REVIEW
Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis

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Male hypogonadism has a multifactorial etiology that includes genetic conditions, anatomic abnormalities, infection, tumor, and injury. Defects in the hypothalamic-pituitary-gonadal axis may also result from type II diabetes mellitus and treatment with a range of medications. Circulating testosterone levels have been associated with sexual function, cognitive function, and body composition. Apart from reduced levels of testosterone, clinical hallmarks of hypogonadism include absence or regression of secondary sex characteristics, reduced fertility (oligospermia, azoospermia), anemia, muscle wasting, reduced bone mass (and bone mineral density), and/or abdominal adiposity. Some patients, particularly those with partial androgen deficiency of the aging male, also experience sexual dysfunction, reduced sense of vitality, depressed mood, increased irritability, difficulty concentrating, and/or hot flushes in certain cases of acute onset. As many patients with male hypogonadism—like patients with erectile dysfunction—do not seek medical attention, it is important for clinicians to be acquainted with the signs and symptoms of hypogonadism, and to conduct appropriate laboratory testing and other assessments to determine the causes and inform the treatment of this condition.

Etiology

Hypogonadism is characterized by low serum testosterone (T) levels (<300 ng/dl) together with $\geqslant 1$ clinical symptom or sign. Symptoms of post-pubertal hypogonadism include[1–3] (1) sexual dysfunction, such as reduced libido, erectile dysfunction (ED), diminished penile sensation, difficulty attaining orgasm, as well as reduced ejaculate with orgasm; (2) reduced energy, vitality, or stamina; (3) depressed mood or diminished sense of well-being; (4) increased irritability; (5) difficulty concentrating and other cognitive problems; and/or (6) hot flushes in some cases of acute onset.

Signs of hypogonadism include (1) anemia; (2) muscle wasting (sarcopenia); (3) reduced bone mass or bone mineral density (BMD); (4) absence or regression of secondary sex characteristics;

(5) abdominal adiposity (i.e. 'pot belly' obesity); and/or (6) oligospermia or azoospermia.

A number of hypothalamic-pituitary-gonadal (HPG) axis defects may induce hypogonadism (Table 1).[2,4] The term *primary (hypergonadotropic) hypogonadism* refers to testicular disorders and is characterized by low serum T despite high levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Causes of primary hypogonadism include (1) genetic conditions (e.g. Klinefelter syndrome, gonadal dysgenesis); (2) anatomic defects; (3) infection; (4) tumor; (5) injury; (6) iatrogenic causes (surgery or certain medications); and/or (7) alcohol abuse.[3]

The term *secondary (hypogonadotropic) hypogonadism* denotes deficient release of gonadotropin-releasing hormone (GnRH) and is characterized by low–normal or low levels of FSH, LH, and T. Causes or manifestations of secondary hypogonadism include (1) hyperprolactinemia (often secondary to pituitary adenoma); (2) GnRH deficiency with anosmia (Kallmann syndrome); (3) hypothalamic lesions or disorders; and (4) pituitary lesions or disorders. The term *normogonadotropic hypogonadism* denotes symptoms or signs of hypogonadism together with low serum T and normal LH levels.

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Table 1 Differential diagnosis of male hypogonadism

Primary (hypergonadotropic) hypogonadism
  Testicular disorders (primary gonadal failure)
    Undescended testes
    Acquired bilateral torsion of testes
    Orchitis (e.g. mumps orchitis)/cryptorchidism
    Vanishing-testes syndrome (congenital anorchism or prepubertal functional castrate)
    Seminiferous tubule dysgenesis (Klinefelter syndrome)
    Pure gonadal dysgenesis (46XX and 46XY)
    Sweyer syndrome (phenotypic female with gonads and genitalia identical to gonadal dysgenesis)
    Noonan (Boonevie–Ullrich) syndrome
    Hemochromatosis
    Impaired Leydig cell activity
      Inborn errors of testosterone biosynthesis
    Leydig cell hypoplasia
    Testicular unresponsiveness (LH receptor failure?)
    Androgen-resistant states and enzyme defects
      Testicular feminization (absence of androgen receptors)
      Incomplete androgen insensitivity (Reiffenstein syndrome)
      5α-Reductase deficiency
  External testicular insults
    Trauma
    Radiation treatment
    Chemotherapy
  Autoimmune syndromes (e.g. anti-Leydig cell antibody-associated disorders)
  Sertoli-cell only syndrome

Secondary (hypogonadotropic) hypogonadism
  GnRH deficiency
    Hypothalamic lesions
      Tumors
      Encephalitis
      Granuloma
      Abscess
      Craniopharyngioma
    Isolated GnRH deficiency
      Idiopathic (Kallmann syndrome or fertile-eunuch syndrome)
    Prader–Willi syndrome
    Lawrence–Moon–Bardet–Biedl syndrome
    Alström syndrome
    Fertile-eunuch syndrome
    Familial cerebellar syndrome

  Hyperprolactinemia
    Prolactinoma
    Certain drugs
    Hemochromatosis
    Neurosarcoid
    Myotonic dystrophy

  Pituitary disorders (gonadotrophin deficiency)
    Isolated LH deficiency
      Pasqualini syndrome
      Eunuchoidism
      Absent secondary sexual characteristics
      Oligospermia
    Tumors
    Pituitary infarction, apoplexy
    Empty sella syndrome
    Hemochromatosis
    Cranial trauma with or without pituitary-stalk transection
    Irradiation
    Hypophysitis

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH, luteinizing hormone.
Sources: AACE guidelines[2] and Rehman *et al.*[4]

Conditions that may be associated with hypogonadism include type II diabetes mellitus (DM); cancer; acquired immune deficiency syndrome; cirrhosis of the liver; renal failure; hyperthyroidism or hypothyroidism; Cushing syndrome; protein-calorie malnutrition (and anorexia nervosa); morbid

Table 2 Agents that may cause low circulating testosterone

Cytotoxic agents
Spironolactone
Corticosteroids, ketoconazole, aminoglutethimide, ethanol
Decrease Leydig-cell testosterone production
Anticonvulsants, hepatic microsomal liver enzyme inducers
Augment testosterone metabolism
Gonadotropin-releasing hormone agonists, estrogens, anabolic steroids, psychotropic medications, post-transplant immunosuppressants, corticosteroids, ethanol
Reduce gonadotropin secretion

Adapted with permission from Hameed et al.[3]

obesity; hemochromatosis or sickle-cell anemia; paraplegia and myotonia dystrophica; as well as certain psychiatric disorders, including depressive disorders.[5] In addition, several agents are associated with low circulating testosterone[3] (Table 2).

Pathophysiology

Effects of testosterone on sexual function
It has been suggested that normal or low–normal T levels are necessary to maintain normal sexual function, whereas increases in fat-free and lean-tissue mass rise in a dose-dependent manner over the normal range of circulating T.[6,7]

In a recent study of androgen-deficient patients undergoing subdermal T implantation (T pellets), Handelsman's group determined thresholds for T and free T (FT) below which symptoms of androgen deficiency returned as T levels declined.[8] Reduced libido and lack of motivation and/or energy recurred when T reached approximately 280 ng/dl in patients with secondary (hypogonadotropic) hypogonadism and 337 ng/dl in patients with primary (hypergonadotropic) hypogonadism.

Testosterone appears to play a role in maintaining sexual function, especially libido, although androgen deficiency per se is infrequently the sole cause of ED in hypogonadal males, particularly elderly men.[9] Preclinical evidence suggests that T promotes erectile responses via both the central and peripheral nervous systems.[10–12] For instance, T modulates α-adrenergic (antierectile) sensitivity of cavernosal smooth muscle.[13]

Preclinical work in DM-prone rats also suggests that decreases in penile nitric oxide synthase (NOS) expression or activity associated with low serum androgens contribute to the pathophysiology of diabetic ED.[14] Other investigations have suggested that androgen deprivation blunts erectile responses via structural changes in the corpora that culminate in decreased blood storage (i.e. veno-occlusive dysfunction) without influencing NOS activity.[15]

In man, it is believed that androgens mediate nocturnal penile tumescence, whereas erectile responses to visual stimuli are androgen independent.[9,16] It has also been suggested that the influence of T on erectile function may be mediated partly via effects on genital sensitivity and that the T metabolite 5α-dihydrotestosterone may also play a role in maintaining erections.[17,18]

T levels in the corpora cavernosa and peripheral blood during transitions from penile flaccidity to tumescence and rigidity, and then detumescence were compared in healthy subjects and ED patients.[19] In healthy volunteers, T levels increased significantly in corporal blood during the transition from flaccidity (2.9 ng/ml) to tumescence (4.3 ng/ml; $P < 0.001$) and rigidity (4.4 ng/ml), followed by a return to 3.5 ng/ml during detumescence. In ED patients, the rise in cavernous T was of lower magnitude: from 2.6 to 3.0 ng/ml during tumescence ($P < 0.05$). Similar patterns were observed with respect to T concentrations in peripheral blood.

The rise in cavernous T levels from flaccidity to tumescence was also somewhat more marked in patients with psychogenic rather than organic ED.[19] The investigators suggested that the difference between peripheral and cavernous T concentrations during the flaccid phase might serve as a useful marker of bioavailable T (BT) and T receptor density in corporal smooth muscle.[19]

Effects of testosterone on cognitive function and affect
Cognitive performance, including mental-rotation tasks, is related to androgen levels across the normal range in healthy volunteers.[20,21] In addition, certain studies have shown that androgen replacement enhances cognitive and language functions (but not memory).[22–24]

In vivo studies have also suggested that endogenous androgens confer potentially beneficial neuroprotective effects within the hippocampus and limit accumulation of β-amyloid protein—a central pathophysiologic defect in Alzheimer's disease.[25,26] In addition, a study of nondemented patients with Parkinson's disease demonstrated that the degrees of patient- and informant-reported apathy were in-versely related to FT levels.[27]

On the other hand, Kenny and co-workers recently determined that intramuscular T (i.m. T) injections did not significantly affect a wide range of cognitive indices in elderly hypogonadal men with early cognitive impairment and $BT < 128$ ng/dl.[28] I.m. T also did not affect activities of daily living or depression ratings.

In the Rancho Bernardo Study, depression rating scales were inversely related to BT levels ($P = 0.0007$) irrespective of age, physical activity, or alterations in body weight.[29] Although certain elderly dysthymic men and patients with treatment-refractory depression have low T levels, there

is no strong evidence that reduced T levels play a pivotal pathophysiologic role in major depression.

At the time of writing, there is insufficient evidence to recommend testosterone replacement therapy (TRT) as first-line therapy for major depressive disorder in men with hypogonadism, although adjunctive T treatment may enhance clinical outcomes in patients with treatment-refractory depression.[30–33] Moreover, certain elderly men report an enhanced sense of well-being on TRT,[34,35] although this may be an indirect effect of other physiologic changes.

Effects of testosterone on body composition
Androgens may promote bone formation. In two recent studies of young healthy men, serum sex hormone binding globulin (SHBG) emerged as an independent positive predictor of bone turnover or BMD.[36,37] The decrease in bone mass with advancing age may be associated with declining insulin-like growth factor (IGF-1) levels as well as T concentrations.[38]

Partly by facilitating commitment of pluripotent mesenchymal cells, androgens may also foster skeletal-muscle hypertrophy and hence promote lean body mass.[39] Exogenous T increases satellite-cell populations within muscles, with attendant rises in numbers of myoblasts and large-myofiber myonuclei, as well as formation of larger motoneurons. On the other hand, data suggesting that reduced muscle strength in elderly men relates to reversible declines in androgen levels are conflicting.[38,40–42]

Androgens also attenuate adipogenesis in man. The effects of TRT on adipogenesis may differ in different anatomic regions. In a recent study of men randomized to a GnRH agonist together with i.m. testosterone enanthate (TE) injections at five doses over the range of 25–600 mg weekly,[7] lowering T levels was associated with increases in adipose-tissue stores, with particularly marked rises in subcutaneous depots. However, increasing T levels above baseline via i.m. T injections preferentially mobilized smaller, deeper i.m. adipose-tissue deposits. Overall fat mass was inversely correlated with TE doses across all sites.[7]

Diagnosis

In addition to recognizing presenting symptoms, conducting appropriate laboratory testing is central to diagnosing male hypogonadism.[3] According to the Second International Consultation on Erectile Dysfunction of the World Health Organization (WHO),[43] a blood sample for serum T determination should be obtained between 0800 and 1100 hours, when T levels typically peak in healthy young men. This circadian rhythmicity may be abolished or blunted in men with advancing age[44] or during certain forms of TRT.

A morning T level $\leqslant 300$ ng/dl should be confirmed and if there is a need to differentiate primary from secondary hypogonadism, levels of LH and FSH should be evaluated.[43] According to the guidelines of the American Association of Clinical Endocrinologists (AACE), exceedingly low T levels ($\leqslant 150$ ng/dl) warrant pituitary imaging even in the absence of other signs or symptoms.[2] Some authorities recommend sellar magnetic resonance imaging with thyroxine, cortisol, and prolactin assessments when secondary hypogonadism is considered likely.[45] According to Australian consensus guidelines:[46]

- primary (hypergonadotropic) hypogonadism is indicated by serum $T < 231$ ng/dl with LH > 1.5 times the upper limit of normal ($1.5 \times$ ULN);
- secondary (hypogonadotropic) hypogonadism is indicated by $T < 231$ ng/dl without LH elevations;
- Leydig-cell failure is indicated by $T = 231–432$ ng/dl with LH $> 1.5 \times$ ULN; and
- androgen resistance is indicated by $T > 864$ ng/dl with LH $> 1.5 \times$ ULN.

Total T assays may not indicate true androgenic status, particularly in elderly men. According to the most recent WHO guidelines,[43] BT (normal range $= 92–420$ ng/dl) and FT (normal $= 5–21$ ng/dl) are the most reliable assays to establish male hypogonadism. As serum T may be normal in patients with primary testicular disorders (e.g. Klinefelter syndrome) or increased SHBG, obtaining FT or BT may also be useful.[2] However, the validity and accessibility of a number of diagnostic tests (e.g. equilibrium dialysis) and other, dynamic assessments are matters of ongoing debate.

Recent data from the Massachusetts Male Ageing Study (MMAS) provide perspectives on normal androgen ranges.[47] In the MMAS, the threshold for abnormally low total T as established by the 2.5th percentile was 251 ng/dl for healthy men aged 40–49 years, 216 ng/dl for ages 50–59, 196 ng/dl for ages 60–69, and 156 ng/dl for ages 70–79. Corresponding 2.5th-percentile values for FT were 5.3, 4.2, 3.7, and 2.2 ng/dl, while corresponding values for BT were 99.7, 79.8, 69.7, and 41.8 ng/dl.

In the MMAS, the mean FT in men aged 40–49 years was 14.3 ng/dl, with a range of 3.7 ng/dl (mean-2 standard deviations (s.d.)), to 24.9 ng/dl (mean$+2$ s.d.). The mean FT in men aged 70–79 was 7.6 ng/dl (0.8–14.4 ng/dl). The mean BT in men aged 40–49 years was 270.9 ng/dl (69.2–469.7 ng/dl) and the mean BT in men aged 70–79 was 144.1 ng/dl (14.4–270.9 ng/dl).[47]

As with ED, signs and symptoms of hypogonadism often go unreported to physicians. Therefore, it is important to maintain a proactive dialogue with the patient about possible symptoms such as low

libido, ED, impaired concentration, and fatigue to uncover hypogonadism. It is also often important to inquire about *increased* fatigue during TRT because this may be a manifestation of treatment-related sleep apnea.

Conclusions

In summary, male hypogonadism has a multifactorial etiology that includes congenital abnormalities, injury, infection, cancer, diabetes, treatment with certain medications, and alcohol abuse. In addition to obtaining androgen and other hormone levels, it is important to be familiar with the signs (e.g. anemia, oligospermia/azoospermia, muscle wasting) and symptoms (e.g. sexual dysfunction, mood disturbances, cognitive problems) because many patients do not report these manifestations. Assessment of presenting signs and symptoms, in concert with evaluations of the HPG axis, enables diagnosis of primary (hypergonadotropic) or secondary (hypogonadotropic) hypogonadism, which may prompt further work-ups and treatment.

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