Testosterone and the Prostate

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ABSTRACT

Introduction. Late-onset hypogonadism, lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE), and prostate cancer commonly coexist in the aging male. Due to a better understanding of the physiology and impact of testosterone on benign and malignant diseases of the prostate, the view toward testosterone replacement therapy (TRT) in these individuals has changed dramatically over time.
Aim. This communication evaluates the effects of testosterone on benign prostatic growth and prostate cancer and reviews the evidence for TRT for men with BPE and prostate cancer.
Methods. A literature review was performed with regards to TRT in men with prostate cancer as well as the effect of testosterone on the growth of benign prostate tissue and prostate cancer carcinogenesis.
Main Outcome Measure. To evaluate the evidence for an effect of testosterone on the growth of benign prostate tissue and the development of prostate cancer and TRT in men with prostate cancer.
Results. TRT does not exacerbate LUTS. Current evidence is lacking but suggests that TRT may not increase the risk of subsequent diagnosis of prostate cancer, and is unlikely to impact recurrence or progression for men with treated prostate cancer, but longer follow-up is needed.
Conclusions. There is no evidence to suggest that TRT is contraindicated in men with BPE or effectively treated prostate cancer. **Tan RBW, Silberstein JL, and Hellstrom WJG. Testosterone and the prostate. Sex Med Rev 2014;2:112–120.**

Key Words. Testosterone Replacement Therapy; Testosterone Deficiency Syndrome; Late-Onset Hypogonadism; Prostate Cancer; Radical Prostatectomy; External Beam Radiotherapy; Brachytherapy; Saturation Model; Androgen Receptors

Introduction

Testosterone deficiency (TD) has been a topic of interest since the beginning of time, with the aging male always striving to regain his lost manhood with an elixir from the fountain of youth. The taboo effects of the androgen "elixir" surfaces with Huggins' Nobel prize publication [1] that castration and diminishing serum androgen levels slows down the growth of prostate cancer and the largely erroneous assumption that administering androgens to a hypogonadal man promotes the growth of prostate cancer. Only with the dissemination of the saturation model [2] many years later did patients diagnosed with the most common cancer in males in the United States start to benefit from testosterone replacement therapy (TRT). Besides prostatic cancer, there is also concern with regards to lower urinary tract symptoms (LUTS) from benign prostatic obstruction due to the effect of dihydrotestosterone (DHT) on benign prostatic hyperplasia (BPH). A number of important clinical questions arise with respect to who, and under what circumstances, patients should receive TRT: Are patients who are already experiencing problems from an enlarged prostate

Table 1 Causes of alterations in SHBG concentration

Increased SHBG	Decreased SHBG
HIV infection	Use of opioids
Liver cirrhosis	Use of androgenic steroids
Use of estrogens	Nephrotic syndrome
Use of anticonvulsants	Use of glucocorticoids
Hyperthyroidism	Hypothyroidism
Aging (1%/year)	Moderate obesity

HIV = human immunodeficiency virus; SHBG = sex hormone-binding globulin.

at risk of deteriorating LUTS? What about patients who have no LUTS? Will TRT bring with it another set of clinical problems requiring curative polypharmacy and possible adverse sexual dysfunction effects from alpha-blockers and 5-alpha reductase inhibitors? Is it safe to provide TRT to men with a history of high-grade or margin-positive prostate cancer?

Endogenous Testosterone

Testosterone is a steroid hormone that is produced primarily by the Leydig cells of the testes, with the adrenals contributing a smaller percentage. The testes produce 3–10 mg of testosterone daily, corresponding to serum concentrations of 10.4–34.7 nmol/L (300–1,000 ng/dL) that peak in the morning. Testosterone acts directly on androgen receptors (AR) and via its conversion into two active metabolites, DHT (by the enzyme 5-alpha reductase) and estradiol (by the enzyme aromatase). Both testosterone and estradiol negatively feedback on the hypothalamus and pituitary to suppress gonadotropin secretion.

Testosterone is secreted according to a circadian rhythm, with peaks in the morning and troughs during evening hours. This rhythm is noted to be blunted in men older than 60 years [3]. Total testosterone is 58% loosely bound to albumin, 40% tightly bound to sex hormone-binding globulin (SHBG), and the remaining 0.5–2% circulates freely (free testosterone), which is the fraction taken to be biologically active [4]. Bioavailable testosterone refers to free plus albumin-bound testosterone owing to the fact that since testosterone is loosely bound to albumin, it dissociates during tissue transit and becomes bioavailable [5]. However, the level of SHBG can change under different circumstances, and thereby affect the bioavailable testosterone (Table 1).

Is Testosterone Fully Responsible for Benign Prostatic Growth?

In the human embryo, the development of Wolffian-derived sex accessory glands is stimulated by testosterone, while prostatic growth is influenced by DHT. In the early postnatal periods, there is an involution of the gland due to maternal estrogens, followed by a surge in testosterone. These hormone-imprinting events are fundamental to the long-term growth of the prostate gland. The AR gene contains a polymorphic region in exon 1 that consists of variable CAG microsatellite repeats that are associated with differences in AR activity. The shorter the CAG repeat length, the higher the activity of the AR. It has been demonstrated that estrogen increases the nuclear AR content in the prostate cell and the length of CAG repeats of the AR influence the action of both androgens and estrogens [6]. Coetzee and Ross first suggested that variations in CAG repeat length is associated with prostate cancer [7]. Many studies on the relationship between CAG repeat length and prostate cancer have conflicting results. A nested case–control study of 1,159 cases and 1,353 controls from the Prostate Cancer Protection Trial (PCPT) showed that there is no association of AR CAG repeat length with prostate cancer risk and the knowledge of AR CAG repeat length provides no clinically useful data to predict the risk of prostate cancer [8]. The prostate gland is composed of epithelial cells, basal cells, neuroendocrine cells, stromal cells, tissue matrix, and even stem cells. This makes the effect of testosterone on the prostate gland somewhat complex. This is especially the case in stromal–epithelial interactions where androgens, estrogens, prolactin, and other growth factors working through the endocrine system, paracrine mechanisms are involved in regulating the growth of the prostate [9].

It is generally believed that DHT is produced from the 5-alpha reduction of circulating testosterone before being inactivated by 3-alpha-hydroxysteroid dehydrogenase, which converts DHT into 5α–androstane–3α,17β-diol. A nested case–control study [10] of serum steroid concentrations and risk factor for developing BPH, using data from the placebo arm of the PCPT, showed that high testosterone levels, estradiol levels, and testosterone : 17β-diol-glucuronide ratio are associated with reduced BPH risk, which may reflect decreased activity of 5-alpha reductase. Hence these scientific observations refute a common misconception that high serum levels of testosterone from TRT would result in BPH. It is also noted that the presence of various steroidogenic enzymes in the prostate and the availability of high levels of various steroid precursors such as dehydroepiandrosterone sulphate, dehydroepiandrosterone,