Trends in Cardiovascular Medicine 25 (2015) 250–257

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/tcm

Testosterone therapy and cardiovascular risk

James P. Walsh, MD, PhD[a,b,*], *and Anne C. Kitchens, MD*[a]

[a]*Division of Endocrinology, Indiana University School of Medicine, Indianapolis, IN*
[b]*Endocrinology Section, Roudebush Veterans Affairs Medical Center, Indianapolis, IN*

ABSTRACT

Endogenous testosterone levels are inversely associated with cardiovascular risk in older men and men with cardiovascular disease. Current data on cardiovascular outcomes of testosterone therapy include only observational studies and adverse event monitoring in short-term trials that were not designed to measure cardiovascular outcomes. These studies have yielded conflicting results, and some have raised concerns that testosterone therapy may increase cardiovascular risk. A well-designed, adequately powered, prospective trial will ultimately be required to clarify whether testosterone therapy impacts cardiovascular outcomes. This review describes the findings and limitations of recent studies of cardiovascular risk in older men on testosterone therapy and discusses some of the mechanisms through which testosterone may modify cardiovascular risk.

Introduction

Serum testosterone declines gradually as men age. About 20% of healthy men over the age of 60 years have a total testosterone below the normal range determined in healthy young men [1]. The high prevalence of lower testosterone in older men and aggressive marketing of new formulations for nonspecific symptoms have resulted in a marked increase in testosterone prescribing over the last decade [2–4]. In addition, men receiving testosterone are often not being diagnosed or monitored in accordance with the current guidelines [4]. Testosterone replacement in younger men with diseases of the pituitary–gonadal axis is clearly beneficial, but there are little data on the risks or benefits of testosterone in men with age-related declines in testosterone. Controversy over the risks of testosterone is thus focused on older men without demonstrable pituitary–gonadal disease.

It has been suggested that testosterone may be associated with cardiovascular (CV) risks based on gender differences in atherosclerotic disease and observations of CV events in anabolic steroid abusers [5]. More recent studies demonstrating that low testosterone in men is inversely associated with CV risk have led to suggestions that testosterone replacement may be beneficial [6]. Safety concerns about testosterone came to the forefront after the recent publication of two observational studies suggesting associations of testosterone therapy with adverse CV outcomes [7,8]. These studies were widely covered by the media, and cardiologists are likely to see patients with questions about testosterone and CV risk. This article reviews testosterone's CV effects in adult men, focusing on recent clinical studies. While there are concerns that testosterone therapy may increase CV events in older men, limitations of existing data leave significant uncertainty. A well-designed, adequately powered, prospective trial of testosterone therapy focused on CV outcomes will be required to address these questions.

Physiology of testosterone actions on the vasculature

The gonadal axis in adult men is regulated by gonadotropin-releasing hormone (GnRH) from the hypothalamus

The authors have no conflicts of interest to disclose.

*Corresponding author at: Endocrinology Section, Roudebush VAMC, 1481 West Tenth Street, Indianapolis, IN 46202. Tel.: +1 317 988 3073; fax: +1 317 988 2641.
E-mail address: jpwalsh@iu.edu (J.P. Walsh).

http://dx.doi.org/10.1016/j.tcm.2014.10.014
1050-1738/Published by Elsevier Inc.

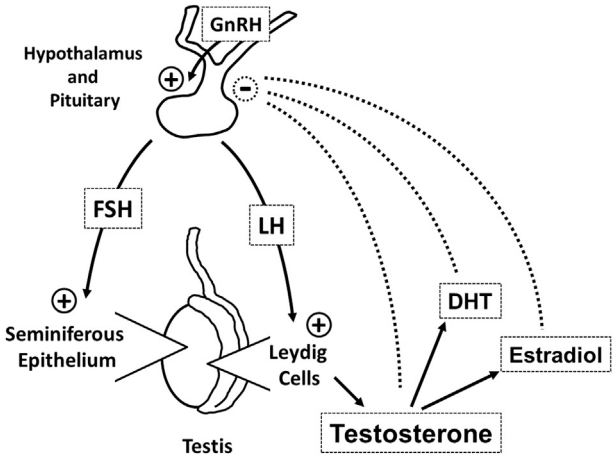

Fig – Regulation of the pituitary–gonadal axis in adult men. The pituitary is stimulated by gonadotropin-releasing hormone (GnRH) from the hypothalamus to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Luteinizing hormone stimulates testosterone synthesis in the Leydig cells of the testis, while FSH stimulates spermatogenesis. Testosterone is converted in peripheral tissues to two other hormones: dihydrotestosterone (DHT) and estradiol. Testosterone, DHT, and estradiol all feedback to the hypothalamus and the pituitary to inhibit secretion of GnRH, LH, and FSH.

(Fig.). GnRH stimulates secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary [9]. Luteinizing hormone acts on Leydig cells in the testis to stimulate testosterone synthesis, while FSH acts on Sertoli cells in the seminiferous tubules to stimulate spermatogenesis [9]. Testosterone binds to cytosolic androgen receptors found in most tissues [10]. The testosterone–androgen receptor complex migrates to the nucleus, where it stimulates transcription of numerous genes. There is also evidence for nongenomic testosterone actions through both a membrane-associated form of the classical androgen receptor and a distinct receptor with pharmacologic characteristics of a heterotrimeric G protein-coupled receptor [11].

Testosterone is a prohormone. It is converted to estradiol in many tissues by aromatase, which is expressed in many CV cell types. Circulating estradiol levels in adult men are 10–20% of those in premenopausal women. Testosterone is also converted to dihydrotestosterone by 5α-reductase. Circulating dihydrotestosterone levels are lower than those of testosterone, but dihydrotestosterone is a more potent androgen than testosterone and contributes significantly to testosterone's effects. Testosterone, dihydrotestosterone, and estradiol exert negative feedback at the hypothalamus and pituitary to inhibit LH and FSH release [9].

Most circulating testosterone is bound to sex hormone-binding globulin (SHBG) or albumin [12]. Only 1–3% of total testosterone is not bound to plasma proteins. This unbound, free testosterone is the biologically active hormone fraction. Many clinical conditions alter SHBG concentrations and cause corresponding changes in total testosterone. Obesity, type 2 diabetes, nephrotic syndrome, hypothyroidism, and glucocorticoids decrease SHBG, whereas advanced age, cirrhosis and hepatitis, hyperthyroidism, some anticonvulsants, estrogens, and HIV infection increase SHBG [12]. Total testosterone should not be used to diagnose hypogonadism when a condition that alters SHBG is present. In this situation, it is important to use free rather than total testosterone. Widely available direct free testosterone assays lack precision [12]. A calculated free testosterone is a better marker. Serum testosterone also undergoes diurnal variation driven by nocturnal LH surges from the pituitary. Levels rise overnight and then decline through the day [12]. A diagnosis of hypogonadism should be based on testosterone measurements early in the morning when levels are at their peak.

Testosterone and dihydrotestosterone exert numerous CV actions through androgen receptors in the endothelium, vascular smooth muscle, and cardiomyocytes [13]. Estrogen, which is derived from testosterone, also has direct CV effects. In addition, sex steroids modulate inflammation, coagulation, and other functions that indirectly affect the vasculature [13,14]. Rapid CV actions of sex steroids, such as vasodilation, are mediated by nongenomic pathways [11,15,16]. Longer term actions occur via testosterone's transcriptional pathway [17]. Numerous effects of testosterone on CV physiology have been described, and plausible mechanisms for beneficial or adverse clinical outcomes of testosterone therapy can be proposed [13,14]. It is thus difficult to predict effects of testosterone on cardiovascular events based on its physiologic actions. Clinical trials are needed to clarify the CV outcomes of testosterone therapy in older men.

Endogenous testosterone in older men

In healthy men, total testosterone declines about 10% per decade after the age of 40–50 years [18]. Low testosterone is also associated with many chronic conditions. Obesity is strongly associated with low testosterone, and levels recover with weight loss [19]. Other conditions associated with low testosterone include sleep apnea, type 2 diabetes, hypertension, hyperlipidemia, C-reactive protein and other inflammatory markers, chronic kidney disease, chronic obstructive pulmonary disease, HIV/AIDS, and chronic opioid use [20]. Levels of LH and FSH do not increase in response to the declining testosterone and generally remain in the normal range. Many, but not all, studies have found low testosterone to be associated with CV disease. A recent meta-analysis of prospective observational trials found inverse associations of testosterone with all-cause and CV mortality [21]. Inverse associations with incident CV events have also been noted, but only in studies that included men over 70 years of age [6]. The relative risk for an increase of one standard deviation of testosterone was 0.84 (95% CI: 0.76–0.92). Another meta-analysis confirmed the association of low testosterone with mortality but failed to demonstrate a significant association with incident CV disease [22]. The point estimate suggested increased CV disease incidence with lower testosterone, but the 95% CI included no effect. In men with chronic heart failure, testosterone is inversely associated with the New York Heart Association class, and lower testosterone predicts reduced 3-year survival [23].