely, ranging from 2-39%, due to differing definitions of TD in the literature. In the *Hypogonadism in Men* study, morning serum T levels <300ng/dl were seen in 39% of men 45 years or older recruited from physician waiting rooms.[13] In contrast, the prevalence of TD (defined as T <320ng/dl plus three sexual symptoms) observed in the *European Male Aging Study* was only 2.1% in men 40-79 years of age.[14] There is consensus from multiple sources that the **diagnosis of TD requires the presence of both characteristic symptoms** in combination with **serum T concentrations below the lower reference value provided by any given laboratory**.[1,3,15,16] However, the use of an individual laboratory's reference range can often set an arbitrarily rigid prevalence of TD at 2.5%, since laboratory reference values are most commonly established by categorizing the upper and lower 2.5% set of values (two standard deviations from the mean) of a reference population as abnormal. **As a result, strict reliance on laboratory reference ranges alone to make the diagnosis of TD in clinical practice may lead to many false negative results** which may arbitrarily deprive some symptomatic men the potential benefits of T therapy.

4. Pathophysiology

4.1 Classification

Primary hypogonadism refers to failure of the testes to produce normal serum T and sperm in response to adequate LH and FSH stimulation and thus **indicates failure of testicular function**. **Secondary hypogonadism** refers to low serum T levels from a defect in production of GnRH or LH, thus **indicating pituitary or hypothalamic dysfunction**, which in turn leads to inadequate testicular production of T. Etiologies for hypogonadism are listed in **Table 1**. **Mixed primary and secondary hypogonadism** occur when there is a subnormal LH response in combination with reduced production of T, such as **when TD is associated with normal LH levels**. This is the **situation most commonly encountered with aging**. The different subtypes of TD can be determined by assaying serum levels of T and LH. FSH does not play a significant role in stimulating production of T. However, FSH is a more sensitive indicator of testicular insufficiency than LH and thus may be measured together with LH to aid in the diagnosis (**Table 2**). Measurement of FSH is also essential for the evaluation of male factor infertility. Please refer to the AUA Core Curriculum Modules on Male Factor Infertility and the 2020 AUA/ASRM Guidelines regarding the Diagnosis and Treatment of Infertility in Men [17] for more details.

Table 1: Mixed Primary and Secondary Hypogonadism

Primary Hypogonadism (Testicular Failure)	Secondary Hypogonadism (Hypothalamic/Pituitary Failure)	
Gonadotoxins	**Genetic Disorders**	**Drugs**
• Chemotherapy	• Kallman's Syndrome	• Opioid narcotics
• Heavy Metals	**Metabolic Disorders**	• Marijuana
• Pesticides	• Diabetes	• Anabolic Steroids
• Radiation	• Metabolic Syndrome	**Injury**
Neoplasia	• Hypertension	• Traumatic Brain Injury
• Testicular Cancer	• Renal Failure	• Pituitary Infarction
Injury	• Malnutrition	• Sub-arachnoid hemorrhage
• Testicular Torsion	• Liver Failure	**Autoimmune / Infiltrative**
• Testicular Trauma	**Neoplasia**	• Sarcoidosis
Infectious Disease	• Prolactinoma	• Wegener's Granulomatosis
• Mumps Orchitis	• Craniopharyngioma	• Lymphocytic hypophysitis
• HIV infection	• Other Pituitary Tumors	**Infectious Disease**
Congenital	**Iatrogenic**	• Tuberculosis
• Cryptorchidism	• Surgical Resection	• Tertiary Syphllis
• Anorchia	• Cranial Radiation	• Meningitis
• Klinefelter's Syndrome	• Corticosteroids	**Other**
• AZF Deletions	• Opioid	• Obstructive sleep apnea
Medications		• Disordered sleep
• Spironolactone		
• Ketoconazole		
Anatomic		

• Varicocele		

Table 2: Hormonal Pattern of Testosterone Deficiency

	Total Testosterone	LH / FSH	Prolactin	Free Testosterone
Eugonadal State	Normal	Normal	Normal	Normal
Pituitary Insufficiency	↓	↓	Variable	↓
Prolactinoma	↓	↓ /Normal	↑↑	↓
Mixed Testosterone Deficiency	↓	↓ /Normal	Variable	↓
Opiate / Anabolic Medication	↓	↓	Variable	↓
Primary Testicular Failure	↓	↑↑	Variable	↓
Elevated SHBG	Normal	↓ /↔	Variable	↓

4.2 Associated Conditions

A number of common medical conditions are associated with TD. These include obesity, diabetes, hypertension, chronic obstructive pulmonary disease, renal failure, liver failure, obstructive sleep apnea, hypertension, and HIV infection.[18] Approximately 40-50% of men with diabetes and metabolic syndrome have serum T less than 300ng/dl.[13,15,18] There is a strong association between TD and the metabolic syndrome.[18] The incidence of TD is approximately 15% in cancer survivors exposed to chemotherapy or radiation.[19] Not surprisingly, this figure is substantially higher for patients who have a history of testicular cancer; these men carry a 40% incidence of TD.[20]

A number of medications can also reduce serum T concentrations; the most commonly noted agents include LHRH agonists, ketoconazole, high-dose glucocorticoids, and opioid analgesics.[21] The latter often produce profoundly reduced serum T concentrations into the near-castrate range via central inhibition of LH production. Anabolic steroids can cause irreversible sub-normal T production due to negative effects on both the hypothalamus and the pituitary. The duration of exposure to anabolic steroids that is required to cause irreversible changes following opiate and anabolic steroid use is unclear.[21] It is likely that irreversible secondary hypogonadism from anabolic steroids is a stochastic event that may occur after any degree of exposure but is more likely with chronic use.

5. Evaluation

5.1 Defining Male Hypogonadism

Male hypogonadism is defined by the Endocrine Society as “a clinical syndrome that results from failure of the testis to produce physiological levels of T and sperm due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis.”[1] In a 2018 AUA Guideline, the term “Testosterone Deficiency” was preferred to refer specifically to the syndrome of low serum T in the presence of symptoms consistent with the disorder, without regard to spermatogenic potential.[2] In this core curriculum module we will address management of TD. Readers are referred to Core Curricula on Male Factor Infertility and the AUA Best Practice Statement on Management of the Infertile Male for more details on hypogonadism management.

T therapy has seen a marked increase in utilization over the past decades. In 2002 an estimated 0.5% of men over the age of 30 years were on T therapy; utilization peaked at 3.2% in 2013 and more recently has declined to 1.7% in 2016.[3] It remains controversial whether this increase represents an increase in medically indicated therapy or not. A separate study reported that direct to consumer advertising is associated with increasing utilization of T therapy, including T therapy without recent serum assessment.[4]

5.2 Evaluation of TD

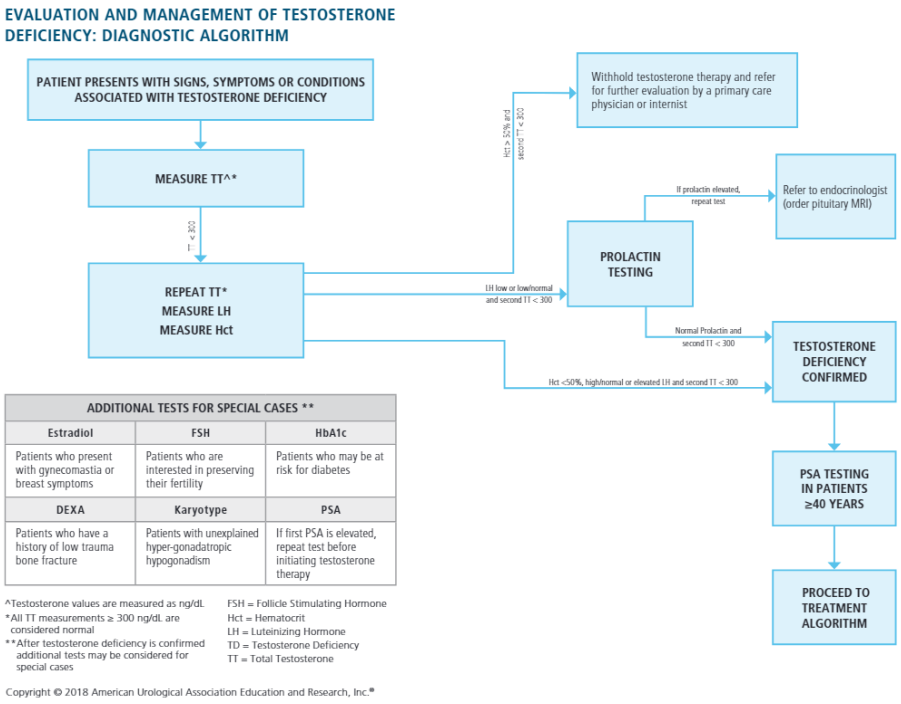

Figure 2: Testosterone Algorithm One - Diagnostic

A diagnostic algorithm adapted from the 2018 AUA Guidelines on Evaluation and Management of TD is depicted in **Figure 2**.[5] Briefly, a man who presents with signs/symptoms of TD should have a morning (before 10 AM) T assay. Testing should not occur based solely on completion of validated or unvalidated questionnaires.[2]

Men with total T less than 300 ng/dL should have repeat testing to include LH and hematocrit; additional testing of the HPG axis and/or other hormones is optional and may be indicated based on other symptoms/signs. If repeat testing confirms low serum T in the presence of symptoms potentially referable to low T, treatment may be considered assuming there are not competing considerations that may warrant further evaluation (e.g. elevated PSA, hyperprolactinemia)[2]

In addition to men with symptoms consistent with TD, T testing should be considered in men with unexplained anemia, bone density loss, diabetes, a history of chemotherapy, prior testicular radiation, HIV/AIDS, chronic opioid use/abuse, infertility, pituitary dysfunction, and chronic corticosteroid use.[2]

A variety of assays are available to test serum T. Each assay has particular limitations and advantage, articulated in the table published in the AUA Guidelines (**Figure 3**).[2] It is desirable that all testing be performed at a single lab to minimize the issue of intra-assay variability, which can be substantial.[2] If possible, testing should be performed in a lab that is certified by the Center for Disease Control.[2]

Free T is advocated by some experts as a marker for potentially relevant TD, even in the presence of a normal total T level greater than 300 ng/dL. One recent study suggested that men with normal total T and low free T tend to be older, more obese, and have more comorbidities than men with normal

total and free T. However, low free T was an independent predictor of ED, decreased libido, and depressive symptoms even in the context of normal total T and after adjustment for these other factors.[5] A cut-off of free T less than 64 pg/mL was associated with increased prevalence of symptoms consistent with TD.[22] The use of free T as a metric by which to diagnose and treat remains controversial and is not recommended at this time by the AUA Guidelines on TD.[2]

5.3 Signs and Symptoms

The symptoms of TD can be grouped into **sexual and non-sexual categories** (**Table 3**).[18,23] Sexual symptoms include **diminished libido, decreased spontaneous erections, erectile dysfunction, and decreased responsiveness to phosphodiesterase type 5 inhibitors (PDE5I)**. Non-sexual symptoms include **fatigue (especially afternoon), lack of energy and vitality, depressed or blunted mood, irritability, reduced motivation, decreased cognitive acuity (loss of short-term memory, reduced attention and ability to focus), decreased strength and stamina, reduced muscle mass (known as sarcopenia) or strength, and increased fat** In addition, several objective signs are associated with TD. These include **anemia, gynecomastia, and reduced bone mineral density** including osteoporosis.[18] The chronicity of these symptoms should be assessed.

Understanding the symptoms of TD helps place its clinical benefits into appropriate context (**Table 4**). T supplementation may provide many of the listed beneficial effects to well-selected men, but it is important to remember that the signs and symptoms of TD are non-specific. Consequently, TD should be considered in the context of these findings but providers and patients must also consider that there may be other causes for some or even all of a man's presenting complaints. Additional targeted interventions may be important as alternatives and/or adjuvant therapies for men with symptoms consistent with TD. Some of the potential adverse effects of T therapy are listed in **Table 5**.

Table 3: Testosterone Deficiency – Signs and Symptoms		
Sexual	**Non-Sexual / Psychological**	**Physical/Metabolic**
Diminished Libido	Diminished energy, sense of vitality, or well-being	Decreased bone mineral density
Decreased spontaneous erections	Fatigue	Decreased muscle mass and strength
Erectile Dysfunction	Depressed mood	Increased body fat
Diminished response to PDE5I	Irritability	Gynecomastia
	Impaired cognition	Reduced testicular size, firmness
	Reduced motivation	Anemia
		Insulin resistance

Table 4: Summary of Purported Beneficial Effects of Testosterone Therapy in Testosterone deficient Men
Symptom
Body Composition, Physical Activity, Strength
Increased lean body mass
Decreased fat mass
Improved bone mineral density
Sexual Function and Libido
Improved libido
Improved morning erections
Improved erectile function
May improve response to PDE5s in those previously refractory to PDE5s
Medical Comorbidities
DM - Improved fasting glucose, HbA1c, insulin sensitivity
Lipids - Improved TG, total cholesterol; variable results on HDL and LDL

Psychological / Cognition
Improved mood

Table 5: Summary of Purported Adverse Effects of Testosterone Therapy in Testosterone deficient Men
Symptom
Cardiovascular Events and Mortality
No definitive evidence for worsened cardiovascular outcomes or increased mortality
Beneficial effects on cardiac perfusion, ischemic threshold, exercise threshold, cardiac output
Dermatologic Changes
Increased sebum production
Increased acne
Increased hair loss
Hematologic Changes
Increased hematocrit
Increased deep venous thrombosis
Fertility

Exogenous T used alone results in reduced spermatogenesis
Gynecomastia
Hypothetical increased risk of gynecomastia and breast cancer
Prostate Events
Conflicting results on increasing PSA, PSA>4ng/ml, and rate of prostate biopsies
No increased risk of worsening urinary symptoms or flow
No increased risk of development of prostate cancer
Deleterious effects in locally advanced or metastatic prostate cancer
Unknown risks of prostate cancer progression in localized prostate cancer or in treated prostate cancer
Sleep Apnea
Early worsening of sleep apnea in patients with severe baseline symptoms (3-6 months)
* Level of evidences are assigned by the authors based on Oxford criteria and utilizing the data provided in the current review.

5.4 Patient History

A diagnostic algorithm adapted from the 2018 AUA Guidelines on Evaluation and Management of TD is depicted in **Figure 2**.[5] Evaluation should begin with a focused patient history. This should assess for both sexual and non-sexual symptoms of TD and establish the need for diagnostic confirmation. The most prominent symptoms tend to be diminished libido, erectile dysfunction, and decreased energy. A current list of medications should be obtained, with particular attention to corticosteroids, opioids, and drugs that interfere with T synthesis. Social history should be explored for occupational exposure to chemicals and radiation as well as drugs of abuse such as opiates and marijuana. Patients should be evaluated for history of current or previous anabolic steroid use/abuse. Surgical history should be obtained for history of cranial/pituitary as well as testicular interventions. It is also important to assess for a history of testicular injuries or insults to the testicle (cryptorchidism, mumps, trauma, cancer, torsion, orchitis, etc). A general medical history should evaluate for HIV infection, components of the metabolic syndrome (diabetes, hypertension, obesity, high cholesterol), renal failure, sleep apnea, intracranial processes, liver disease and other health conditions. (see **Table 6**)

Table 6: Physical History and Examination

History Factors	Physical Examination
Medications • Corticosteroids • Opioids • Chemotherapeutics • Spironolactone • Ketoconazole **Exposures** • Pesticides • Heavy Metals • Radiation • Anabolic Steroids • Marijuana **Surgeries** • Cranial/Pituitary • Testicular **General Medical History** • HIV infection • Sleep Apnea • Intracranial Processes • Metabolic Syndrome	**General** • Beard Growth • Body Hair • Muscular development/atrophy **Chest** • Gynecomastia **Penis** • Development • Penile Fibrosis **Scrotum** • Varicocele • Testis Size • Testis Consistency • Testicular Masses • Location/Cryptorchidism **Prostate** • Size Nodularity **Abdomen** • Hepatomegaly

• Diabetes
• Hypertension
• Diabetes
• Renal Failure
• Autoimmune disorder
• Genetic Disorders
• Hepatic Insufficiency

Testicular History

• Testicular Cancer
• Testicular Torsion
• Testicular Trauma
• Mumps Orchitis
• Other infectious processes
• Cryptorchidism
• Anorchia

Sexual and Non-Sexual Symptoms

see **Table 3**

5.5 Physical Examination

The physical examination should include assessment of secondary male sexual characteristics such as beard growth and body hair, the presence of gynecomastia, genital examination and digital rectal examination of the prostate. The scrotal exam should note whether both testicles are **descended, their size and consistency, as well as the presence of any testicular mass,** or **varicocele**. Although the physical examination is usually normal in men with TD, a number of genital abnormalities may suggest the presence of TD, including **cryptorchidism, small or soft testes, and varicocele.**[24] The penis should be examined for any abnormalities including the presence of plaque as Peyronie's may complicate the treatment of co-morbid erectile dysfunction. Although there has been debate regarding whether a link exists between TD and the degree of deformity in men with Peyronie's disease, more recent data would suggest there is not.[25,26] (see **Table 4**)

5.6 Biochemical Determination of TD

Table 4: Assays for the Diagnosis of Testosterone Deficiency

Assay	Units	Co-efficient of Variation	Advantages	Disadvantages
Total Testosterone				
Immuno-assay (including radio-immunoassay and enzyme immunoassay)	ng/dL	Intra-assay: -14% to +19% CV most pronounced at lower T values (40% in samples with TT <100 ng/dL)	• Rapid • High throughput • Reference range data available	• Reduced accuracy at low/high T levels • Interfering factors (heterophile antibodies in patients' serum) • Significant inter-assay variability
LCMS	ng/dL	±6.4% (to maintain CDC approval status)	• Gold standard • Excellent sensitivity and specificity at low T concentrations (<40)	• Not FDA approved • Labor intensive • Low throughput
Salivary	pmol/L	Intra-assay: 13% Inter-assay: 13%	• Simplicity • Patient access • Correlates with calculated free serum testosterone	• Not FDA approved • Extensive sample preparation requiring high skill • Concerns about specimen (saliva) stability
Free Testosterone				
Equilibrium Dialysis	pg/dL	Intra-assay: 10.0% Inter-assay: 6.8%	• Gold standard • Excellent sensitivity and specificity	• Labor intensive • Low throughput
Calculation methods (Law of Mass Action Equations after Nanjee & Wheeler, Sodergard, or Vermeulen)	pg/mL	Inter-assay: 18-30%.	• Rapid • Simple • Has correlated in some series (but not all) well with equilibrium dialysis	• Relies on TT and SHBG assay accuracy • Accuracy relies on equilibrium dissociation constants for binding of

Figure 3: Lab Assays for the Diagnosis of Testosterone Deficiency

Morning blood testing for total T (before 10 AM) is recommended for all men due to diurnal variation.[27] However, it is worth noting that the diurnal changes commonly seen in younger men lessen with age, potentially reducing the need for mandatory morning lab testing in older men.[28] **The 2018 AUA Guidelines on Evaluation and Management of Testosterone Deficiency consider a serum total T below 300 ng/dL as being consistent with TD.** This value is a subject of debate and others have advocated for using a serum total **T less than 350 ng/dl** as a reasonable threshold for the diagnosis of TD **in a symptomatic individual.**[15,16] **Some experts advocate that younger men (<40 years of age), may benefit from a higher threshold of 400 ng/dL.**[29] Controversy regarding

the appropriate serum T cut-point to qualify for the diagnosis of TD continues.

The decision on whether or not a man with borderline T (specifically, 300-350 ng/dL) should be considered for T therapy is ultimately an issue of clinical judgement and should be made after careful review of benefits and risks. Some expert panels have advocated for a 6-month empirical trial of T in these patients to assess for clinical benefit before committing to life-long therapy.[30] Patients who have a T over 300 ng/dL should be advised that their potential for benefit is less than men who have levels that are clearly low. There is scant high-level evidence to suggest that men with total T greater than 400 ng/dL benefit from additional supplementation.

Multiple assays have been used to assess serum T levels (**Figure 3**). There has been a recent attempt to standardize laboratory assays for total T by using liquid chromatography/mass spectroscopy (LCMS), and many large laboratories have already made this change.[3,31] **However, several studies have found little difference in results between LCMS and the more widely used chemiluminescence immunoassay.**[32,33]

Since the interpretation of total T concentrations can be confounded by SHBG concentrations, some experts recommend that free T levels be obtained in conjunction with total T, particularly in cases where the clinical presentation is strongly suggestive of TD despite a normal serum total T concentration. Free T can be measured directly by radioimmunoassay (RIA) or calculated from total T and SHBG concentrations. Equilibrium dialysis assay is the gold standard in calculation of free T but is labor intensive and primarily useful as a research tool. Free T values obtained by equilibrium dialysis correlate strongly with those obtained via calculated free T measurement or by RIA.[15,16,34]

Reference ranges for free T provided by laboratory reports should be used cautiously, with the knowledge that they vary widely from lab to lab, and are not clinically based. A number of authorities have suggested the use of **calculated free T values less than 80- 100 pg/ml, and RIA free T values less than 1.0-1.5 ng/dl,** as **consistent with TD in symptomatic men.**[15,35] In contrast, many labs provide a lower reference limit for free T at 35-50 pg/ml without supporting clinical evidence. **The current AUA Guidelines on Testosterone do not recommend treating for TD based on low free T levels in the context of normal total T.**[1] However, some recent evidence suggests that free T is a predictor of symptoms consistent with TD even in the setting of normal total T;[8] some experts advise that symptomatic men with low values of free T may be considered candidates for a trial of T therapy.

5.7 Additional Tests

The current AUA guidelines recommend that morning serum total T is sufficient for initial screening for TD. If the level returns at less than 300 ng/dL, total T should be repeated with LH and hematocrit. If a patient's LH is low or low-normal and their repeat total T is still low, a prolactin level should be obtained to rule out a metabolically active pituitary adenoma. **Pituitary MRI** should be obtained in men with TD who have serum prolactin more than twice the upper limit of normal, secondary TD with severe hypogonadism (total T <150ng/dl), or men with TD and with LH and FSH below the normal range.[3] Some experts have proposed using a prolactin-to-T ratio of 0.1 combined with a prolactin

cutoff of 25 ng/dL.[36] When applied retrospectively to a cohort of 141 men retrospectively, these criteria showed a 90% sensitivity and 48% sensitivity in the detection of pituitary abnormalities.

If a patient is found to have hypergonadotropic hypogonadism and small testes, consideration should be given to obtaining a karyotype to rule out the diagnosis of Klinefelter's syndrome.[3,34,37] Patients at risk for diabetes should have a Hgb A1C drawn while men with gynecomastia or breast symptoms should have their serum estradiol checked.

If the diagnosis of TD is confirmed, men over the age of 40 should have a screening PSA drawn prior to the initiation of therapy **based on expert opinion.**[1] **Additional diagnostic testing** should be considered if indicated by abnormal prostate exam or elevated PSA.

For men who desire future fertility, a semen analysis to establish baseline semen quality can be offered. This desire and these lab values must be taken into consideration when making treatment decisions.[38] Men who desire fertility should be counseled that most exogenous T suppresses spermatogenesis; it is essential that men be informed that recovery of spermatogenesis after administration of exogenous T occurs in about 2/3rds of men within 6 months but make take up to 2 years although recovery is not guaranteed.[39] Currently, the only form of exogenous T shown to preserve spermatogenesis in the majority of men is intranasal T gel.[40] However, this preservation is not universal and almost all men in this study still displayed a drop in total motile sperm count.

5.8 Questionnaires

A number of validated questionnaires have been used in the assessment of low T. These include the Androgen Deficiency in the Aging Male (ADAM) questionnaire,[41] the Aging Male's Symptoms (AMS) scale[42] and the New England Research Institute (NERI) Hypogonadism Screener.[43] These instruments focus on common sexual and non-sexual symptoms of TD and can be useful as screening tools. However, the utility of these questionnaires in clinical practice has not been demonstrated, and there is controversy regarding their sensitivity and specificity.[44,45] The AUA Guidelines on Testosterone Deficiency do not recommend the use of these scales to either define patients who are candidates for T therapy or to monitor symptom response in patients on TRT.[27] Use of these questionnaires does not take the place of careful clinical assessment.

5.9 Additional Resources

Patient education material is available at ***www.urologyhealth.org/educational-materials***.

Also see Low Testosterone Poster download.

Other relevant Core Curriculum sections:

- **Anatomy and Physiology: Testis, Epididymis and Vas Deferens**

Presentations

HYPOGONADISM PHYSIOLOGY, EPIDEMIOLOGY, PATHOPHYSIOLOGY, EVALUATION

References

☆ † Mulhall et al AUA Testosterone Therapy Guidelines 2018

1 This evidence based guidelines provides up to date guidance for practicing urologists on appropriate evaluation and management of men with TD

2 Morgentaler, A., Traish, A. M., & Khera, M. (2019). A Critique of the AUA Guidelines on Testosterone Deficiency. The Journal of Sexual Medicine. doi:10.1016/j.jsxm.2019.10.019

3 † Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

This reference provides a rigorous overview of testosterone deficiency as a clinical state and tools available to aid in initial diagnosis. Also provides a conservative perspective on what normal testosterone levels are.

4 Zitzmann M. Mechanisms of disease: pharmacogenetics of testosterone therapy in hypogonadal men. Nat Clin Pract Urol; 2007; 4(3):161-166. PMID: 17347661

5 Tirabassi G, Corona G, Biagioli A, Buldreghini E, delli Muti N, Maggi M, Balercia G. Influence of androgen receptor CAG polymorphism on sexual function recovery after testosterone therapy in late-onset hypogonadism. J Sex Med; 12(2):381-8. PMID: 25443437

6 Francomano D, Greco EA, Lenzi A, Aversa A. CAG repeat testing of androgen receptor polymorphism: is this necessary for the best clinical management of hypogonadism? J Sex Med; 10(10):2373-2381. PMID: 23844628

† Wu FC et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363:123-135.

7 This reference reports cut-off values below which the prevalence of TD symptoms become increasingly prevalent. These data provide support for objective cut-off criteria for testosterone levels that may merit consideration of testosterone supplementation.

8 Boeri et al J Sex Med 2017;14:1549

9 Welliver et al J Urol. 2014 Jul;192(1):165-9

10 Braunstein G. Testes Basic and Clinical Endocrinology 5th ed 1997 403-33

11 Vermeulen A, et al. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999; 84:3666 –3672

12 Holmboe SA, Skakkebaek NE, Juul A, Scheike T, Jensen TK, Linneberg A, Thuesen BH, Andersson AM. Individual testosterone decline and future mortality risk in men. Eur J Endocrinol 2018; 178:123-130

† Mulligan T, et al.: Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006; 60(7):762-769.

13 This clinical paper depicts the surprising prevalence of low testosterone in clinical primary care populations. The data demonstrate from a physiologic perspective how often low testosterone exists as a biologic entity.

14 Allan C, McLachan R; Age related changes in testosterone and the role of replacement therapy in older men. Clin Endocrinol. 2004; 60(6): 653-670.

† Traish AM, et al. Testosterone deficiency. Am J Med. 2011; 124(7): 578-87.

15 Excellent overview of testosterone deficiency as a clinical syndrome including treatment. Also offers correlation of testosterone deficiency to other disease processes and organ systems.

16 Buvat J, et al. Endocrine aspects of male sexual dysfunctions. J Sex Med 7:1627-56, 2010.

17 ☆ Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, Mulhall JP, Niederberger C, Sandlow JI, Sokol RZ, Spandorfer SD, Tanrikut C, Treadwell JR, Oristaglio JT, Zini A. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. J Urol. 2021 Jan;205(1):36-43. doi: 10.1097/JU.0000000000001521. Epub 2020 Dec 9. PMID: 33295257.

18 Morley J et al.: Evaluation of assays available to measure free testosterone. Metabolism 2002, 51:554–559.

19 Greenfield D et al. Quality of life, self-esteem, fatigue, and sexual function in young men after cancer: a controlled cross-sectional study. Cancer. 2010;116(6):1592-601.

20 Garcia J et al. Hypogonadism in male patients with cancer. Cancer. 2006; 106(12):2583-91.

21 Morley et al.: Longitudinal changes in testosterone, luteinizing hormone and follicle-stimulating hormone in healthy older men. Metabolism 1997; 46(4):41–3.

22 Ryan et al Am J Phys Anrhtopol 2017;163:317

23 Travison T et al. A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab. 2007;92:196-202.

24 Tanrikut C, et al. Varicocele as a risk factor for androgen deficiency and effect of repair. BJU Int. 2011; 108(9): 1480-4.

25 Moreno SA, Morgentaler A. Testosterone deficiency and Peyronie's disease: pilot data suggesting a significant relationship. J Sex Med 2009;6:1729-35.

26 Mulhall JP, Matsushita K, Nelson CJ. Testosterone Levels Are Not Associated With Magnitude of Deformity in Men With Peyronie's Disease. The journal of sexual medicine 2019;16:1283-9.

27 Mulhall et al J Urol 2018; 200;423-432

28 Paduch D, Brannigan R, Fuchs E, Kim E, Marmar J, Sandlow J. Laboratory Diagnosis of Testosterone Deficiency. Urology 2014; 83(5):980-8. PMID: 24548716

29 Scovell JM, Ramasamy R, Wilken N, Kovac JR, Lipshultz LI. Hypogonadal symptoms in young men are associated with a serum total testosterone threshold of 400 ng/dL. BJU international 2015;116:142-6.

30 Morgentaler A, Traish A, Hackett G, Jones TH, Ramasamy R. Diagnosis and Treatment of Testosterone Deficiency: Updated Recommendations From the Lisbon 2018 International Consultation for Sexual Medicine. Sexual medicine reviews 2019.

31 Rosner W, Vesper H. Toward Excellence in Testosterone Testing: A Consensus Statement. J Clin Endocrinol Metab 2010; 95 (10): 4542-4548. PMID: 20926540

32 Rastrelli G, Corona G, Vignozzi L, Maseroli E, Silverii A, Monami M, Mannucci E, Forti G, Maggi M. Serum PSA as a Predictor of Testosterone Deficiency. J Sex Med. 2013 epub Jul 16, 2013

33 Finkelstein JS et al. Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men. NEJM 2013;369:1011-22.

34 Kacker R, Hornstein A, Morgentaler A. Free testosterone by direct and calculated measurement versus equilibrium dialysis in a clinical population. Aging Male 2013; 16(4):164-8.

35 Morgentaler A. Commentary: Guideline for male testosterone therapy: a clinician's perspective. J Clin Endocrinol Metab. 2007; 92:416-7.

36 ☆ Naelitz B, Shah A, Nowacki AS, Bryk DJ, Farber N, Parekh N, Shoskes D, Hatipoglu B, Vij SC. Prolactin-to-Testosterone Ratio Predicts Pituitary Abnormalities in Mildly Hyperprolactinemic Men with Symptoms of Hypogonadism. J Urol. 2021 Mar;205(3):871-878. doi: 10.1097/JU.0000000000001431. Epub 2020 Oct 20. PMID: 33080146.

† Bhasin S, et al.: Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010; 95(6) 2356-59.

37 This reference provides a rigorous overview of testosterone deficiency as a clinical state and tools available to aid in initial diagnosis. Also provides a conservative perspective on what normal testosterone levels are.

38 Tatem AJ, Beilan J, Kovac JR, Lipshultz LI. Management of Anabolic Steroid-Induced Infertility: Novel Strategies for Fertility Maintenance and Recovery. The world journal of men's health 2019.

39 Liu et al Lancet 2006;367:1412-1420

40 ☆ Ramasamy R, Masterson TA, Best JC, Bitran J, Ibrahim E, Molina M, Kaiser UB, Miao F, Reis IM. Effect of Natesto on Reproductive Hormones, Semen Parameters and Hypogonadal Symptoms: A Single Center, Open Label, Single Arm Trial. J Urol. 2020 Sep;204(3):557-563. doi: 10.1097/JU.0000000000001078. Epub 2020 Apr 15. PMID: 32294396.

41 Morley J, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000; 49: 1239–42.

42 Heinemann A et al, A new aging males' symptoms (AMS) rating scale. Aging Male. 1999; 2: 105–114.

43 Rosen R, Araujo A, Connor M, Gerstenberger E, Morgentaler A, Seftel A, Miner M, Shabsigh R. The NERI Hypogonadism Screener: psychometric validation in male patients and controls. Clin Endocrinol 2011; 74(2):248-56. PMID: 21114509

44 Chueh K. et al The comparison of the aging male symptoms (AMS) scale and androgen deficiency in the aging male (ADAM) questionnaire to detect androgen deficiency in middle-aged men. J Androl 2012; 33(5): 817-23.

45 Bernie A, Scovell J, Ramasamy R. Comparison of questionnaires used for screening and symptom identification in hypogonadal men. Aging Male 2014; 17(4):195-8. PMID: 25247629