# REVIEWS

## Are Androgens Critical for Penile Erections in Humans? Examining the Clinical and Preclinical Evidence

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**ABSTRACT**

Androgens are deemed critical for penile-tissue development, growth, and maintenance of erectile function, however, their role in erection, especially in humans, remains controversial. In this review, we summarize information from clinical and animal model studies to provide a comprehensive and rational argument for the role of androgens, or lack thereof, on penile erection ability in humans. The goal of this review is to present the clinical and preclinical evidence available in the literature with regard to testosterone and erectile physiology and engage the reader in this discussion. Ultimately, each reader will have to form his or her own conclusions based on the existing evidence.

In humans, androgen-deficiency manifestations are noted in clinical situations such as: (i) inadequate development of the penis; and (ii) loss of erectile function in prostate cancer and benign prostatic hyperplasia patients managed with medical or surgical castration or antiandrogen therapy. Androgen treatment causes: (i) improvement in sexual function in hypogonadal patients treated with androgen supplementation; (ii) improvement in nocturnal penile tumescence in hypogonadal patients treated with androgens; (iii) improvement in erectile function with androgen supplementation in patients who did not respond to phosphodiesterase type 5 inhibitor therapy initially; and (iv) improvement in the well-being, mood, energy, and sexual function in aging men who have testosterone deficiency treated with androgen therapy. In contrast to animals, especially rodents in which the adrenal cortex does not synthesize androgens, the human adrenal is a source of peripherally circulating androgen precursors, thus, complete androgen insufficiency may not be observed in men at a younger age. Furthermore, in light of the concept that a threshold of androgen levels exists in animals and humans below which sexual function is diminished, further contributes to the complexity of understanding androgens role in erections, especially in humans. Nevertheless, based on the preclinical and clinical data available in the literature, to date, we infer that androgens play a critical role in maintaining erectile physiology in humans. **Traish AM, and Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. J Sex Med 2006;3:382–407.**

***Key Words.*** Endocrinologic Studies of Sexual Function; Phosphodiesterases; Hypogonadism; Sex-Steroid Replacement

### Overview of the Role of Androgens in Erectile Physiology

Erectile function is a complex neurovascular process, regulated by multiple biochemical and physiological factors. Normal penile erection is dependent on the overall health of the individual, the penile vascular bed, and the perineal and ischiocavernous muscles that support the proximal penis. Man's ability to achieve normal penile erections depends on adequate arterial blood inflow and trapping within the cavernosal bodies (veno-occlusion) to maintain increasing pressure and volume to achieve penile rigidity. The veno-occlusive mechanism depends on the integrity of neural, vascular, and endocrine systems as well as the fibroelastic properties of the corporal cavernosal tissue [1–3]. This observation was also made in animal models in which castration resulted in

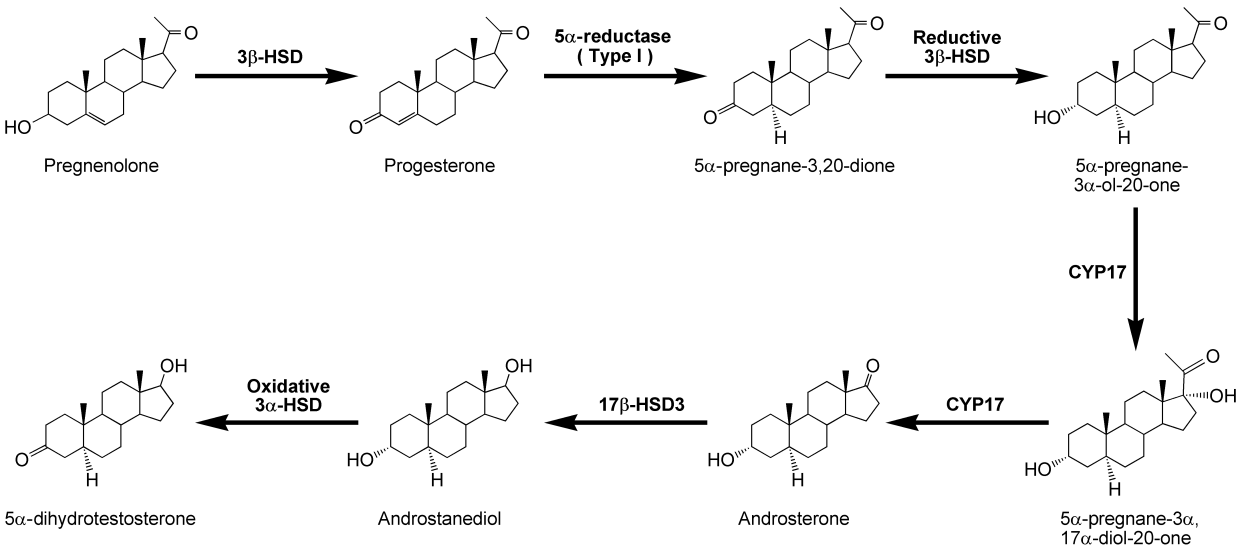


**Figure 1** Transformation of progesterone to 5α-DHT via the backdoor pathway (adopted from Auchus 2004 [7]). 5α-DHT, 5α-dihydrotestosterone; 3β-HSD, 3β-hydroxysteroid dehydrogenase, $\Delta^{4,5}$isomerase; CYP17, cytochrome P450c17,17-α-hydroxylase/17,20-lyase; 17β-HSD3, 17β-hydroxysteroid dehydrogenase type 3.

erectile dysfunction (ED) [4,5], indicating that alterations in penile-tissue structure in humans may be similar to those observed in laboratory animals.

### *Effects of Androgens on Sexual Organs*

Castration in rodents produces demonstrable changes in penile size, marked changes in sexual behavior, and reduced erectile function. This may be attributed to the fact that the rodents' adrenal does not produce sufficient androgen precursors [6]. Further, as shown in Figure 1, progesterone can be reduced and converted into 3α, 17β, 5 α-androstanediol, and ultimately to 5α-dihydrotestosterone (5α-DHT) without formation of testosterone [7]. This recently described "backdoor pathway" may mediate some of the androgen-dependent responses in humans that persist in spite of low levels of plasma testosterone.

Finally, while some clinicians hold the view that androgens are not critical for erections, this view may be distorted by the fact that the threshold of androgen levels required for maintaining erections in humans is lower than that needed for maintaining other tissue functions. Clearly, the clinical data from studies on prostate cancer with androgen ablation and in hypogonadal men with androgen deficiency suggest that the threshold levels of androgen needed for erectile function may indeed be lower than that needed for other tissue functions [8,9].

### *The Relationship Between Testosterone, Libido, and Other Aspects of Sexual Function*

It is well recognized that testosterone affects sexual function in men, but a good part of the literature on the subject discusses the relationship of hypogonadism to decreased sexual desire. Erections and sexual desire are two interrelated processes that vary significantly with androgen deprivation, but both tend to decline gradually and may disappear entirely, with some exceptions being noted [10]. This may be explained by the fact that the local biosynthesis of androgens from adrenal precursors could maintain some sexual function in some individuals.

Testosterone replacement has been used for the past six decades in the treatment of male hypogonadism [11]. Several forms of hypogonadism exist, including primary testicular failure or insufficient testicular stimulation due to the lack of pituitary gonadotropins. Primary hypogonadism is depicted in Klinefelter's syndrome, anorchia, or acquired disturbances of testicular function. Insufficient biosynthesis of pituitary gonadotropins, as a result of pituitary failure or hypothalamic suppression, is known as secondary hypogonadism.

In addition to hypogonadism attributed to endocrine disorders, advancing age causes a marked decline in androgen-plasma levels. It has been suggested that approximately 15–25% of men over the age of 50 years are expected to have serum-testosterone levels that fall below that of