## EVALUATION AND MANAGEMENT OF MALE HYPOGONADISM

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### DISCLOSURES

None

### **DEFINITION OF HYPOGONADISM:**

Refers to a decrease in one or both of the two major functions of the testes: sperm production or testosterone production.

These abnormalities can result from disease of the testes (**primary hypogonadism**) or disease of the hypothalamus or pituitary (**secondary hypogonadism**).

### CAUSES OF PRIMARY HYPOGONADISM IN MALES

#### **Congenital abnormalities**

- Klinefelter syndrome
- Other chromosomal abnormalities
- Mutation in the FSH and LH receptor genes
- Cryptorchidism
- Disorders of androgen synthesis
- Myotonic dystrophy

#### **Acquired diseases**

- Infections, especially mumps
- Radiation therapy
- Chemotherapy (eg, alkylating agents such as cyclophosphamide)
- Suramin
- Ketoconazole
- Environmental toxins
- Trauma- including testicular torsion
- Autoimmune damage
- Chronic systemic illnesses (hepatic cirrhosis; CKD; AIDS)
- Idiopathic

### CAUSES OF SECONDARY HYPOGONADISM IN MALES

#### Acquired

- Tumors
  - Benign tumors and cyst
  - Craniopharyngiomas
  - Germinomas, meningiomas, gliomas, astrocytomas
  - Metastatic tumors (breast, lung, prostate)
- "Functional" gonadotropin deficiency
- Infiltrative diseases
  - Hemochromatosis; granulomatous disease; histiocytosis
- Head Trauma
- Pituitary apoplexy

#### Congenital

- Kallmann syndrome
- Prader-Willi syndrome

### "FUNCTIONAL" HYPOGONADISM

Refers to a man with a low serum testosterone and symptoms of hypogonadism, but there is no overt ("organic") pathology of the hypothalamic-pituitary-testicular axis.

Causes:

Chronic systemic disease

Acute illness

- Malnutrition (Anorexia nervosa, bulimia)
- Hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease
- Obesity
- Post-androgen abuse
- Drugs marijuana, opioids, anabolic steroids, glucocorticoids

### **CLINICAL FEATURES OF HYPOGONADISM**

Depend upon the age of onset, severity of testosterone deficiency, and whether there is a decrease in one or both of the two major functions of the testes: sperm production and testosterone production.

If the deficiency occur:

- First trimester-> Ambiguous genitalia at birth
- Third trimester-> Micropenis at birth
- After birth-> Failure to undergo or complete puberty
  - Small testes

#### • Adult

- Decrease in beard and body hair growth
- Decrease in muscle mass
- Development of breast tissue (gynecomastia)
- Loss of bone mass (osteoporosis)

### SYMPTOMS OF HYPOGONADISM:

Erectile dysfunction

Infertility

Mental and emotional changes. (depression)

Fatigue

Decreased sex drive

Difficulty concentrating

Hot flashes

### WHO NEED TO BE SCREEN FOR HYPOGONADISM?

#### **Endocrine Society guidelines**

- Sellar diseases
- Medications that affect testosterone production.
  - high-dose glucocorticoids for a prolonged period
  - sustained-release opioids
- HIV with weight loss
- ESRD and maintenance hemodialysis
- Moderate to severe COPD
- Infertility
- Osteoporosis or low-trauma fracture
- T2DM

\* Men with acute or subacute illness should not be assessed for hypogonadism, as they will have a transient functional secondary hypogonadism\*

# EVALUATION OF THE MALE WITH POSSIBLE HYPOGONADISM.



# EVALUATION OF THE MALE WITH POSSIBLE HYPOGONADISM.

#### Effect of abnormal SHBG (sex hormone-binding globulin)

 If a man is suspected of having an abnormality in SHBG: free testosterone by equilibrium dialysis should be performed.

#### **Decreased SHBG concentrations**

- Obesity (\*)
- Insulin resistance, type 2 diabetes
- Hypothyroidism
- Growth hormone excess
- Exogenous androgens/anabolic steroids glucocorticoids
- Nephrotic syndrome

#### Increases SHBG concentrations

- Aging (\*)
- Hyperthyroidism
- High estrogen concentrations
- Liver disease
- HIV
- Antiseizure medications

### WHEN TO DO PITUITARY MRI?

In men with secondary hypogonadism:

- If patient has other pituitary hormonal abnormalities
- A visual field abnormality
- Other neurologic abnormalities

If there is no other evidence of pituitary or hypothalamic disease, finding a mass lesion on MRI is more likely the younger and healthier the patient and the lower the serum testosterone concentration.

#### As for testosterone levels:

- In a man <40 y/o with testosterone value of <250 ng/dL
- In a man >60 y/o, with testosterone value of value of <150 ng/dL

### TREATMENT OPTIONS FOR PATIENTS WITH LOW TESTOSTERONE

### EVOLUTION OF TESTOSTERONE THERAPY OVER TIME



Figure 1. Timeline of various testosterone formulations available since Brown-Sequard's experiments in 1889.

### MOST FREQUENTLY PRESCRIBED TESTOSTERONE IN US

Table 1. Average testosterone form by specialty across CMS utilization data records (2013–2017).

	Overall	Endocrinology	Family medicine	Internal medicine	Urology	Other Specialty	<b>P</b> *
n	537,789	69,167	132,167	146,345	116,310	73800	
Testosterone form (%)							< 0.001
Injection	276,148 (51.35)	27,329 (39.51)	79,064 (59.82)	74,180 (50.69)	54,068 (46.49)	41507 (56.24)	
Pellet	120 (0.02)	20 (0.03)	0 (0.00)	17 (0.01)	56 (0.05)	27 (0.04)	
PO	199 (0.04)	20 (0.03)	71 (0.05)	49 (0.03)	11 (0.01)	48 (0.07)	
Transdermal/topical	261,322 (48.59)	41,798 (60.43)	53,032 (40.12)	72,099 (49.27)	62,175 (53.46)	32218 (43.66)	

### **INTRAMUSCULAR TESTOSTERONE**

- First used in 1930s and main form of testosterone therapy until late 1990s.
  - Formulations:
- T. cypionate (long-acting)
- T enanthate (long-acting)
- T. undecanoate (very-long acting)
- Classically injected IM but SQ injection is now available.
- Occasional issues with "Peak/trough" effects.
- Dosed +/- 100 mg q week or 200 q 2 weeks.
- The fluctuation in serum testosterone levels can result in mood swings or changes in libido.
- Local inflammation and pain at the site of injection can occur.



#### **INTRAMUSCULAR TESTOSTERONE: PHARMACOKINETICS**



Figure 1. Daily serum testosterone levels (ng/mL) are higher in normal men after receiving 300 mg of intramuscular TE weekly in treatment month 6 (mean  $\pm$  SEM). \* indicates significant at P < .05 from placebo, 25 mg, 50 mg, and 100 mg groups; +, significant at P < .05 from placebo.

### INTRAMUSCULAR TESTOSTERONE: SQ VS. IM



### TESTOSTERONE ENANTHATE: SQ

- Pharmacokinetics of SQ administration very similar to IM for usual replacement doses (e.g. 100 mg Testosterone cypionate weekly).
- Appears to be less painful than IM.
- Some patient report skin reactions/inflammation.
- Xyosted<sup>™</sup> "autoinjectors" of testosterone enanthate is given in SQ form.



### INTRAMUSCULAR TESTOSTERONE: UNDECANOATE

#### Dosing strategy:

• 750 mg given IM in the gluteus medius ➡ followed by 750 mg 4 weeks later ➡ 750 mg every 10 weeks thereafter.

After each injection a healthcare provider must observe the patient for 30 minutes due to the serious adverse reactions of pulmonary oil microembolism (POME) and anaphylaxis.

• Symptoms: urge to cough, shortness of breath, throat tightening, chest pain, dizziness, and syncope.

Only available through a restricted use program (Aveed<sup>®</sup> REMS Program).

### TRANSDERMAL TESTOSTERONE

- Patches-used uncommonly due to 30-50% risk of skin reactions.
- Testosterone Gel form:
- Lower risk of skin irritation.
- Variable absorption between and within an individual.
- Reported cases of hirsutism in female partners and precocious puberty in children of men.
- Need to cover application area and showering before skin-to-skin contact.
- Must WASH HANDS after applying it.



### TRANSDERMAL TESTOSTERONE: FORMULATIONS AVAILABLE IN US

#### AndroGel/generic:

- **1.0%**:
  - Available only in packets.
  - Dose is 50-100 mg applied once a day in the morning to the shoulders, upper arms, and/or stomach area.
- **1.62%**:
  - Available in pump bottles and packets.
  - Dose is 40.5 mg (each pump depression yields 1.25 g of gel containing 20.25 mg of testosterone) applied once a day in the morning to the shoulders and upper arms. (not abdomen area).
  - The maximum total dose is 81 mg once a day.

#### <u>Testim</u>:

- 1% gel supplied in unit-dose tubes.
- Dose is 50-100 mg applied once a day to the shoulders and/or upper arms.

### TRANSDERMAL TESTOSTERONE

#### Fortesta:

- 2% gel supplied in a metered-dose pump.
- Dose is 40 mg (each pump depression yields 10 mg of testosterone) applied once a day to the inner thighs in the morning.
- The maximum total dose is 70 mg once a day.

#### <u>Axiron:</u>

- 2% solution in metered-dose pump
- Dose is 60 mg (each pump depression yields 30 mg of testosterone) applied once a day to each axilla.
- Maximum total dose is 120 mg once a day.

#### Androderm:

- Dose is 4 mg/day patch. Applied every 24 hrs at night to the back, abdomen, upper arms, or thighs.
  Sites should be rotated and not re-used within 7 days.
- The efficacy is limited by lack of adherence or discontinuation due to skin blistering, pruritus, or irritation.



#### Serum testosterone concentrations during the course of chronic administration of three different testosterone preparations.

- (A) During the 14 days following the injection of 200 mg of testosterone enanthate.
- (B) During the 24 hrs after application of one or two testosterone patches that deliver approximately 5 mg of testosterone each.
- (C) During the 24 hrs after application of testosterone gel containing 50 or 100 mg of testosterone.

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### **TESTOSTERONE PELLETS**

#### **Testopel:**

- Applied 2-6 75 mg testosterone pellets every three to six months.
- The pellets are inserted into the subdermal fat of the buttocks, lower abdominal wall, or thigh with a trocar under sterile conditions using a local anesthetic (surgical procedure).
- Adverse events include infection, and/or fibrosis.



Image from https://aaopm.com/courses/hormone-pellettraining-course

### **TESTOSTERONE PELLETS**



### NASAL TESTOSTERONE

#### Natesto:

- Dose is 11 mg (each pump depression yields 5.5 mg of testosterone) applied one pump to each nostril- 3 times a day (total 33 mg/day).
- Hard regimen to follow.
- Minimal risk of gel transfer to a partner or child.
- Men with allergies or underlying nasal or sinus pathology may have trouble tolerating the formulation (rhinorrhea, epistaxis, nasopharyngitis, sinusitis, and nasal scab seen).
- Studies in mice showed brain levels of testosterone that are twice as high with the nasal gel. It is not known if this occurs in men treated with the nasal gel.



### ORAL TESTOSTERONE UNDECANOATE

#### <u>Jatenzo:</u>

 Initial dose: 237 mg BID (158 to 396 mg BID also available)

#### Kyzatrex:

Initial dose: 200 mg BID (100 mg once daily to 400 mg BID available)

#### <u>Tlando:</u>

Dose: 225 mg twice daily (no titration available)

New oral options are safe with regards to liver toxicity!!.

Not appropriate for patients with chronic diarrhea, malabsorption (e.g. CF), or s/p gastric bypass.

A major concern is its potential inappropriate use in older men with age-related low testosterone.



### **ORAL TESTOSTERONE UNDECANOATE**



Swerdloff & Dudley Ther Adv Urol 2020 12:1-16

### **TESTOSTERONE FORMULATION COSTS**

Formulation (brand name)	Usual Dosage	Cost for 30-days (wholesale acquisition costs)
Testosterone cypionate-generic	100-200 mg IM q 1-2 weeks	\$77
Testosterone enanthate autoinjector— (Xyosted)	50-100 mg SC q week	\$523
Testosterone undecanoate injections- (Aveed)	750 mg IM q 10 weeks	\$1416
Testosterone implants	150-450 mg SQ q3-6 months	\$216 + procedure fees
Testosterone gel 1% (generic)	50-100 mg to skin daily	\$313
Testosterone gel 1% (brand-Androgel or Testim)	50-100 mg to skin daily	\$590-640
Testosterone gel 1.62% (generic)	40.5-81 mg to skin daily	\$552
Testosterone patch (Androderm)	2-4 mg patch to skin daily	\$615
Intranasal testosterone gel (Natesto)	11 mg intranasally tid	\$577
Oral testosterone undecanoate (Jatenzo, Tlando, Kvzatrex)	158-316 mg po bid (with food)	\$460-800





### WHICH THERAPY WOULD YOU OFFER HIM FIRST?

Phobia to needles? Dependent of someone to administer injection? >Consider gel or oral (especially if good insurance)

Cost is a problem? No issue with needles? >Consider injections (IM vs. SQ).

Trouble remembering medications and OK mind quarterly doctor visits? >Consider pellets.

Is fertility an issue? Consider semen analysis prior to any treatment.

>Avoid testosterone in anyone trying to conceive.

Option: hCG- stimulates the testes to make testosterone and is especially useful in stimulating both testosterone and sperm production. Given SQ or IM injections 2-3 times weekly.

Patients will often switch between formulations depending on insurance personal preference, etc.

### MONITORING TESTOSTERONE REPLACEMENT

- Monitoring should be done 2-3 months after initiation or after changing dose, then every 6-12 months when stable.
- Check total testosterone concentrations (goal mid normal range: 400-700 ng/dL) (Free Testo OK if markedly abnormal SHBG)
- With gels and patch: check levels 2-8 hrs after application
- With orals: 2-5 hrs after intake
- With injections: check midway between injections
- Check **HCT** at baseline and 3-6 months after treatment initiation.
- **PSA** +/- for men 40-70 or 55-69 if low risk.
- Consider DEXA if bone fracture or BMD was in the osteoporotic range at the time hypogonadism was dx.

### POTENTIAL ADVERSE EFFECT OF TESTOSTERONE REPLACEMENT

#### **Erythrocytosis:**

- Stop therapy if Hct >54%.
- Re-evaluate in 2 months. If Hct normalizes, restarted T. at lower dose.
- If Hct cannot be kept below the upper limit of normal, evaluate patient for hypoxia and sleep apnea.
- If no treatable cause is found, phlebotomy can be considered.

#### Prostate cancer:

- No study or review has definitively shown evident that T. replacement is an independent risk factor for development of prostate cancer.
- Refer to urologist if PSA increases by more than 1.4 ng/mL in any one-year period or to >4 ng/mL.

#### Benign prostatic hyperplasia (BPH)

• No difference in prostate symptoms.

#### Venous thromboembolism (DVT)

- Consequence of erythrocytosis.
- Appears only in those with thrombophilia.
  - Importance of a careful personal and family DVT history prior to initiating treatment.

#### Cardiovascular risk

Uncertain-> mixed evidence-> but...

### THE TRAVERSE TRIAL (2023)

### Cardiovascular Safety of Testosterone-Replacement Therapy

A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Travison, and S.E. Nissen, for the TRAVERSE Study Investigators\*

New Eng J Med, 389(2):107-117

### THE TRAVERSE TRIAL (2023)

 Double-blinded, randomized, placebo-controlled trial of testosterone therapy in older men with hypogonadism and CAD or CAD risks.

Treated with daily T gel or placebo for up to five years.

CV events independently adjudicated by cardiologist.

Incidence of CV events the same in each group.





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Characteristic	Testosterone Group (N=2601)	Placebo Group (N=2603)
Mean age — yr	63.3±7.9	63.3±7.9
Age ≥65 yr — no. (%)	1241 (47.7)	1211 (46.5)
Race or ethnic group — no. (%)†		
White	2070 (79.6)	2084 (80.1)
Black	445 (17.1)	432 (16.6)
Other	86 (3.3)	87 (3.3)
Hispanic or Latinx	409 (15.7)	439 (16.9)
Body-mass index <u>;</u>	35.0±5.7	34.8±6.0
Median testosterone level (IQR) — ng/deciliter	227 (189–258)	227 (188–258)
Cardiovascular risk category — no. (%)		
Preexisting cardiovascular disease	1410 (54.2)	1437 (55.2)
Increased cardiovascular risk	1191 (45.8)	1166 (44.8)
History of coronary artery disease — no. (%)	1158 (44.5)	1160 (44.6)





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### TESTOSTERONE TREATMENT: NO IMPACT ON CAD



### **OTHER OUTCOMES FROM TRAVERSE**

- Prostate cancer no different (0.5% vs. 0.4%)
- Death from any cause similar (5.5% vs. 5.7%)
- No difference in heart failure
- Thromboembolism (1.7% vs. 1.2%)\* Men with h/o VTE excluded!
- Diabetes, COVID19, BPH, Urinary retention, Prostate Cancer— same between groups
- Slight increase in risk of atrial fibrillation (3.5% vs. 2.4%; p=0.02)
- Slight increase in risk of AKI (2.3% vs. 1.5%; p=0.04)





### REFERENCES

Amory, J (2023). Update on Various Modalities of Testosterone Replacement. Clinical Endocrinology Update.

Shoskes, J; Spinnel, M; Wilson, M. (2016). Pharmacology of testosterone replacement therapy preparations.

Snyder, P. (2024). Testosterone treatment of male hypogonadism. Up-To-date.

Snyder, P (2024). Clinical features and diagnosis of male hypogonadism. Up-To-date.

## Thank You!