Hypogonadism
Its Prevalence and Diagnosis

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KEYWORDS

• Hypogonadism • Prevalence • Diagnosis • Androgen deficiency

KEY POINTS

- It is important to distinguish organic hypogonadism due to known diseases of the testes, pituitary, and the hypothalamus for which testosterone therapy is indicated from the age-related decline in testosterone levels, in which neither the clinical benefits nor the long-term risks have been clearly demonstrated in randomized trials.
- The prevalence of organic hypogonadism due to known diseases of the testes, pituitary, and the hypothalamus is not known.
- The diagnosis of hypogonadism should be based on the ascertainment of signs and symptoms of androgen deficiency along with unequivocally low levels of circulating testosterone on at least 2 occasions, using a reliable assay.
- Measure free testosterone using an accurate method when alterations in binding protein concentrations are suspected.
- Primary hypogonadism can be distinguished from secondary hypogonadism by measurement of luteinizing hormone and follicle-stimulating hormone concentrations.

INTRODUCTION

Androgen deficiency syndromes in men result from diminished production of testosterone due to defects at one or more levels of the hypothalamic-pituitary-testicular axis. Testosterone is the most important androgen in men; more than 90% of circulating testosterone is derived from the Leydig cells under the influence of pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and luteinizing hormone (LH) secretion from the pituitary. Although LH is the primary regulator of testicular testosterone production, follicle-stimulating hormone (FSH), in conjunction with high intratesticular testosterone concentrations, is essential for initiating and maintaining spermatogenesis. Circulating testosterone is bound largely to sex hormone–binding globulin (SHBG)

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and to albumin, and to a much smaller extent to orosomucoid and cortisol-binding protein; only 1.0% to 4.0% is free.[1–5] Defects anywhere in the hypothalamic-pituitary-gonadal (HPG) axis can lead to testosterone deficiency. Primary hypogonadism results from primary defects in the testes and is associated with low testosterone levels and elevated levels of gonadotropins. Secondary or hypogonadotropic hypogonadism results from disorders of the hypothalamus and/or pituitary and is associated with low testosterone levels and low or inappropriately low LH and FSH concentrations. The authors review here a stepwise approach to the diagnosis and the epidemiology of androgen deficiency syndromes in men.

PRIMARY HYPOGONADISM

Primary hypogonadism results from congenital or acquired disorders of the testes (Table 1). Primary congenital hypogonadism may be due to chromosomal disorders, defects in testosterone biosynthesis, uncorrected cryptorchidism, congenital anorchia, or androgen resistance. Acquired disorders result from external damage to the testes from surgery, trauma, toxins, inflammation, or infection.

Primary Congenital Hypogonadism

Klinefelter syndrome (KS), classically associated with the 47, XXY karyotype, is the most common cause of congenital hypogonadism, affecting one in 660 men[6,7] and is characterized typically by small, firm testes (<2 mL), low testosterone levels, eunuchoidal proportions, gynecomastia, elevated LH and FSH levels, and impaired spermatogenesis.[8,9] However, there is considerable phenotypic variation due to mosaicism, variable polyglutamine tract length in exon 1 of the androgen receptor or other polymorphisms in the androgen receptor, other genetic factors, and variable testosterone levels; KS may present with learning difficulties and behavioral problems in childhood and with infertility, gynecomastia, or sexual dysfunction in adulthood. Registries of patients with KS have reported higher overall mortality and increased risk of breast cancer, non-Hodgkin lymphomas, lung cancer, and autoimmune diseases, such as systemic lupus erythematosus and Sjögren syndrome, and lower incidence of prostate cancer.[10–12] Although most men with 47, XXY karyotype are azoospermic, pregnancies have been achieved by testicular sperm extraction combined with intracytoplasmic sperm injection.[13–15]

Up to 15% to 20% of patients with KS demonstrate 46, XY/47, XXY mosaicism, which is associated with a milder phenotype. Patients with KS with more than one extra X chromosome have a more severe phenotype, increased risk of congenital malformations, and lower intelligence than individuals with 47, XXY.[16–18] The true prevalence of KS, especially KS mosaicism, may be underestimated as many men with KS remain undiagnosed; a Danish study found that only 25% of adult men with KS had received a diagnosis; of these, less than 10% were diagnosed before puberty.[19]

Structural chromosomal aberrations, including deletions, duplications, and translocations, and other rearrangements can lead to hypogonadism.[20] For example, Noonan syndrome, an autosomal dominant disorder, is caused by a mutation in the *PTPN11* gene and is characterized by dysmorphic facial features, short stature, and heart disease and is associated with abnormal Sertoli and Leydig cell function.[21,22] Leydig cell hypoplasia as a result of LH receptor mutations leads to testosterone deficiency during the first trimester of pregnancy and complete lack of virilization of the external genitalia at birth.[23,24] Additional diagnoses to consider in newborns with 46, XY with ambiguous genitalia include defects of testosterone biosynthesis, 5α-reductase deficiency, or androgen insensitivity due to mutations of the androgen receptor.[25]

Cryptorchidism, if left uncorrected by 2 years of age, predisposes men to an increased risk of infertility, androgen deficiency, and testicular cancer. Cryptorchidism may also be associated with an increased risk of inguinal hernias and testicular torsion.[26] Even unilateral cryptorchidism,

Table 1
Causes of primary hypogonadism

Primary Congenital	Primary Acquired
Klinefelter syndrome	Bilateral testicular trauma/torsion
Other chromosomal abnormalities	Orchiectomy
Noonan syndrome	Cancer chemotherapy and radiation
Defects of testosterone biosynthesis	Bilateral orchitis
Androgen resistance syndromes	Systemic disease
Uncorrected bilateral cryptorchidism	Sickle cell disease
Congenital anorchia	—
Varicocele	—
Myotonic dystrophy	—