Hypogonadism

Therapeutic Risks, Benefits, and Outcomes

John T. Sigalos[a], Alexander W. Pastuszak, MD, PhD[b,c], Mohit Khera, MD, MBA, MPH[c,*]

KEYWORDS

• Hypogonadism • Cardiovascular risk • Testosterone therapy • Outcomes

KEY POINTS

- Hypogonadism is a common condition defined by the presence of low serum testosterone levels and hypogonadal symptoms, and most commonly treated using testosterone therapy (TTh).
- The accuracy of diagnosis and appropriateness of treatment, along with proper follow-up, are increasingly important given the large increase in testosterone prescriptions and the recent concern for cardiovascular (CV) risk associated with TTh.
- Only a few recent studies with significant methodological flaws have supported an increased CV risk in men on testosterone. In contrast, the body of literature evaluating TTh over the past 75 years, as well as more recent work, has shown that TTh may improve CV outcomes rather than increase risks.
- Given the association between low serum testosterone levels and CV events and morbidity, it is prudent to treat hypogonadal men until studies that more definitively elucidate the risk of TTh on CV outcomes become available.

INTRODUCTION

According to the Endocrine Society practice guidelines, hypogonadism is defined as "a clinical syndrome that results from failure of the testis to produce physiological

A.W. Pastuszak is a K12 scholar supported by a Male Reproductive Health Research (MRHR) Career Development Physician-Scientist Award (grant # HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Program.
Conflicts of Interest: Endo Pharmaceuticals, speaker and advisor; Boston Scientific/AMS, research support (Dr A.W. Pastuszak). Consultant for Endo, ATYU, Coloplast, Boston Scientific, Abbvie (Dr M. Khera). None (J.T. Sigalos).
[a] Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA; [b] Center for Reproductive Medicine, Baylor College of Medicine, 1 Baylor Plaza, Room N730 Houston, TX 77030, USA; [c] Scott Department of Urology, Baylor College of Medicine, 7200 Cambridge Street, Houston, TX 77030, USA
* Corresponding author. Scott Department of Urology, Baylor College of Medicine, 7200 Cambridge Street, Houston, TX 77030.
E-mail address: mkhera@bcm.edu

Med Clin N Am ■ (2017) ■–■
https://doi.org/10.1016/j.mcna.2017.10.011 **medical.theclinics.com**

levels of testosterone (T) (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis."[1] In contrast, the US Food and Drug Administration (FDA) defines hypogonadism as a serum T level less than or equal to 300 ng/dL. The production of T in the testis is stimulated by secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, resulting in secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland.[2] LH and FSH stimulate production of T and spermatogenesis, respectively. Over the lifetime, T is essential for maintaining the male phenotype. Specifically, T facilitates the development and maintenance of secondary sex characteristics, muscle mass, bone density, stimulation of erythropoiesis, and libido. T also has central nervous effects on mood and cognition.[3]

Given these benefits, it is imperative to assess men for gonadal function. The reported prevalence of hypogonadism in men 30 to 79 years old from the Boston Area Community Health survey using a combination of hypogonadal symptoms and T level of less than 300 ng/dL is ~6%.[4] This rate increases with increasing age.[4,5] Increased awareness of hypogonadism by the lay public, as well as direct-to-consumer marketing of T products, has led to dramatic increases in T use around the world.[6] Between 2000 and 2011 the prevalence of T use increased 10-fold in the United States, and 40-fold in Canada.[6] In economic terms, US sales of T products increased from $324 million in 2002 to $2 billion in 2012, and the number of T doses prescribed increased from 100 million in 2007 to 500 million in 2012, not including prescriptions filled by compounding pharmacies, the Internet, and direct-to-patient clinic sales.[7] Up to 25% of men who were prescribed T did not have baseline serum T levels checked before obtaining a prescription.[8,9] Potential misuse of T therapy (TTh) and conflicting data regarding the therapeutic risks of TTh have led to increased scrutiny by the FDA, which in March 2015 mandated a change to T labels warning of potential cardiovascular (CV) risks related to TTh.[10] However, the FDA's stance is based on several recent studies that supported a weak, but significant, association between increased CV risk and TTh that the FDA decided could not be ignored. Given this controversy, as well as the clear missteps in the diagnosis and treatment of hypogonadism that have come to light in recent years, this article discusses the diagnosis and treatment of hypogonadism and reviews the literature regarding the association between TTh and CV risk.

DIAGNOSIS OF HYPOGONADISM

The causes of hypogonadism can be divided into 2 categories: primary hypogonadism, which represents a failure of the testes to produce T, and secondary (hypogonadotropic) hypogonadism, which is failure of the pituitary gland to secrete sufficient LH to stimulate testicular T production. Primary hypogonadism is associated with increased LH levels, whereas secondary hypogonadism is reflected by low or inappropriately normal LH levels.[1] The common causes of primary and secondary hypogonadism are summarized in **Table 1**.[11]

The diagnosis of hypogonadism relies on the presence of low serum T levels, considered to be less than 300 ng/dL by most practice recommendations,[1,12] as well as the presence of clinical symptoms associated with low T levels.[1,13] However, a standardized definition of hypogonadism is lacking. Clinical signs and symptoms suggestive of T deficiency that warrant further laboratory work-up include delayed puberty, decreased libido, decreased spontaneous erections, erectile dysfunction, gynecomastia and breast tenderness, loss of body hair, testicular atrophy, low sperm count, low bone mineral density, and hot flashes. Other symptoms that are less