# Testosterone Deficiency and the Prostate

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**KEYWORDS**

• Testosterone deficiency • Benign prostatic hyperplasia • Prostate cancer • Dihydrotestosterone • Sexual development

**KEY POINTS**

- Testosterone and dihydrotestosterone are important to normal prostate development and function.
- Blockade of dihydrotestosterone production results in reduced prostate size and reduced risk of prostate cancer.
- Testosterone supplementation may alter prostate size.
- Further study of the prostate and its relationship to testosterone physiology is warranted.

## INTRODUCTION

The prostate is a male reproductive organ of both endodermal and mesodermal origin; it is located in the pelvis, immediately superior to the muscles of the pelvic floor. The prostate is intimately associated with the bladder neck and the posterior urethra, which it encircles. It has both a glandular and muscular component, which enables it to perform its unique function with respect to ejaculation. Prostatic secretions from the glandular component comprise most of the seminal fluid that is ejaculated; coordinated contractions of the muscular component (along with the muscles of the pelvic floor and the bladder neck) enable antegrade ejaculation of seminal fluid. The observation that the prostate is centrally important to reproductive function is an accurate one.

The growth and development of the functioning prostate depends on the actions of testosterone and its metabolite dihydrotestosterone (DHT). These two potent hormones enable in particular the growth and proliferation of the glandular component of the prostate through binding and activation of androgen receptor (AR) within the cytoplasm of prostatic epithelial cells.[1] Extensive research has established that the activation of this receptor also enables proliferative growth of this component, which in turn causes benign prostatic hyperplasia (BPH); in addition, this pathway enables carcinogenesis within prostatic epithelial cells, leading to prostate cancer (PCa).[2–4] Both diseases are common and burdensome conditions in aging men.[5,6] However, the relationship between testosterone and these two conditions is unclear; hypogonadism (low testosterone level), BPH, and PCa are all age-related conditions.

This article reviews the existing data regarding these relationships. Pharmacologic treatments for both conditions depend on manipulation of these pathways; this article reviews these treatments, as well as outlining future directions for treatment that are being explored. In addition, the need for further research into the nature of these two conditions is reviewed.

## EMBRYOLOGY OF THE PROSTATE

Prostate development is an early fetal event in all male mammals; in humans this event occurs at 10 to 12 weeks.[7] The prostate arises from the urogenital sinus, which consists of an epithelial

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layer (derived from endoderm) surrounded by a mesenchymal layer derived from mesoderm. Invagination of the epithelial folds into the mesenchyme results in the glandular architecture of the prostate.[8] The proliferation of these epithelial cells occurs under the influence of testosterone.[7]

Levels of testosterone in the male fetus are high; postpartum, this increase in testosterone level persists into the second year of life. Testosterone is also constantly being converted by the intracellular enzyme 5-alpha reductase (5-AR) into DHT.[7] DHT is a more potent activator of AR, binding to the receptor with a 10-fold greater affinity.[9] In the male fetus, DHT drives organogenesis of both the male external genitalia and the prostate. As testosterone levels decrease after the second year of life, DHT levels decrease correspondingly. High levels of 5-AR are found within cells of the prostatic epithelium as well as follicular cells of the scalp. This second fact is important given the observation the DHT levels in part drive male pattern baldness.[10]

Disruptions in these pathways can result in abnormal sexual differentiation and ambiguous genitalia; these intersex conditions are characterized by predictable phenotypes that relate to the disruption in question. For example, testicular feminization syndrome is characterized by normal-appearing female external genitalia.[11] This condition is caused on a cellular level by absent or nonfunctioning AR. In spite of increased testosterone and DHT levels, the cellular changes that result from activated AR do not occur. Importantly, patients with testicular feminization syndrome fail to develop a prostate (because of the absence of DHT activity). They do develop a normal female external phenotype because of conversion of testosterone into estrogen through action of the enzyme aromatase. This process, aromatization, is the only source of estrogen in male patients, and represents an important pathway for metabolism of testosterone. Aromatase is found in lipid cells, and aromatization can therefore be a more robust effect in obese patients. Patients with testicular feminization have a rudimentary vagina; however, there is an absent uterus, cervix, and proximal vagina. These structures fail to develop under the influence of a müllerian inhibiting substance (MIS), another important regulator of reproductive organogenesis in the fetus.[12] MIS is normally produced in the Sertoli cells of the male testis; in patients with testicular feminization, the testis is present (albeit undescended) and partly functional. The local actions of MIS in both types of patient (and the normal male fetus) include driving the regression of müllerian duct structures (which normally develop into the proximal portion of the vagina, the cervix, the uterus, and the fallopian tubes).[13]

Another condition that shows the role of AR in reproductive development is 5-alpha reductase deficiency, an autosomal recessive disease recognized in a small population of men from the Dominican Republic.[14] 5-AR–deficient patients are born phenotypically female, again in spite of normal levels of testosterone. The absence of activity of 5-AR results in deficient levels of DHT; without DHT there is a failure to drive organogenesis of normal male external genitalia. Normal production of MIS by Sertoli cells of the testis again results in regression of müllerian duct structures. During puberty, the larger spike in testosterone levels drives the development of a male external phenotype through adequate activation of AR (even without measurable levels of DHT). The result is that these patients are born appearing female, but eventually develop a male appearance. This phenomenon is recognized within this community and the transition these children make during puberty is anticipated as being fairly common. The absence of DHT throughout the adult life of these patients results in other important phenotypic traits. These patients are highly unlikely to develop urinary symptoms because of BPH, and they are less likely to develop prostate cancer or male pattern baldness.[15]

Other conditions resulting in incomplete virilization are well described, most importantly congenital adrenal hyperplasia.[16] In this spectrum of conditions resulting in varying degrees of ambiguous genitalia, there are defects in the steroid biosynthesis of testosterone. The result is varying deficiencies in terms of testosterone production as well as DHT levels (See Patricia Freitas Corradi, Renato B. Corradi, Loren Wissner Greene: Physiology of the Hypothalamic Pituitary Gonadal Axis in the Male, in this issue for further details).

## TESTOSTERONE AND PROSTATE GROWTH (PUBERTY, MIDDLE AGE, OLD AGE)

As boys enter puberty just after the age of 10 years, testosterone and DHT levels spike again in a predictable fashion, assuming an intact hypothalamic-pituitary-gonadal axis. This event drives the physical changes associated with sexual maturity as well as the onset of reproductive maturity[17]; spermatogonial stem cells in the testis begin to undergo meiotic division into spermatozoa. In the prostate, proliferation of prostatic epithelial cells initiates a period of prostate growth; in addition, prostatic secretion from these cells begins and patients begin to experience seminal emission.[18]