Androgens and Erectile Function: A Case for Early Testosterone Replacement Following Radical Prostatectomy

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Neither I or my partner have any relevant commercial financial relationships to disclose.

Can testosterone replacement therapy in a hypogonadal post-prostatectomy patient improve erectile function rates?

- Objectives
  Counsel patients on the importance of testosterone in erectile function; develop and implement a treatment plan
  Manage patient hormone therapy for erectile function following radical prostatectomy
Are Urologist Implementing Erection Preservation Programs?

- Survey of 301 Urologists from 41 countries: 83.7% offered some type of erection preservation program
  - 95.4% - PDE-5i
  - 75.2% - ICI
  - 30.2% - VED
  - 9.9% - MUSE
- Timing of initiating program
  - 48.1% - after the urethral catheter came out
  - 36.8% - within 4 months of RRP

Teloken et al. J Sex Med 2006; 394

Basic Science Evidence
Androgens and Erectile Function

- Nitric Oxide Synthase
- Phosphodiesterase Type 5 Activity
- Androgens
- Veno-occlusive Erectile Function
- Penile Nerve Function

Androgens Regulate NOS Activity

- Androgens regulate the expression of nNOS and eNOS in corpora cavernosa \(^1\)^ \(^2\)
- Castrated animals have a significant decrease in nNOS expression in the penis \(^2\)
- Testosterone replacement results in normal nNOS expression in penile nerve fibers \(^3\)
- NO-mediated relaxation of cavernosal smooth muscle is thought to be androgen dependent \(^3\)

\(^1\) Baba et al. BJU Int 2000; 85;953
\(^3\) Syme et al. J Urol. 2007 Jan;177(1):390-4

Androgens Regulate Phosphodiesterase type 5 (PDE5) Expression

- Organ bath assays with isolated cavernosal strips: \(^1\) \(^3\)
  - Androgen deprivation reduced the muscle relaxation effects of PDE5 inhibitor (sildenafil) after nerve stimulation
  - Testosterone replacement restored this muscle relaxation effect
- PDE5i were administered to castrate and control animals before pelvic nerve stimulation \(^1\)
  - Control- PDE5i significantly enhanced intercavernosal pressures (ICP)
  - Castrate- PDE5i did not enhance ICP

\(^1\) Traish et al. Endocrinology 1999; 140:1861
\(^2\) Morelli et al. Endocrinology 2004; 145:2253
\(^3\) Traish et al. J Androl 2003; 24:381
Androgens and Penile Nerve Function

- 45 rats underwent bilateral cavernosal neurotomy
- All had unilateral nerve graft using the genitofemoral nerve
- Rats randomized to castrate, intact (non-castrate), and testosterone treated (supraphysiological levels) arms
- At 3 months, grafts were explored and electrostimulation was performed with intracavernous pressure responses recorded


Androgens and Penile Nerve Function

- Animals were treated for 7 days with vehicle alone, testosterone, or estradiol one week after bilateral orchiectomy
- Intact control animals received vehicle only
- Systemic arterial blood and intracavernosal pressures (ICP) were measured in each animal before and after electrical stimulation of the cavernosal nerve

Traish et al. Endocrinology 1999; 140:1861

Results

Traish et al. Endocrinology 1999; 140:1861

PNS= Peripheral Nerve Stimulation
Androgens and Erectile Function

Nitric Oxide Synthase
Phosphodiesterase Type 5 Activity
Androgens
Veno-occlusive Erectile Function
Penile Nerve Function

Androgens and Erectile Function

Loss of Fibroelastic Properties
Increased Deposition of Connective Tissue
Veno-occlusive Erectile Dysfunction
Increased Subtunical Fat Deposition
Loss of Trabecular Smooth Muscle

Androgens and Corpora Cavernosa Fibroelastic Properties

- Tunica albuginea of corpora cavernosa of animals 4 weeks after castration were compared to controls
- Thickness of the tunica albuginea
  - Controls = 0.16 ± 0.03 mm
  - Castrated = 0.04 ± 0.01 mm
  \( p<0.05 \)
- Elastic fibers in the tunica were replaced by collagen fibers resulting in a loss of its elasticity


Controls Castrate

[Diagrams of controls and castrate showing changes in tissue structure]
Androgens and Cavernosal Connective Tissue

- Decreased androgens result in increased connective tissue and corporal fibrosis by casing a:
  - Decrease in:
    - Vascular Endothelial Growth Factor (VEGF),
    - Fibroblast Growth Factor (FGF)
    - Insulin-like Growth Factor (IGF-1)
  - Up-regulation of:
    - Connective tissue growth factor (CTGF)
    - Transforming Growth Factor Beta 1 (TGF-β1)

$$\downarrow \text{Androgens} = \uparrow \text{corporal fibrosis}$$


Androgens and Cavernosal Smooth Muscle

- Animals were treated for 7 days with vehicle alone, testosterone, or estradiol one week after bilateral orchiectomy
- Intact control animals received vehicle only
- Smooth muscle content was assessed by Masson’s trichrome staining and computer-assisted histomorphometry

Traish et al. Endocrinology 1999; 140:1861

C= control, V= castrate, T= testosterone treated, E= estradiol treated

Results

Traish et al. Endocrinology 1999; 140:1861
Results

Androgens and Subtunical Adipose Deposition

• Penile tissue from orchiectomized animals demonstrated subtunical adipose deposition.¹
• Differentiation of pluripotent stem cells are androgen dependent and testosterone promotes muscle lineage and inhibits adipogenic lineage.²

² Singh et al. Endocrinology 2003; 144:5081.

Clinical Evidence
Testosterone Alone to Treat ED

- Chang et al.
  - 40 men with ED
  - DB, R, PCT
  - Results (IIEF-5)
    - Intervention: 10.7 to 16.9 (p=0.001)
    - Control: 13.9 to 12.2

- Khera et al.
  - Multicenter registry of hypogonadal men (n=849) treated with TRT and followed for 12 months
  - BMSFI scores significantly increased from baseline at 12 months (27.4 to 33.8, P < 0.001) and at each visit in all domains (sex drive/libido, erectile function, ejaculatory function)

Current Medical Management for Erection Preservation following Radical Prostatectomy

Androgens Enhance PDE5i Efficacy

- Shabsigh et al.¹
  - 75 hypogonadal men (T<400 ng/dl) failed sildenafil 100mg
  - Randomize to testosterone gel or placebo
  - All men received sildenafil 100 mg as needed for 12 weeks
  - IIEF significantly improved in TRT vs placebo (4.4 vs 2.1, p=0.029)

- Rosenthal et al.²
  - 24 hypogonadal men failed 3 trials of sildenafil 100mg within 3 months
  - Started on 4 weeks of testosterone gel and then restarted on sildenafil
  - After 16 weeks, 92% of men who initially failed sildenafil therapy reported improvements in potency

- Khera et al.³
  - Multicenter registry of hypogonadal men (n=849) treated with TRT and followed for 12 months
  - Patients already on PDE5i therapy also had a significant increase in BMSFI scores after starting TRT

²Rosenthal et al. Urology 2006 Mar; 67(3):571-4
³Khera et al  JSM 2011 Nov;8(11):3204-13
**Question**

- If you use PDE5i for penile rehabilitation in hypogonadal patients following radical prostatectomy, why would you not also use testosterone to maximize the efficacy of the PDE5i and thus the rehabilitation program?

**Predictor of PPED: Veno-occlusive Dysfunction**

- The presence of venous leak after RP has a poor prognosis for the recovery of spontaneous erectile function.
  - The incidence of post-RP venous leak was time dependent:
    - 14% at 4 months
    - 30% at 8 months
    - 50% at 12 months
  - After 18 months following RP, return of non-medication-assisted erections:
    - Venous leak: 8%
    - No venous leak: 47%
  - Patients that failed to regain erections after RP in both the treatment and control arms had venous leak on duplex Doppler ultrasound of the penis.

¹ Mulhall et al. J Urol 2002; 167:1371
² Montorsi et al. J Urol 1997; 158: 1408

**Can TRT Reverse Veno-occlusive Disease?**

- 29 hypogonadal patients with ED who were non-responsive to PDE5i
- 20 patients with venous leak on doppler confirmed with cavernosometry
- All men treated with testosterone undecanoate injections
- Plasma testosterone levels were determined in all patients at baseline and after 18 and 30 weeks of TRT

Can TRT Reverse Veno-occlusive Disease?

**Results:**
- After 30 weeks of TRT, 69% patients demonstrated marked improvement in IIEF-5 (11±0.2 to 27±0.4 (p<0.05))
- After 30 weeks of TRT in patients with just venous leak (n=20):
  - Significant improvement in IIEF-5 (9.4±1.8 to 25±0.4 (p<0.05))
  - 17 patients had significant improvement in EDV on penile duplex
  - 9 patients with clinically demonstrated venous leakage fully recovered their erectile function

Kurbatov et al. J Androl 2008 29: 630-637

Can TRT Reverse Veno-occlusive Disease?

**Case reports of 12 hypogonadal men with moderate to severe ED**
- PDE5i did not improve erectile function
- Each patient underwent baseline cavernosometry demonstrating veno-occlusive dysfunction
- All men treated with testosterone undecanoate injections
- Cavernosography was repeated in all patients at the end of 3 months


Can TRT Reverse Veno-occlusive Disease?

**Results:**
- Five of 12 patients had significant improvements in erectile function within 12-20 weeks of androgen treatment
- Repeat cavernosography in these 5 patients did not demonstrate venous leak
- The patients who responded to androgens also noted improvement in IIEF scores

Increased Levels of Cavernosal Androgen Activity in Post-Prostatectomy Men with Erectile Dysfunction

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OBJECTIVE:
• To determine differences in levels of androgen receptors (AR), 5-alpha reductase (5-AR), testosterone and dihydrotestosterone (DHT) in cavernosal tissue of men with post-prostatectomy erectile dysfunction (PPED) versus men with organic erectile dysfunction (OED).

MATERIAL AND METHODS:
• Population and treatment:
  • Men with erectile dysfunction (PPED or OED) refractory to oral, intra-urethral and injectable therapies who were scheduled to have a penile prosthesis placement.
  • Methods
  • Patients separated based on etiology of erectile dysfunction
  • Cavernosal tissue collected at the time of penile prosthesis placement.
  • Tissue assessed for androgen receptor density and 5-AR using western blot analysis and densitometry.
  • Tissue assessed for testosterone and DHT levels with ELISA.
  • Results between the two groups were compared.

RESULTS:
• Cohort:
  • 18 patients with PPED; 12 Patients with OED (Mean age: 64.9 yrs vs. 64.3 yrs)
• Cavernosal Testosterone Levels:
  • No significant difference found between men with PPED vs. OED (0.55 ng/ml vs 0.51 ng/ml, p = 0.64) (Fig. 1)
• Cavernosal DHT Levels:
  • PPED group with significantly higher levels of DHT (141.5 pg/ml vs. 109.9 pg/ml, p=0.02) (Fig. 2).
• Cavernosal AR Density:
  • PPED group with significantly higher levels of AR (2.2 vs 1.1, p=0.02) (Fig. 3)
• Cavernosal 5-AR density:
  • PPED group with significantly higher levels of 5-AR (2.7 vs 1.8, p = 0.02) (Fig. 4).

CONCLUSION:
• This data suggests that the PPED patients' cavernosal tissue may be more functional and have greater androgen activity than men with OED.

The Focus of Erectile Preservation Following Radical Prostatectomy

Nerves
Trabecular Smooth Muscle
Endothelium

The Focus of Erectile Preservation Following Radical Prostatectomy

Adverse

Antigens

NET EFFECT

Normal

Treatment/Intervention

Trabalcular Smooth Muscle

Endothelium

Current Medical Management for Erectile Preservation Following Radical Prostatectomy

Conclusion

• Androgens play a key role in overall erectile function through their effects on nitric oxide synthase, PDE5 activity, penile nerve function, and veno-occlusive disease
• Erectile preservation strategies focusing on the preservation of nerve function, cavernosal smooth muscle, and the endothelium may be enhanced by the use of androgens
• A hypogonadal man may be at a disadvantage compared to a eugonadal man in recovering his erectile function following radical prostatectomy
• Testosterone replacement therapy in a hypogonadal post-prostatectomy patient can potentially improve erectile function rates

Thank you for your attention