JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 5, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.12.005

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Testosterone and Cardiovascular Disease

Robert A. Kloner, MD, PhD,[a,b] Culley Carson III, MD,[c] Adrian Dobs, MD,[d] Stephen Kopecky, MD,[e] Emile R. Mohler III, MD[f]

ABSTRACT

Testosterone (T) is the principal male sex hormone. As men age, T levels typically fall. Symptoms of low T include decreased libido, vasomotor instability, and decreased bone mineral density. Other symptoms may include depression, fatigue, erectile dysfunction, and reduced muscle strength/mass. Epidemiology studies show that low levels of T are associated with more atherosclerosis, coronary artery disease, and cardiovascular events. However, treating hypogonadism in the aging male has resulted in discrepant results in regard to its effect on cardiovascular events. Emerging studies suggest that T may have a future role in treating heart failure, angina, and myocardial ischemia. A large, prospective, long-term study of T replacement, with a primary endpoint of a composite of adverse cardiovascular events including myocardial infarction, stroke, and/or cardiovascular death, is needed. The Food and Drug Administration recently put additional restrictions on T replacement therapy labeling and called for additional studies to determine its cardiac safety. (J Am Coll Cardiol 2016;67:545–57) © 2016 by the American College of Cardiology Foundation.

Testosterone (T) is the principal male sex hormone, secreted primarily by the testes and, to a lesser extent, by adrenal glands. This hormone's androgenic effects are responsible for the maturation of male sexual organs, as well as for secondary sexual characteristics (growth of beard, axillary, and pubic hair, and deepening of voice). T is needed for the development of normal sperm production and contributes to sex drive. It also has anabolic effects, including promotion of muscle mass, strength, bone density, and maturation. T is also produced in small quantities in the ovaries; women have a much lower level of T than men. T levels decrease with age, and this decrease has been associated with an increase in atherosclerosis and cardiovascular risk. One might conclude that replacing T would reduce the risk; however, clinical studies on this concept have shown discrepant results. The purpose of this review is to discuss the basic endocrinology of T, hypogonadism in the young and the elderly, the association between low T and cardiovascular (CV) risk, and approaches to treating hypogonadism. This review will also discuss controversies regarding the administration of exogenous T to patients with hypogonadism, the use of T in heart failure, its effect on thromboembolism and ischemia/reperfusion injury, and recent changes in labeling for T replacement therapy (TRT).

THE HYPOTHALAMUS-PITUITARY-TESTES AXIS

The controller of the gonadal axis is gonadotropin-releasing hormone (GnRH), which is released from the hypothalamus (Figure 1). GnRH acts on the anterior pituitary to stimulate release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In men's testes, LH stimulates T synthesis by Leydig cells, and FSH stimulates spermatogenesis by

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Huntington Medical Research Institutes, Pasadena, California; [b]Division of Cardiovascular Medicine, Department of Medicine, Keck School of Medicine at University of Southern California, Los Angeles, California; [c]Department of Urology, University of North Carolina, Chapel Hill, North Carolina; [d]Division of Endocrinology, Johns Hopkins University School of Medicine, Baltimore, Maryland; [e]Division of Cardiology, Mayo Clinic, Rochester, Minnesota; and the [f]Section of Vascular Medicine, Division of Cardiovascular Disease, Perelman School of Medicine at the University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania. Dr. Kloner is a consultant to Abbvie and Teso-Rx. Dr. Carson is a consultant for Abbvie, Boston Scientific, and ENDO. Dr. Dobs serves on the advisory board for Abbvie. Dr. Kopecky is a consultant for Prime Therapeutics. Dr. Mohler is a consultant for Clarus and Abbvie.

Manuscript received November 23, 2015; accepted December 1, 2015.

ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

ADT = androgen deprivation therapy

CI = confidence interval

CV = cardiovascular

DHT = dihydrotestosterone

ECG = electrocardiogram

ED = erectile dysfunction

FDA = Food and Drug Administration

FSH = follicle-stimulating hormone

GnRH = gonadotropin-releasing hormone

HF = heart failure

LH = luteinizing hormone

MI = myocardial infarction

SHBG = sex hormone-binding globulin

T = testosterone

TRT = testosterone replacement therapy

Vo_2 = peak oxygen consumption

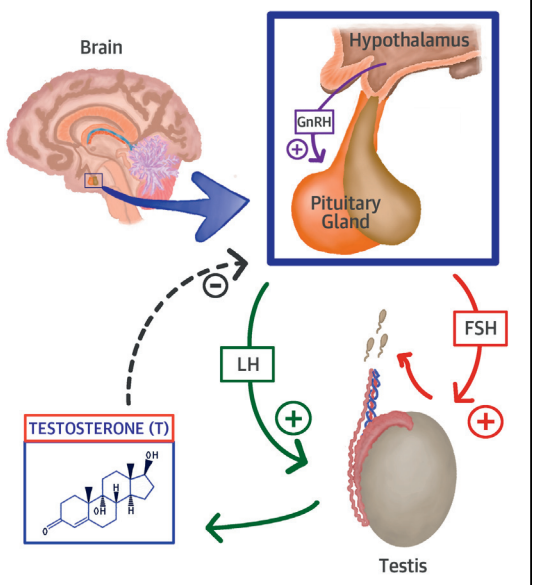
Sertoli cells. Only a small fraction of the total circulating T is in a free form, with the vast majority bound to sex hormone-binding globulin (SHBG) or albumin. Biologically active, free T binds to the androgen receptor present in the cytosol of most tissues (1). The T-androgen receptor complex then migrates to the nucleus, where it stimulates transcription of numerous genes. Interestingly, T serves as a prohormone for estradiol, via the action of the aromatase enzyme (present in many cardiovascular cell types), and dihydrotestosterone (DHT), via 5α-reductase activity. DHT is a more potent androgen than T, on the basis of its greater affinity for the androgen receptor and long residence time. However, circulating levels of DHT are generally one-tenth or less those of T. T, DHT, and estradiol then complete a negative feedback loop to the hypothalamus and pituitary. Several clinical conditions, including obesity, type 2 diabetes mellitus, hypothyroidism, polycystic ovarian syndrome, and nephrotic syndrome decrease SHBG levels (2), which can result in relatively more free T for any given total T. Older age, hyperthyroidism, and cirrhosis increase SHBG levels and can result in a free T concentration in the hypogonadal range, despite normal total T levels.

DEFINITION OF HYPOGONADISM

Male hypogonadism is the term used to describe a deficiency of T secretion from the Leydig cells of the testes (Figure 1). Depending on the pathophysiology, it may or may not be associated with infertility due to reduced spermatogenesis in the seminiferous tubules. Similarly, infertility may or may not be associated with hypogonadism. As an example, there are often microdeletions of the Y chromosome that are associated with male infertility, but with normal T synthesis.

Hypogonadism is classified as primary (testicular failure) or secondary, centrally mediated (hypothalamic or pituitary in etiology). Causes of primary failure include radiation therapy, trauma, infection (mumps), and ischemia (torsion). Common medications, including opioids, suppress release of GnRH from the hypothalamus, and glucocorticoids, which bind to the gonadotropic cell receptors, result in central suppression of the hypothalamus and pituitary. Milder forms of hypogonadism exist and are associated with aging and chronic disease.

FIGURE 1 GnRH Acts on the Anterior Pituitary to Stimulate Release of LH and FSH



In men's testes, LH stimulates testosterone synthesis by Leydig cells, and FSH stimulates spermatogenesis by Sertoli cells. Testosterone then feeds back to the hypothalamus and pituitary, completing a negative feedback loop. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; T = testosterone.

LABORATORY DIAGNOSIS. The laboratory diagnosis of hypogonadism requires documentation of low serum T levels on at least 2 morning samples drawn before 10 AM. Free T is considered the better test because total T can be elevated in situations of elevated SHBG (aging), or the total can be low when SHBG levels are reduced (diabetes, obesity). An analysis for FSH and LH should be done to distinguish between primary versus centrally mediated hypogonadism. If a pituitary tumor is of concern, then a prolactin level should be obtained. Although most agree that a total T of <300 ng/dl is considered low, it is best to use the normal ranges of the specific laboratory making the measurement.

SIGNS AND SYMPTOMS OF HYPOGONADISM. Signs and symptoms of hypogonadism (Central Illustration) are related to the patient's age. For example, delayed puberty is clearly a problem of congenital or childhood-associated hypogonadism. However, the changes in a post-pubertal male can be much more subtle. The Endocrine Society diagnostic guidelines for hypogonadism require both documentation of serum gonadal tests (at least 2 morning samples) and