

Challenges in Diagnosis and Treatment of Male Hypogonadism

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Hypogonadism is a condition characterized by diminished or absent production of sex hormones by the testicles in men and the ovaries in women.¹ Hypogonadism is classified into primary and secondary hypogonadism. Each type of hypogonadism can be caused by congenital and acquired factors. There are many factors that contribute to the occurrence of hypogonadism, including genetic and developmental disorders, infection, kidney disease, liver disease, autoimmune disorders, chemotherapy, radiation, surgery, and trauma.^{2,3} This represents the considerable challenge in diagnosing hypogonadism.

The diagnosis of hypogonadism in males is established based on medical history, physical examination, and gonadal hormone levels in the blood. The onset, disease duration, severity level, presence of comorbid conditions, and history of previous hormone therapy affect the diversity of sign and symptoms of hypogonadism. The signs and symptoms that present in pre-puberty will be different from those appearing post-puberty.² The variety of hypogonadism's causes and symptoms pose a significant challenge for healthcare providers in identifying this condition among those at risk and deciding whether treatment is necessary.

Diagnostic tests recommended for hypogonadism are testosterone measurements (total or free testosterone), ideally taken in the morning for two consecutive days; gonadotropins (FSH and LH or GnRH), to distinguish between primary or secondary

hypogonadism if testosterone levels are low; dynamic tests; prolactin levels; and semen analysis to evaluate patient fertility; a fructose test if azoospermia is present. Dynamic test such as the GnRH stimulation test, clomiphene stimulation test, and hCG stimulation test are valuable for assessing hypothalamic and pituitary response. Additional examinations to determine the cause, comorbidities, location of abnormality, and complications may include bone density scans, pituitary MRI, buccal smears, testicular biopsy and scrotal exploration, and testicular ultrasound.⁴

The goals of treatment include restore sexual functionality and well-being, initiating and sustaining virilization, osteoporosis prevention, normalize growth hormone levels in elderly men if possible, and restoring fertility in instances of hypogonadotropic hypogonadism. The main approach to treating hypogonadism is hormone replacement therapy. Male with prostate cancer, breast cancer, and untreated prolactinoma are contraindicated for hormone replacement therapy.^{4,5} When selecting a type of testosterone therapy for male with hypogonadism, several factors need to be considered, such as the diversity of treatment response and the type of testosterone formulation. The duration of therapy depends on individual response, therapeutic goals, signs and symptoms, and hormonal levels.⁶ The response to testosterone therapy is evaluated based on symptoms and signs as well as improvements in hormone profiles in the blood. Endocrine Society Clinical Practice

Guideline recommend therapeutic goals based on the alleviation of symptoms and signs, as well as reaching testosterone levels between 400 – 700 ng/dL (one week after administering testosterone enanthate or cypionate) and maintaining baseline hematocrit.⁷ Given the diversity of signs and symptoms, which may not always align with hormone levels in the blood, determining therapeutics goals can be challenging. Testosterone therapy may induced the changes of lipid profile, increase platelet aggregation and thrombogenicity, and also increase cardiovascular mortality.^{4,8} To prevent the side effects of prolonged hormone use, regular assessments every 3 – 12 months are advised.⁶

Hormone therapy is the primary modality in the management of hypogonadism. The variety of signs and symptoms makes early diagnosis of this condition challenging. Moreover, administering hypogonadism therapy involves numerous considerations influenced by various patient factors and the potential for adverse effects. This poses a challenge for physicians to provide targeted hypogonadism therapy with minimal complications.

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