REVIEWS

Medical Hypothesis: Loss of the Endocrine Function of the Prostate Is Important to the Pathophysiology of Postprostatectomy Erectile Dysfunction

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DOI: 10.1111/jsm.12574

ABSTRACT

Introduction. Three decades after the first nerve-sparing radical prostatectomy, postoperative erectile dysfunction (ED) remains a challenging and common problem. Despite considerable advances and improvements in surgical techniques, full recovery of erectile function remains elusive even for young, potent men. This suggests, ipso facto, that factors other than surgical technique must be important to recovery of erectile function.

Aim. This study aims to review evidence that the prostate is an endocrine gland with contributions to local and systemic concentrations of 5α-dihydrotestosterone (5α-DHT), a potent androgen shown to be critical to penile physiology.

Methods. Literature review of human and animal studies related to endocrine role of prostate and postoperative recovery of erectile function.

Main Outcome Measures. Effect of 5α-DHT on erectile function and recovery after surgical injury.

Results. We advance the following hypothesis: "Loss of endocrine function of the prostate, specifically reduced local 5α-DHT concentration plays a major role in the failure of full recovery of erectile function following anatomic nerve-sparing radical prostatectomy."

Conclusions. We propose two separate, yet interrelated, mechanisms whereby the loss of 5α-DHT interferes with postoperative recovery of erectile function: (i) 5α-DHT contributes to cavernous nerve integrity and its ability to recover from surgical insult. (ii) 5α-DHT is important to the structural/functional integrity of penile tissues and erectile physiology. **Kacker R, Morgentaler A, and Traish A. Medical hypothesis: Loss of the endocrine function of the prostate is important to the pathophysiology of postprostatectomy erectile dysfunction. J Sex Med 2014;11:1898–1902.**

Key Words. Dihydrotestosterone; Prostate; Erectile Dysfunction; Androgens; 5α-reductase

Sexual Function after Nerve-Sparing Radical Prostatectomy

Since the introduction of the anatomic nerve-sparing radical prostatectomy over 30 years ago [1], prostatectomy has become one of the most commonly utilized treatments for localized prostate cancer. Although preservation of the neurovascular bundles clearly improved erectile outcomes compared with non-nerve sparing surgery, recovery of erections is far from universal and significant recovery of erectile function within the first year of surgery remains uncommon [2]. In a longitudinal study of 1,291 men who underwent bilateral nerve-sparing radical prostatectomy, 56% of men reported erectile dysfunction (ED) 18 months after therapy [3].

The time to erectile function recovery is notably longer than the expected time to recovery from intimate dissection of nerves in other surgical specialties. For example, during radical neck dissection the spinal accessory nerves are susceptible

to crush, stretch, and thermal injury. As with cavernous nerves after radical prostatectomy, an initial period of nerve dysfunction is common. However, unlike radical prostatectomy, there is a near universal return of full nerve function by 6 months [4]. Similarly, radial nerve injury may occur after fracture of the humerus and most cases recover spontaneously within 3–6 months [5]. Complete recovery from isolated neuropathy of smaller nerves, such as the branches of the anterior interosseous nerve, typically occurs after 2–3 months [6].

In contrast, early recovery of satisfactory erectile function is uncommon after radical prostatectomy. Despite introduction of the sophisticated robotic-assisted surgeries and additional technical modifications to minimize neuropraxia, only 15% of previously potent men exhibited any recovery of erectile function within 5 months [7]. The long delay before return of erections can lead to penile structural changes that eventually compromise erectile quality, even with aggressive penile rehabilitation approaches. For men under the age of 50 years, with excellent preoperative erectile function, approximately 30% will not have functional erections 2 years after bilateral nerve-sparing radical prostatectomy and many more will never attain their preoperative erectile function [8]. The persistence of ED after three decades of refinement in nerve-sparing techniques clearly indicates that factors other than purely mechanical injuries to the cavernous nerves must be at play. One logical possibility is that it is the very absence of the prostate that contributes to the failure of erections to recover fully after radical prostatectomy, specifically its endocrine function.

Endocrine Function of the Prostate

Considerable literature exists that points toward a role for the prostate as an important endocrine gland regulating local and systemic androgen levels [9–12]. Testosterone is converted to the more potent androgen 5α-dihydrotestosterone (5α-DHT) by a family of three 5-α-reductase (5α-Rs) isozymes, which are expressed in the prostate, liver, skin, and other tissues [13]. In addition to testosterone, 5α-Rs isoforms also metabolize aldosterone, progesterone, and corticosterone to their respective 5α-dihydro-derivatives, which serve as substrates for 3α-hydroxyl-steroid dehydrogenases, producing a host of neuroactive steroids that modulate a variety of functions in human physiology [14]. In the prostate, the type II isoform of 5α-R predominates and is expressed primarily in the stromal cells and basal epithelium. 5α-DHT is primarily formed from transformation of testosterone but may also be formed through a testosterone-independent pathway that utilizes androstenedione with subsequent 5α-reduction (*the backdoor pathway*) [15]. With its high expression of 5α-R type II, the prostate contains high concentrations of 5α-DHT and is a major contributor to local and systemic 5α-DHT concentrations [9,10].

Miller et al. [11] observed an approximately 15% decreased serum 5α-DHT levels 1 year after prostatectomy, despite increased serum testosterone and gonadotrophin. In a more recent study of 55 men, serum 5α-DHT levels were decreased by 13% at 3 months after prostatectomy with significant increases in gonadotropins [10]. Yu et al. [16] reported that luteinizing hormone, follicular stimulating hormone and testosterone levels were significantly higher 3 years after prostatectomy when compared with the same period in the same patients prior to prostatectomy, suggesting a feedback mechanism from the prostate on the pituitary gonadal axis. These studies support an endocrine role for the prostate, especially in maintaining systemic 5α-DHT levels. In a follow-up study of 24 men undergoing prostatectomy, 5α-DHT levels in local veins near the prostate were more than four times higher than systemic levels. Local 5α-DHT levels and prostate weight correlated with systemic 5α-DHT levels [9]. These results suggest that the prostate is not only a major source of systemic 5α-DHT but also maintains elevated local and regional 5α-DHT levels. The prostate may also exert control over local and regional 5α-DHT levels as a major site of metabolism and elimination of 5α-DHT as 5α-DHT is conjugated by uridine diphospho-glucoronosyl transferase (UGT) enzymes to form more soluble metabolites for elimination and these UGT enzymes are highly expressed in human prostate tissues [12]. Serum concentrations of 5α-DHT metabolites correlate with prostate volume [16].

5α-DHT and Cavernous Nerve Recovery and Function

Androgens have been suggested to be critical for penile nerve network function [17] and androgen deprivation alters the structural integrity of the cavernous nerve [18] as well as the dorsal nerve networks [19,20], and this is thought to be reversed by androgen administration [18–20]. The