MAYO CLINIC

REVIEW

Testosterone and Cardiovascular Health

Andrew Elagizi, MD; Tobias S. Köhler, MD, MPH; and Carl J. Lavie, MD

Abstract

There is an ongoing debate in the medical community regarding the effects of testosterone on cardiovascular (CV) health. For decades, there has been conflicting evidence regarding the association of endogenous testosterone levels and CV disease (CVD) events that has resulted in much debate and confusion among health care providers and patients alike. Testosterone therapy has become increasingly widespread, and after the emergence of studies that reported increased CVD events in patients receiving testosterone therapy, the US Food and Drug Administration (FDA) released a warning statement about testosterone and its potential risk regarding CV health. Some of these studies were later found to be critically flawed, and some experts, including the American Association of Clinical Endocrinologists and an expert panel regarding testosterone deficiency and its treatment, reported that some of the FDA statements regarding testosterone therapy were lacking scientific evidence. This article summarizes the current evidence regarding the relationship between testosterone (endogenous and supplemental) and CV health. A literature review was conducted via search using PubMed and specific journal databases, including the *New England Journal of Medicine* and the *Journal of the American College of Cardiology*. Key search terms included *testosterone and cardiovascular health*, *coronary artery disease*, *heart failure*, *androgen deprivation therapy*, *intima-media thickness*, and *adrenal androgens*. Initial study selection was limited to publications within the past 10 years (January 1, 2007, through December 31, 2016); however, key publications outside of this time frame were selected if they provided important quantitative data or historical perspectives for the review of this topic. The search was further supplemented by reviewing references in selected articles.

 ■ Mayo Clin Proc. 2018;93(1):83-100

There is an ongoing debate in the medical community regarding the effects of testosterone on cardiovascular (CV) health. The combination of the male preponderance of coronary artery disease (CAD), the protective effects of estrogen in premenopausal women, and the increased incidence of CV disease (CVD) death in men abusing anabolic steroids led to the belief that testosterone is deleterious to the male heart.[1] Contrary to this view, there is mounting evidence that normal physiologic levels of testosterone are beneficial to the male CV system and that testosterone deficiency is associated with an unfavorable metabolic profile, including increased adiposity, insulin resistance, diabetes, and adverse CVD events, such as myocardial infarction (MI) and mortality.[2-12] Despite the recurrence of these trends in the literature, no causal association has been proved, and results have been conflicting.

Androgen deprivation therapy (ADT) in patients with prostate cancer has been studied in an attempt to identify an association between testosterone depletion and increased CVD events, which would possibly suggest a causal link between testosterone deficiency and CVD events. The effects of testosterone replacement therapy on CV health has also been intensely scrutinized, with mixed results in the literature. There are multiple reasons for the controversy regarding this therapy, including variability in study designs, variability in definitions of CVD events, and underpowered studies that are unable to draw conclusions about various study outcomes. Also, the Food and Drug Administration (FDA) issued a safety warning regarding the use of testosterone-containing products due to a potential risk of CV harm after the release of studies that reported increased CVD events in patients receiving testosterone therapy, which were later found to be critically flawed. Some experts felt that aspects of the FDA position on testosterone therapy were lacking scientific evidence.[6,13] The aim of this report is to explain the controversy and clarify what the current scientific evidence indicates regarding

From the Department of Internal Medicine, Leonard J. Chabert Medical Center, Houma, LA (A.E.); Department of Urology, Mayo Clinic and Mayo Clinic College of Medicine, Rochester, MN (T.S.K.); and Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School—The University of Queensland School of Medicine, New Orleans, LA (C.J.L.).

ARTICLE HIGHLIGHTS

- Normal physiologic levels of testosterone are beneficial to the male cardiovascular (CV) system, and testosterone deficiency is associated with an unfavorable metabolic profile and increased CV disease events.
- The Food and Drug Administration, the American Association of Clinical Endocrinologists/American College of Endocrinology, and an international consensus panel all state that testosterone therapy is safe and reasonable in patients with symptomatic testosterone deficiency.
- Testosterone treatment should be considered for symptomatic men with clinically confirmed hypogonadism; there is no compelling evidence that testosterone therapy either increases or decreases CV disease risk, and testosterone therapy for men with hypogonadism is effective, rational, and evidence based.
- A major research initiative is needed to explore the possible cardioprotective effects of testosterone therapy.

the relationship between both endogenous testosterone levels and testosterone therapy and CV health and to summarize current recommendations and directions for future research.

A literature review was conducted via search using PubMed and specific journal databases, including the *New England Journal of Medicine* and the *Journal of the American College of Cardiology*. Key search terms included *testosterone and cardiovascular health*, *coronary artery disease*, *heart failure*, *androgen deprivation therapy*, *intima-media thickness*, and *adrenal androgens*. Initial study selection was limited to publications in the past 10 years (January 1, 2007, through December 31, 2016); however, key publications outside of this time frame were selected if they provided important quantitative data or historical perspectives for the review of this topic. The search was further supplemented by reviewing references in selected articles.

ANDROGENS IN THE MALE

Under the control of the pituitary hormones luteinizing hormone and follicle-stimulating hormone (FSH), the Leydig cells of the testes produce testosterone. In males, 95% of circulating testosterone is derived from testicular production (3-10 mg/d).[14] Testosterone causes virilization of the external male genitalia during embryonic development, promotes somatic growth and secondary sexual characteristic development (adrenarche) in puberty, and is necessary for spermatogenesis, stimulation of libido, normal sexual function, and maintenance of muscle and bone mass in adults.[14] Androgen deficiency may be caused by gonadotropin deficiency or primary testis dysfunction. The effects of testosterone include bone formation, increased muscle mass, spermatogenesis, prostate growth, acne, facial/body hair development, and scalp hair loss.[14] Excess testosterone and testosterone therapy have been associated with worsening of sleep apnea, gynecomastia, polycythemia, and prostate-specific antigen level elevation.[15]

UNDERSTANDING THE CONTROVERSY

Several studies have reported an inverse association between endogenous testosterone levels and adverse CVD outcomes, independent of traditional risk factors.[16] These findings suggested a possible cardioprotective effect of testosterone, which may, in part, have led to significant increases in prescriptions for testosterone in the following years.[17,18] One study collected data for testosterone product sales from 2000 through 2011 for 41 countries, including the United States, Canada, the United Kingdom, and Australia, and found that total testosterone sales increased 12-fold globally, rising from $150 million in 2000 to $1.8 billion in 2011.[18] The most dramatic increases in testosterone use were seen in Canada and the United States.

Following the trend of increased testosterone prescriptions, trials emerged that found an increased CVD risk with testosterone therapy. The FDA began investigating the potential increased risk of CVD events with testosterone therapy in 2010 owing to premature cessation of the Testosterone in Older Men With Mobility Limitations (TOM) trial,[19] which was stopped before enrollment was completed due to the higher incidence of CVD events in the testosterone treatment group.[20] The TOM trial was critiqued for the lack of a consistent pattern of CVD events, which ranged from edema to MI and death, as well as the small sample size and small number of CVD events (CVD events occurring in 23 patients in the

Mayo Clin Proc. ■ January 2018;93(1):83-100 ■ https://doi.org/10.1016/j.mayocp.2017.11.006
www.mayoclinicproceedings.org