23

MEN'S HEALTH

Mary Lee and Roohollah Sharifi

OBJECTIVES

After completing this chapter, the reader should be able to

- Develop a plan for monitoring testosterone supplementation for the treatment of late-onset hypogonadism
- Distinguish when serum free testosterone or bioavailable testosterone levels are preferred to serum total testosterone levels in selected patients
- Explain why minimal laboratory testing is used to evaluate a patient with new onset erectile dysfunction
- Make inferences about the presence or absence of voiding symptoms based on test results for peak urinary flow rate and postvoid residual urinary volume in patients with benign prostatic hyperplasia
- Argue for and against the use of prostate specific antigen screening for prostate cancer
- Explain the advantages and disadvantages of PCA3, TMPRSS2-ERG, and epigenetic testing over prostate specific antigen for patients with a total prostate specific antigen of 4–10 ng/dL
- Describe the alteration of prostate specific antigen levels in patients being treated with 5α-reductase inhibitors

(continued on page 594)

This chapter focuses on laboratory and clinical tests used to evaluate several common medical disorders in aging males—androgen deficiency, erectile dysfunction, benign prostatic hyperplasia (BPH), prostate cancer, and prostatitis. Tumor markers for assessing testicular cancer and laboratories for diagnosis of urinary tract infection and venereal diseases are discussed in other chapters.

HYPOGONADISM

Hypogonadism refers to medical conditions when the testes or ovaries fail to produce adequate amounts of testosterone or estrogen in men or women, respectively, to meet the physiologic needs of the patient. For the purposes of this chapter on men's health disorders, hypogonadism will refer to conditions when testicular production of testosterone is inadequate. Increasing patient age is associated with a greater percentage of men with serum testosterone levels that are below the normal range.[1] Out of approximately 900 men in the Baltimore Longitudinal Study, the calculated incidence of hypogonadism was 12%, 19%, 28%, and 49% in men in their fifth, sixth, seventh, and eighth decades of life, respectively.[2]

Testosterone Production and Physiologic Effects

Testosterone secretion is principally regulated by the hypothalamic-pituitary gonadal axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH). This acts on anterior pituitary receptors to stimulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH acts on testicular Sertoli cells to stimulate spermatogenesis, whereas LH stimulates testicular Leydig cells to produce testosterone. Once the serum level of testosterone increases into the normal physiological range, it triggers a negative feedback loop, which inhibits GnRH release from the hypothalamus. Pituitary LH release is inhibited too, but generally less so than GnRH.

Adrenocorticotrophin stimulates the adrenal gland to produce three androgens: dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS), and androstenedione. DHA and DHAS are secreted at a daily rate of 15–30 mg, whereas androstenedione is secreted at a daily rate of 1.4 mg. All three adrenal androgens are weak androgens compared to testosterone. DHA and DHAS combined only contribute to 1% of circulating androgens, so the clinical effect of adrenal androgens is considered minor in normal men.

The principal androgen in males is *testosterone*. Testosterone comprises approximately 90% of circulating androgens. Testosterone enters the bloodstream and is delivered to target cells in muscle, bone, brain, reproductive and genital organs.[3] At some targets, testosterone itself appears to be physiologically active (e.g., central nervous system, bone, skeletal muscle, Sertoli cells). However, at other targets where 5α-reductase enzyme is expressed (e.g., prostate, scalp) testosterone is activated intracellularly by 5α-reductase to dihydrotestosterone (DHT), which has at least twice the potency of testosterone. Two separate forms of 5α-reductase enzymes exist: type I and type II. Each enzyme type tends to predominate in a particular tissue. Type I enzyme concentrates in the skin, liver, and sebaceous glands of the

OBJECTIVES

- Describe the rationale for using age-related normal value ranges for prostate specific antigen, free prostate specific antigen, prostate specific antigen velocity, and prostate specific antigen density levels in evaluating patients with prostate cancer
- Explain the role of histologic Gleason scoring in managing patients with prostate cancer
- Contrast the 4-glass versus the 2-glass method for diagnosis of prostatitis

scalp. Type II 5α-reductase predominates in the prostate and hair follicles of the scalp, and DHT in these tissues contributes to the development of BPH and alopecia, respectively.[3] Testosterone is responsible for various age-related physiologic effects in males, but most notably, it is responsible for development of secondary sexual characteristics in males (**Table 23-1**). In nontarget tissue, including the liver and adipose tissue, aromatase enzyme can convert excess androgen to estrone and estradiol.

In males, excess estrogen or a higher ratio of serum estrogen to androgen can result in gynecomastia and decreased libido. In young men, 4–10 mg of testosterone is produced each day. Testosterone secretion follows a circadian pattern, such that the highest secretion occurs at 7:00 a.m., and the lowest secretion occurs at 8:00 p.m. Testosterone circulates in three different forms: free (unbound) testosterone; bound to albumin or corticosteroid-binding globulin; or bound to sex hormone–binding globulin (SHBG). These forms comprise approximately 1–3%, 38–54%, and 44–60% of circulating testosterone levels, respectively. Free testosterone is physiologically active. Albumin-bound and corticosteroid-binding globulin-bound testosterone are inactive. However, testosterone can be easily released from these serum proteins, which have low affinity for the androgen. Therefore, this portion of testosterone has the potential to be bioavailable and become physiologically active.[4] Total bioavailable testosterone is about 50% of circulating serum testosterone. In contrast, SHBG has high affinity for testosterone, and SHBG-bound testosterone is physiologically inactive.

TABLE 23-1. Physiologic Effects of Testosterone and DHT[2-4]

STAGE OF LIFE OF MALE	PHYSIOLOGIC EFFECT
In utero	Normal differentiation of male internal and external genitalia
At puberty	Male body habitus, deepening of voice, male hair distribution, enlargement of testes, penis, scrotum, and prostate; increased sexual drive and bone growth
In adult	Sexual drive, muscle strength and mass, bone mass, prostate enlargement, male hair growth and distribution, spermatogenesis

DHT = dihydrotestosterone.

TABLE 23-2. Medical Conditions and Drugs That Alter SHBG Concentrations[5]

	INCREASED SHBG	DECREASED SHBG
Medical conditions that produce an alteration of SHBG concentration	Hepatic cirrhosis	Hypothyroidism
	Hepatitis	Nephrotic syndrome
	HIV disease	Obesity
	Anorexia nervosa	Acromegaly
	Hyperthyroidism	Cushing syndrome
	Aging males	Diabetes mellitus
	Prolonged stress	
Drugs that produce an alteration of SHBG concentration	Estrogens	Testosterone supplements, excessive doses
	Phenytoin	Corticosteroids
		Progestins

HIV = human immunodeficiency virus; SHBG = sex hormone–binding globulin.

Multiple factors affect circulating SHBG level (**Table 23-2**). Measurement of SHBG levels is essential in patients when the serum total testosterone level is inconsistent with the clinical symptoms of the patient as it assists in the interpretation of the total serum testosterone level, and can be used to calculate the free or bioavailable testosterone level.

Hormonal Changes Associated with Primary, Secondary, and Tertiary Hypogonadism

Primary hypogonadism occurs when the testicles are absent or surgically removed, or when they are nonfunctional secondary to an acquired disease (e.g., mumps orchitis). *Secondary hypogonadism* occurs when the pituitary fails to release adequate amounts of LH; thus, the testes are not stimulated to produce adequate amounts of testosterone. *Tertiary hypogonadism* refers to a disorder of the hypothalamus such that there is inadequate release of GnRH, and a subsequent decrease in release of LH from the pituitary and testosterone from the testes (**Table 23-3**).

Late-Onset Hypogonadism

Late-onset hypogonadism, also known as *andropause* or *androgen deficiency in aging males* (ADAM), refers to the biochemical changes associated with age-related alterations in the hypothalamic-pituitary-gonadal axis, which may or may not be associated with clinically significant symptoms and signs (**Table 23-4**).[4,6] However, other men with decreased testosterone levels do not complain of their symptoms or have vague, nonspecific symptoms (e.g., malaise or decreased energy) for which they do not seek medical treatment.[6] Although late-onset hypogonadism is often compared to the menopause in aging females, these conditions are different (Table 23-4). In males gonadal function decreases over decades, and symptoms develop slowly and often are not attributed to decreasing hormone levels. In females, gonadal function decreases over a comparatively