In the Aging Male – What Can We Do To Keep Our Body’s Healthy?

Men’s (Sexual) Health: The New Approach

- Introduction
- Diet, Exercise
- PDE-5 Inhibitors
- Testosterone
- Statins
- ACE Inhibitors
- ASA

Do you know your testosterone value?

On the Pathway to Cardiovascular Events: Opportunities for Intervention

Treatments for the Aging Male

- Diet and Exercise
- Daily ASA
- Daily PDE5 inhibitors
- Aging Male
- Daily ACE Inhibitors
- Daily Testosterone
- Daily Statins
What is the History of Testosterone Treatment?

Testosterone first synthesized by German & Dutch scientists - 1935
Chemical modifications in injectable forms (testosterone enanthate) become the preferred delivery method - 1940
Oral forms (17α-methyl-testosterone) synthesized but toxic to liver (hepatitis) – 1940s
Implantable pellets synthesized and approved but never marketed - 1972
Topical patches developed and launched – 1994
Slate acquires and markets Testopel (implantable pellet) - 2008

What is biologically available testosterone?

“Bioidentical hormones” are defined as compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body.
“Bioidentical hormones”: two choices - FDA-approved preparations that are formulated with strict oversight and dispensed by retail pharmacies.

Final hormone formulations of most compounding pharmacies are not subject to FDA monitoring for dose, purity, safety, or efficacy. There may be additional and at this point unknown risks associated with them. Post-market surveys of such hormone preparations have uncovered inconsistencies in dose and quality.


What are current treatment strategies?

Endo Society’s recommended Algorithm of diagnosis

European Urology: Algorithm of management
What else happens when you treat with testosterone?

LH/FSH may decrease
Estradiol may increase
Dihydrotestosterone may increase
SHBG may decrease

What are important adjunctive treatments to testosterone replacement?

Low LH/FSH may lead to infertility
Consider clomiphene citrate 50 mg Monday and Thursday
High estradiol may lead to gynecomastia, tender breasts, small testes, blood clots, anti-androgen effects. Consider arimidex 1 mg po qMonday and Thursday.

High DHT may lead to hair loss, acne. Consider finasteride 1 mg po qMonday and Thursday.

How safe is finasteride?

Effect of androgen deprivation on penile ultrastructure


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<thead>
<tr>
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<th>Control</th>
<th>Finasteride 4.5 mg/kg/day</th>
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<tbody>
<tr>
<td>Testosterone (nmol/L)</td>
<td>13.95 +/- 10.89</td>
<td>11.03 +/- 5.68</td>
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<tr>
<td>Free testosterone</td>
<td>43.91 +/- 25.85</td>
<td>47.33 +/- 32.45</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>106.2 +/- 57.3</td>
<td>47.1 +/- 16.5 *</td>
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Control - smooth muscle fibers in trabeculae were rich and contained a few elastic and collagenous fibers. Structure of sinusoids was perfect and clear.

Finasteride - CC contained considerable amount of thick and irregularly arranged collagenous fibers. Sinusoids partially depressed, but sinusoid structure was retained.

Effect of androgen deprivation on penile ultrastructure

Long-term treatment with 5-alpha reductase inhibitors impairs erectile response in rats. Harbin AC, Gur S, Erdemir F, Goldstein I, Hellstrom WJG.

Rats were treated with finasteride (5mg/kg/day; n=8) or saline (5ml/kg/day; n=10) via gavage, or dutasteride (0.5mg/rat/day; n=10) in drinking water for 30 days. At the conclusion of the treatment, erectile response was measured using cavernosal nerve stimulation (in vivo). Relaxant and contractile responses were investigated using isolated corpus cavernosum strips in organ baths.
Long-term treatment with 5-alpha reductase inhibitors impairs erectile response in rats. Harbin AC, Gur S, Erdemir F, Goldstein I, Hellstrom WJG

Treatment with 5-ARIs caused a reduction in both in vivo stimulation and in vitro EFS. This likely represents a decrease in nitrergic nerve-induced erection. This hypothesis is further supported by the increase in contractile response to adrenergic stimulation. Nitroprusside and sildenafil responses were not different from control, indicating that the ED does not originate from smooth muscle. Future studies should investigate the neurogenic mechanism and elucidate the connection between dihydrotestosterone and nitrergic neurons.

5-Alpha Reductase Inhibitors and Erectile Dysfunction: The Connection
J Sex Med 2008

DHT is more potent than testosterone in raising NOS activity in rats. Because finasteride alters serum levels of DHT, this effect may be responsible for ED by reducing levels of NO and reducing NOS activity in corpus cavernosum. Researchers have documented that at high doses, finasteride impaired erectile function by altering NOS activity in penis.

Multicenter Study on the Prevalence of Sexual Symptoms in Male Hypo- and Hyperthyroid Patients

Does thyroid influence sexual function?

How safe is testosterone?
Does the same level of testosterone have the same effect on all tissues?

**Saturation Theory**

Prostate Cancer Growth

Serum Testosterone Concentration

Do men with higher endogenous levels of testosterone carry a greater risk of prostate cancer?

**Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies**

Do natural levels of a man’s testosterone affect his prostate cancer risk?

3,886 men with prostate cancer and 6,438 healthy controls

Investigators divided serum concentrations into quintiles and compared the highest level with the lowest for testosterone, calculated free testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate, androstenedione, androstanediol glucuronide, estradiol, calculated free estradiol, and sex hormone-binding globulin

The level of sex hormones in the blood has no association with the risk of prostate cancer. Deflates the hypothesis that prostate cancer is driven by endogenous sex hormones.


Testosterone concentrations were significantly lower in patients with prostate cancer than in those with benign prostatic hypertrophy.

Testosterone concentrations were significantly lower in patients with advanced-stage disease than in patients with organ-confined disease.

Testosterone appears to be an independent predictor of disease and enhances the predictive accuracy for benign prostatic hypertrophy and prostate cancer.

In 128 patients with benign prostatic hypertrophy or prostate cancer, testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels were correlated with disease.

In patients with prostate cancer, hormone levels were correlated with prognostic factors. Predictive values were assessed for prostate-specific antigen and testosterone levels only - using multiple logistic regression analysis and receiver operating characteristic curves.

Despite the widespread contraindication of testosterone to men with known or suspected prostate cancer, there is no convincing evidence that the normalization of testosterone serum levels in men with low, but not castrate levels, is deleterious.

In the few available case series describing testosterone replacement after treatment for prostate cancer, no case of clinical or biochemical progression was observed.

Studies on Prostatic Cancer
1. The Effect of Castration of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Cancer of the Prostate
   - Huggins and Hodges 1941
   - Cancer Res. 1941;1:293.

- Testosterone to castrate levels caused regression of Prostate Cancer
- Testosterone caused Prostate Cancer progression (Based on a single patient)
What are the data on testosterone administration to men with hypogonadism causing prostate cancer?

Severity of Testosterone deficiency increases risk of positive prostate biopsy

- 345 men with low Testosterone, PSA < 4.0, age 58.9 yr
- Prostate Cancer found in 52/345 (15.1%)
- If total T < 250 ng/dl: 21% Prostate Cancer
- If total T > 250 ng/dl: 12% Prostate Cancer *(p=0.04)
- Prostate Cancer rate in men with low Testosterone was 30.2% for PSA 2.0-4.0 ng/ml

What is penile rehabilitation?

Testosterone Flare and PSA in Men with Advanced Prostate Cancer

Sexual Rehabilitation Following Radical Prostatectomy- Best Practices

1. Start detailed evaluation process BEFORE localized treatment for prostate cancer; repeat detailed evaluation 1 month later; start rehabilitation 1 month
2. Engage partner
3. Daily low dose PDE 5 inhibitor (at night)
4. Daily penile self-injection (MUSE) therapy (in evening)
5. Twice daily vacuum therapy (following brushing teeth)
Erectile Function Preservation Program:

Pre-Treatment Strategies

Pre-Rx: Identification of PRE-EXISTING Sexual Health Issues
Sexual, Medical, Psychosocial Interview, Physical Examination

Pre-Rx: Patient Sexual Function/Distress Validated Questionnaires
Pre-Rx: Partner Sexual Function/Distress Validated Questionnaires

Pre-Rx: Laboratory Tests - Hormonal, Neurologic
Pre-Rx: Laboratory Tests - Vascular (also assess IC agent response)
Pre-Rx: Assessment of PDE 5 I response (several occasion)

Post-Rx: Identification of CURRENT Sexual Health Issues
Sexual, Medical, Psychosocial Interview, Physical Examination

Post-Rx: Patient Sexual Function/Distress Validated Questionnaires
Post-Rx: Partner Sexual Function/Distress Validated Questionnaires

Post-Rx: Laboratory Tests - Hormonal, Neurologic
Post-Rx: Laboratory Tests - Vascular (also assess IC agent response)
Post-Rx: Laboratory Tests - NPT
Post-Rx: Assessment of PDE 5 I response (several occasion)

Patient (and Partner) Education

Erectile Function Preservation Program

2. Chronic self-injection (MUSE) therapy - every evening

1A. On demand PDE 5 I therapy (need 60% erection adequate for intercourse)

3. Chronic intermittent stretching with Vacuum Erection Device – after brushing teeth

1. Chronic Low Dose PDE 5 I therapy - at night

4. Testosterone therapy (if testosterone is low)

Erectile Function Preservation Program

Androgens and Erectile Function: A Case for Early Androgen Use in Postprostatectomy Hypogonadal Men

Testosterone plays a role in erectile function, particularly for men who have undergone a RP.

Testosterone has been shown to have an effect on nitric oxide synthase release and activity, and in cavernosal nerve function, and to contribute to venoocclusive disease in the penis.

All of these effects are of particular importance to men attempting to preserve erectile function following RP.

Further studies are needed to assess the true safety of TRT following RP.

Testosterone Replacement Therapy Following Radical Prostatectomy

Saturation Theory

Serum Testosterone Concentration
What are side effects of treatment with testosterone?

Testosterone Therapy for 26 weeks on PSA, IPSS in 20 men with Hypogonadism

What about long term (>10 years) treatment with testosterone?
183 hypogonadal men
11 years of continuous treatment
Age 37 ± 12 years (range 15-70) at onset
Cause of hypogonadism:
Primary: n = 99
Secondary: n = 70
Late-onset: n = 14

Total PSA in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)

Hemoglobin in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)

Hematocrit in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)

Resting Systolic and Diastolic Blood Pressure (mm Hg) in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)

LDL-Cholesterol in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)
HDL-Cholesterol in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)

Body Mass Index in 183 Hypogonadal Men after long term testosterone treatment (maximal Treatment Duration 11 years)

Contraindications for TRT

Androgens are contraindicated in men with known or suspected carcinoma of the prostate or carcinoma of the breast.

Androgens are not indicated for use in women

What are contraindications to testosterone treatment?

Key Potential Risks of Testosterone Replacement Therapy

Moderate to high risk of adverse outcomes
- Undiagnosed prostate nodule or induration
- Unexplained PSA elevation
- Erythrocytosis (hematocrit>50%)
- Severe lower urinary tract symptoms associated with BPH (AUA/IPSS>19)
- Unstable severe congestive heart failure (Class III or IV)

Key Potential Risks of Testosterone Replacement Therapy

Adverse events for which there is evidence of association with testosterone administration
- Erythrocytosis
- Acne and oily skin
- Reduced sperm production and fertility
- Detection of subclinical prostate cancer
- Growth of metastatic prostate cancer