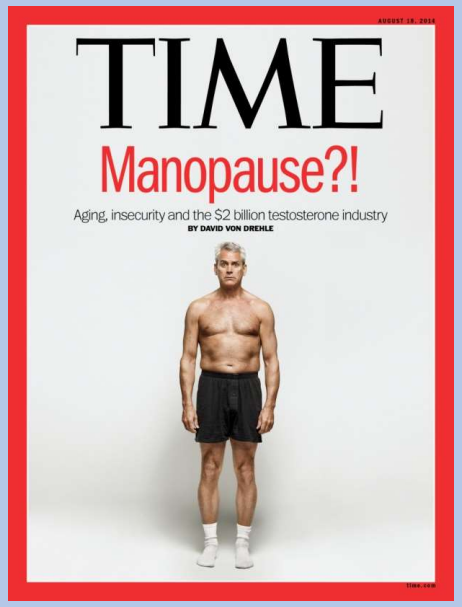
MANopause

Male Hypogonadism



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Immediate Past President, American Society of Endocrine PAs

Senior Medical Science Liaison, Corcept Therapeutics

Disclosure

- None

*Employee of Corcept therapeutics. No conflict of interest in disease state and therapeutic interest.

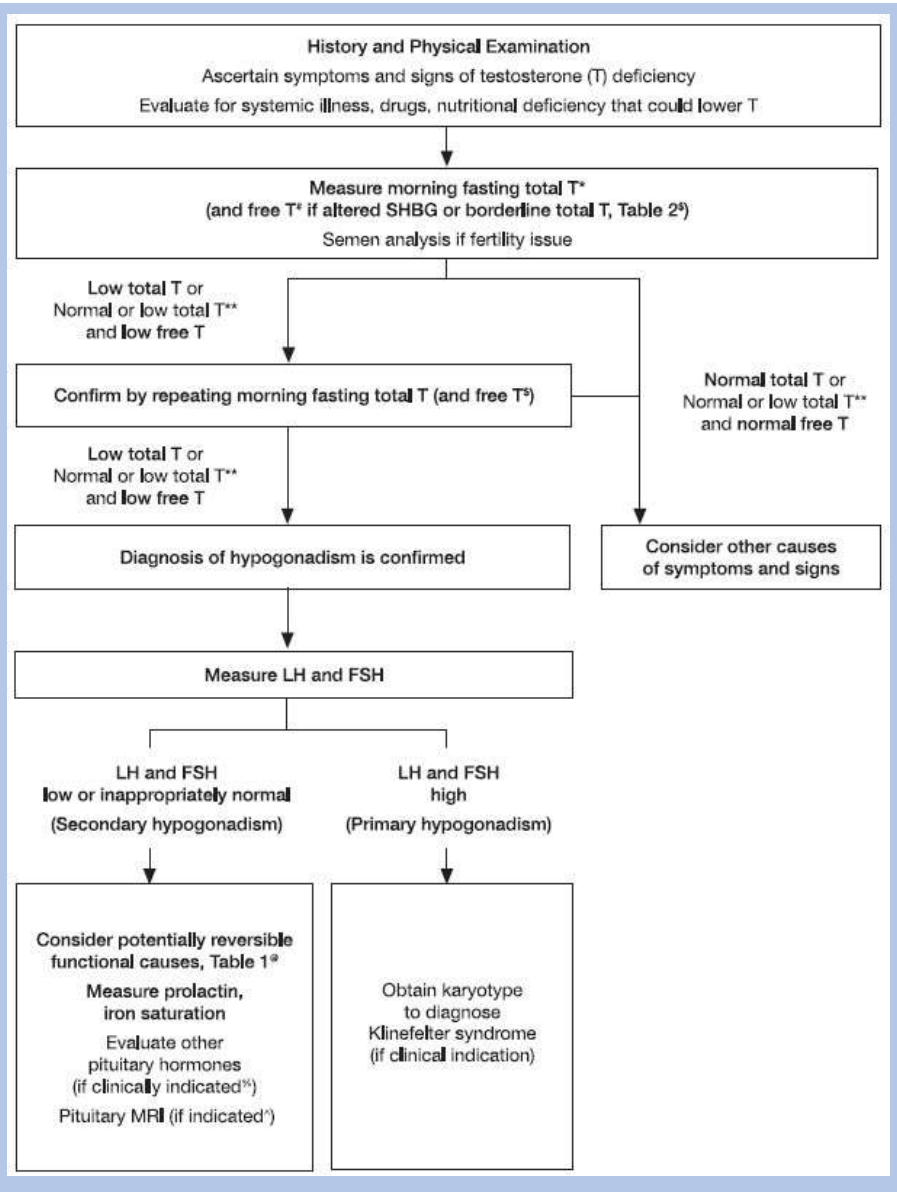
*Ji Hyun Chun (CJ) **does not intend** to discuss the use of any off-label use/unapproved use of drugs or devices

Objective

- Understand the patho/physiology of low testosterone
- Create a comprehensive diagnostic protocol
- Differentiate organic vs functional hypogonadism
- Outline appropriate monitoring of patients on testosterone replacement therapy (TRT)
- Review available testosterone delivery options and recognize the advantages and disadvantages of each options

John

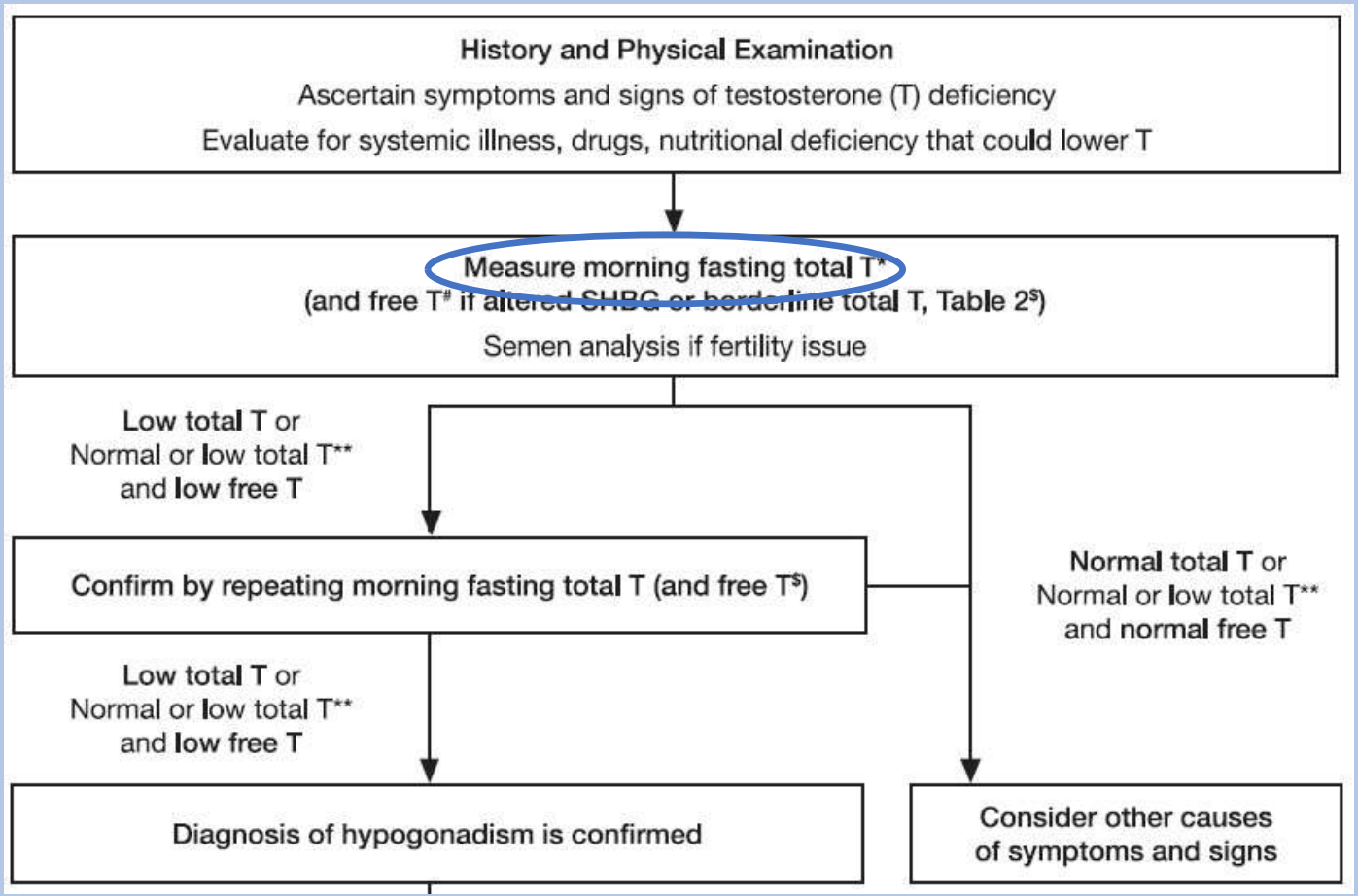
- 67yo male referred for low testosterone. Requested checking testosterone as he felt tired, hard to lose weight, low libido and erectile dysfunction x3-4yrs.
- DM 2/HTN/dyslipidemia, BMI 36
- Total testosterone 245 ng/dL (264-916)
- Repeat morning total testosterone 260ng/dL
- CBC/CMP wnl



Diagnostic Process

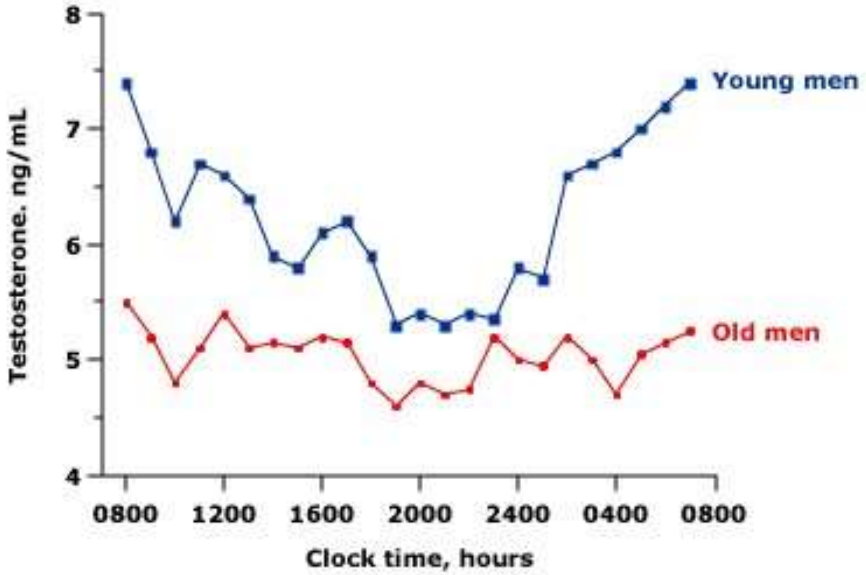
Endocrine Society Guideline 2018

Diagnostic Process



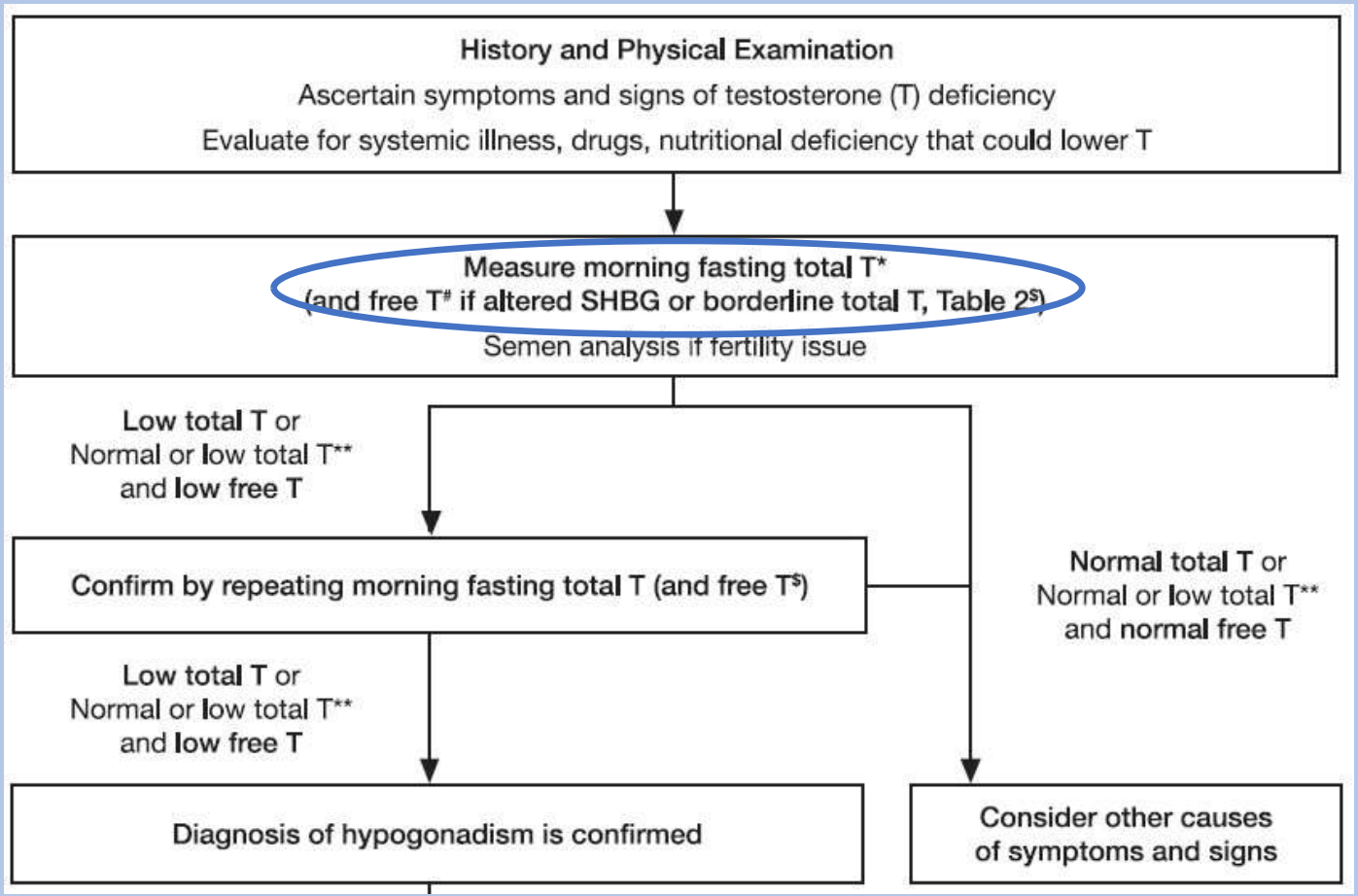
Endocrine Society Guideline 2018

Diurnal pattern of testosterone secretion



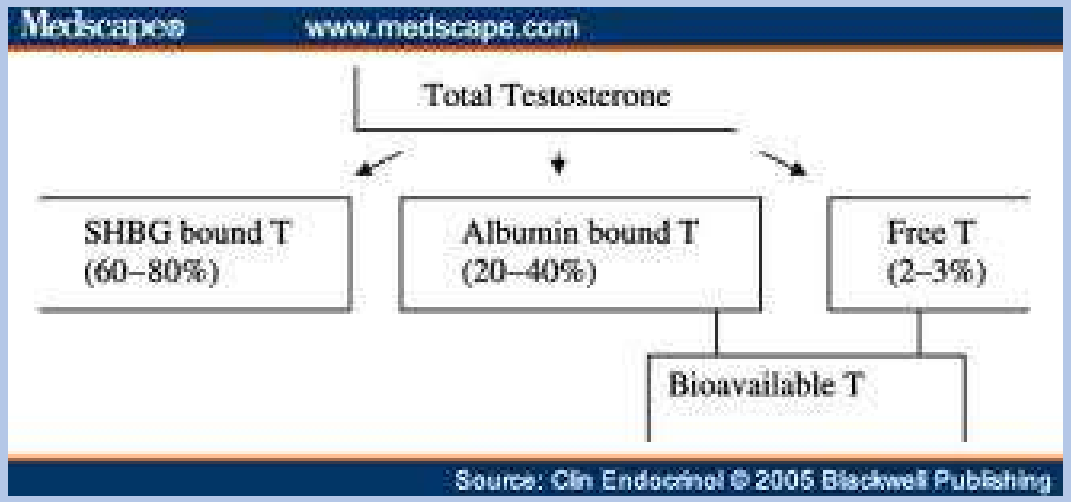
Hourly serum testosterone levels in normal young (n = 17) and old (n = 12) men. The circadian rhythm is lost in old men. Blood samples were obtained using an indwelling peripheral venous cannula, which allowed free movement and normal sleep.
Data from Bremner, WJ, Vitiello, MV, Prinz, PN, J Clin Endocrinol Metab 1983; 56:1278.

Diagnostic Process



Endocrine Society Guideline 2018

“Active” Testosterone



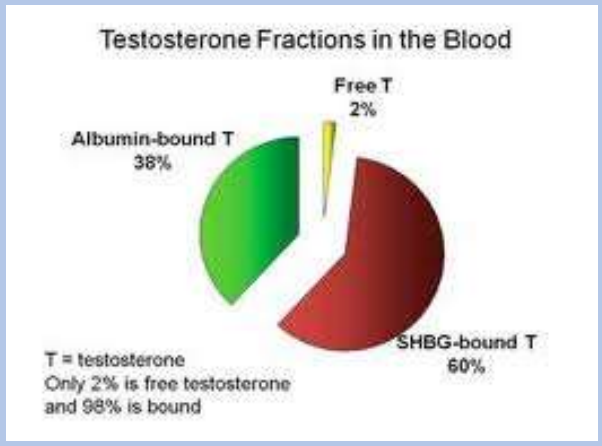


Table 2. Conditions in Which Measurement of FT Concentration Is Recommended

1. Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene
2. Conditions associated with increased SHBG concentrations
Aging
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of estrogens
Polymorphisms in the SHBG gene
3. Total testosterone concentrations in the borderline zone around the lower limit of the normal range (*e.g.*, 200-400 ng/dL)

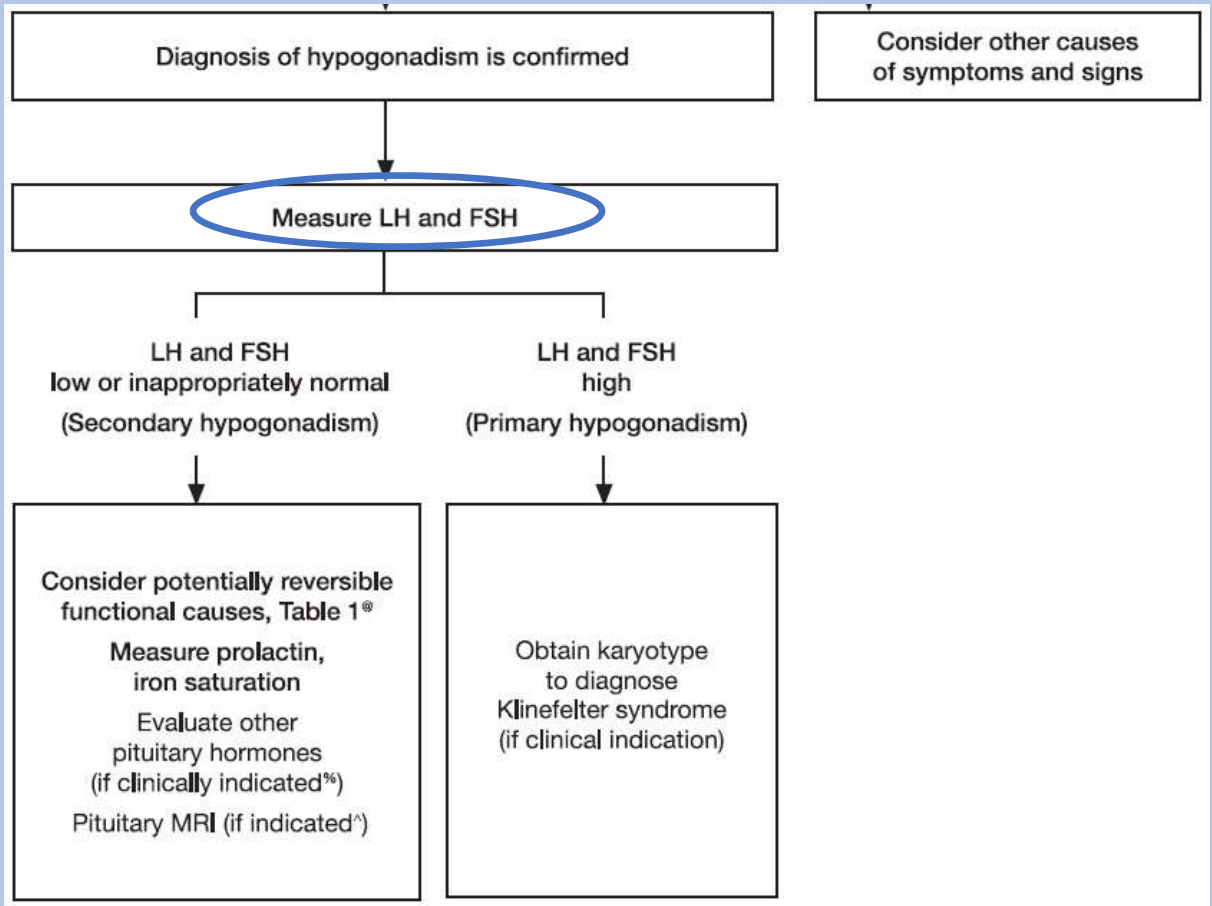
Adapted with permission from Bhasin *et al.* (8).

Endocrine Society Guideline (2018)

John

- Total testosterone 245 ng/dL (264-916)
- Repeat morning lab:
  - Total testosterone: 260 ng/dL
  - Free testosterone by ***equilibrium dialysis***:
    4.2 ng/dL (5.0-21.0)

Diagnostic Process



Endocrine Society Guideline 2018

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- Total testosterone 245 ng/dL (264-916)
- Repeat morning lab:
  - Total testosterone: 260 ng/dL
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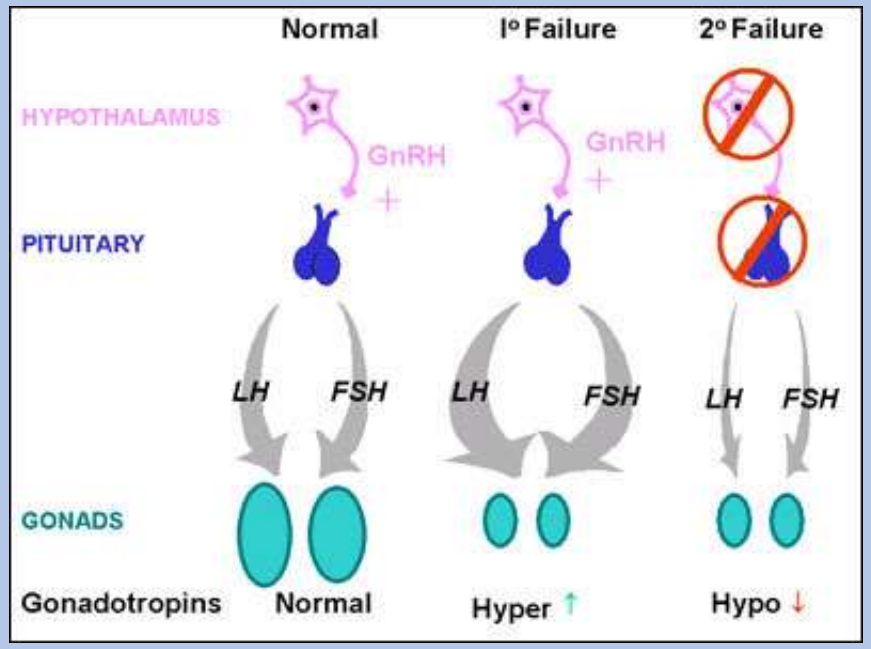
- LH: 2.7 mIU/mL (1.7-8.6)
- FSH: 3.1 mIU/mL (1.5-12.4)

Question

- Based on the following lab, where is the defect?
  - Total testosterone: 260 (264-916)
  - Free testosterone 4.2 (5.0-21.0)
  - LH: 2.7 (1.7-8.6) FSH: 3.1 (1.5-12.4)

A. No where
B. Testicles
C. Pituitary/Hypothalamus
D. Extra chromosome (XXY)

Classification



- Primary: Failure of **testes** to produce hormones → **elevated** LH/FSH
- Secondary: Failure of **hypothalamus** and/or pituitary to stimulate testes → **low/low normal** LH/FSH

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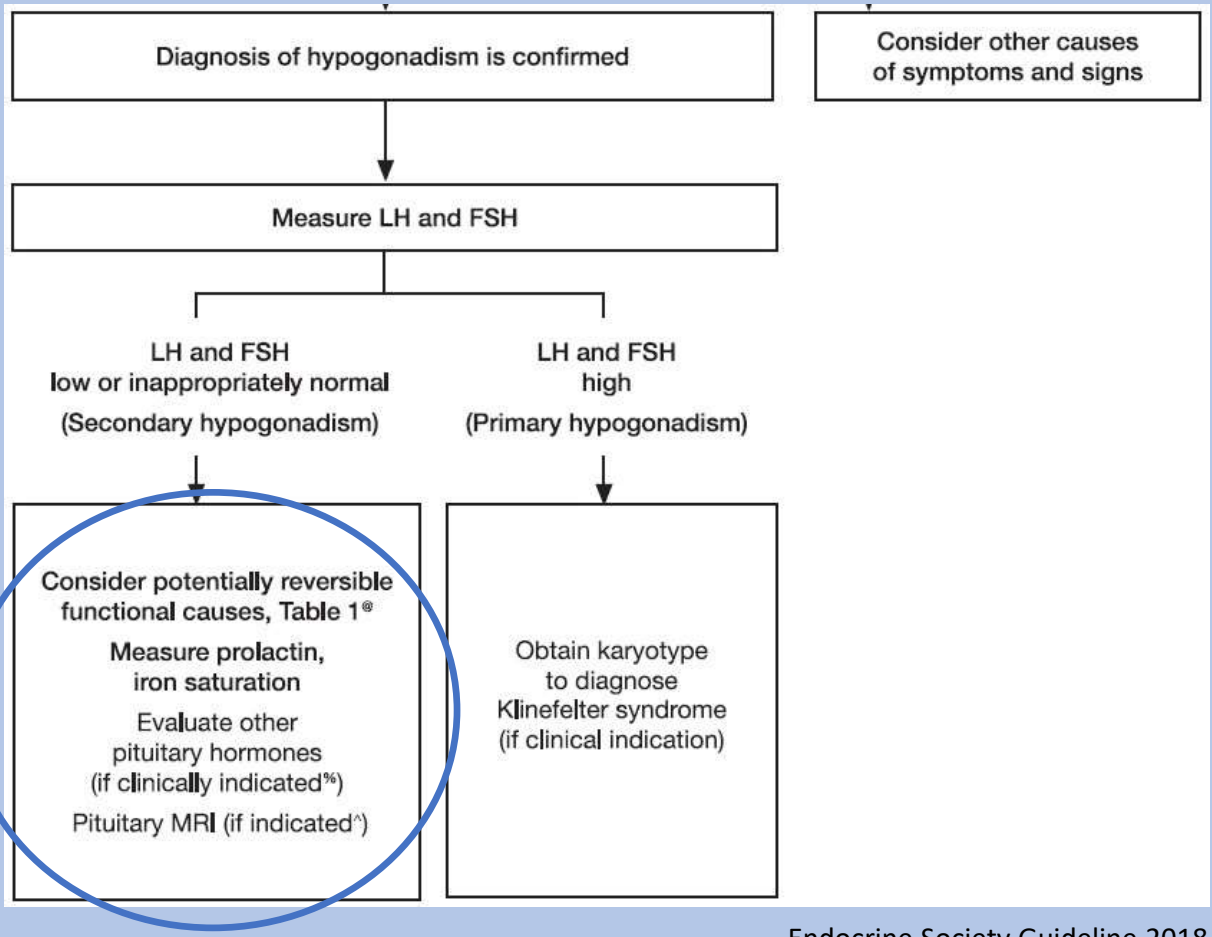
- LH: 2.7 mIU/mL (1.7-8.6)
- FSH: 3.1 mIU/mL (1.5-12.4)

→ Secondary hypogonadism and defect is somewhere in hypothalamus/pituitary

Diagnostic Process



Endocrine Society Guideline 2018

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

Primary Hypogonadism	Secondary Hypogonadism
	ORGANIC
KS	Hypothalamic/pituitary tumor
Cryptorchidism, myotonic dystrophy, anorchia	Iron overload syndromes
Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy	Infiltrative/destructive disease of hypothalamus/pituitary
Orchitis	Idiopathic hypogonadotropic hypogonadism
Testicular trauma, torsion	
Advanced age	
	FUNCTIONAL
Medications (androgen synthesis inhibitors)	Hyperprolactinemia
End-stage renal disease[a]	Opioids, anabolic steroid use, glucocorticoids
	Alcohol and marijuana abuse[a]
	Systemic illness[a]
	Nutritional deficiency/excessive exercise
	Severe obesity, some sleep disorders
	Organ failure (liver, heart, and lung)[a]
	Comorbid illness associated with aging[a]

[a]Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin *et al.* (7).

Endocrine Society Guideline (2018)

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- LH: 2.7 mIU/mL (1.7-8.6)
- FSH: 3.1 mIU/mL (1.5-12.4)
- Prolactin: 9 ng/dL (4-15.2)
- Iron studies wnl

Further Diagnostic Tools

- Consider MRI:
  - Total testosterone <150ng/dL in secondary hypogonadism
  - Other pituitary dysfunction
  - symptoms of mass effect (visual disturbance, HA)
- Sleep study: to r/o sleep apnea
- BMD for height loss or fracture
- Testicular U/S: abnormal testicular exam

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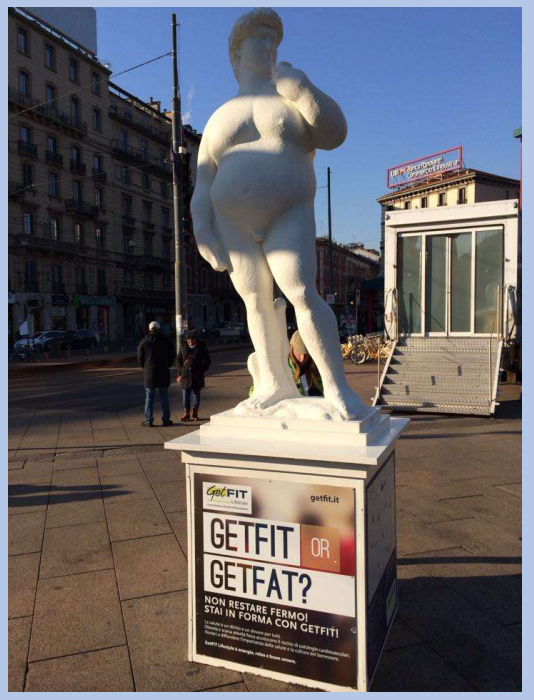
Endocrine Society Guideline (2018)

Classification

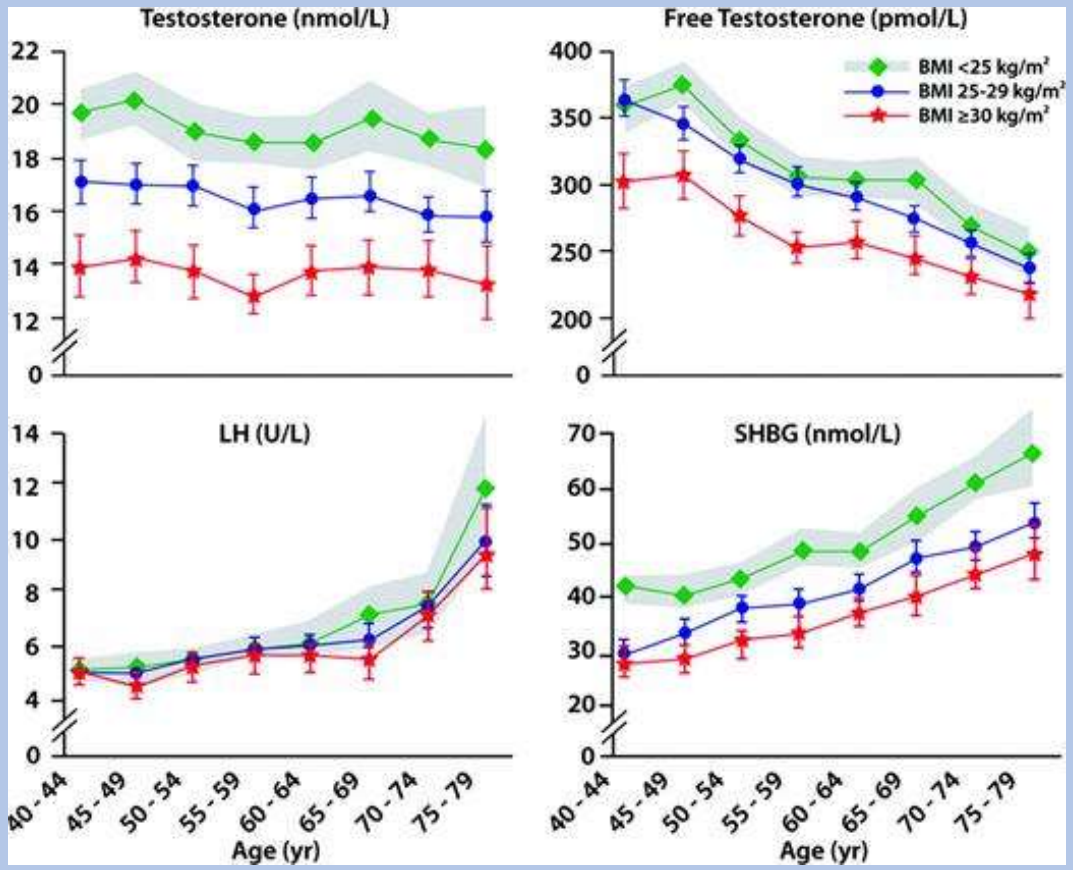
Organic **VS** **Functional**

- "classic" hypogonadism
- Congenital, structural, or destructive disorder that results in **permanent** hypogonadism

- Conditions that suppress gonadotropin (LH/FSH) and T concentrations but that are **potentially reversible** with treatment of the underlying etiology.


getfit.it
GETFIT OR
GETFAT?
NON RESTARE FERMO!
STAI IN FORMA CON GETFIT!

Testosterone and BMI



- Risk of secondary hypogonadism in:
  - Overweight men: 3.3x
  - Obese men: 8.7x

European Male Aging Study (N=3200 men, age 40-79) Wu FC et al. JCEM 2008 / Tajar A et al. JCEM 2010

John

- Has secondary and functional hypogonadism.
- Treat or Not Treat?

Late onset hypogonadism (LOH)

- Middle aged man with borderline low T…
- Is this real? Treat? Not treat?

Organic vs LOH

	Female Menopause	Organic Male Hypogonadism	LOH
Rate of Hormonal Decline	Rapid	Generally Rapid (may vary)	Gradual
Degree of Hormone Deficiency	Profound	Profound	Mild (most cases)
Nature of Deficiency	Pathologic (climacteric ovary)	Pathologic (hypothalamic, pituitary or testicular disease	Unclear (probably more functional than pathologic)
Symptoms	Specific	Specific	Non-specific

Shehzad Basaria. Testosterone Therapy in Older Men with Late-onset Hypogonadism. Endocr Pract. 2013;19(5):853-863

TRT in LOH?

Yes!	Maybe?	No!
• Shores et al. TRT and mortality in hypogonadal males. JCEM 2012. • Muraleedharan et al. TRT improve survival in men with DM II. EJE 2013 • Yassin et al. TRT in men with hypogonadism prevents progression from preDM to DM. Diab care 2019	• Snyder et al. Lessons from The Testosterone Trials. Endocr Rev 2018 • Witter et al. TRT to prevent/revert DM2 in men enrolled in a lifestyle programme (T4DM). Lancet 2021	• Basaria et al, Adverse events associated with testosterone administration. NEJM 2010 • Vigen et al, Association with TRT and mortality, MI, and stoke in men with low T levels. JAMA 2013 • Finkle et al, Increased risk of nonfatal MI following TRT. PLoS One 2014

MIXED

FDA statement 2014

- T products are approved for….organic hypogonadism… . TRT is not approved for men with low levels w/o the associated medical condition.

Endocrine Society Statement

- Recommend against “routine” use in >65yo
- >65yo with confirmed low T and symptoms, clinicians should offer TRT on an individualized basis after explicit discussion of the potential risks and benefits

Endocrine Society Guideline (2018)

ACP guideline 2020

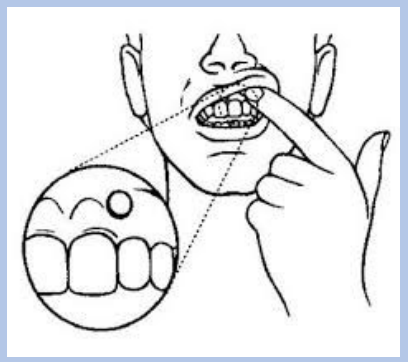
- Guideline specifically on TRT for adult men with age-related low testosterone
  - Suggest only men with **sexual dysfunction** who want to improve sexual function but not for energy, vitality, physical function, or cognition improvement.
  - Reassess symptoms within 12mo and periodically thereafter. D/C if no improvement noted
  - Consider intramuscular injection over transdermal due to considerably lower cost with similar benefit/risk
    - $156.24 vs $2135.32 per 2016 Medicare Part D Drug Claims data

ACP Guideline (2020)

Treatment options








New-comers

FDA approved Sep 2018

Disposable SC Auto injector:

Testosterone enanthate

approved Mar 2019

Oral testosterone:

Testosterone undecanoate

Treatment

Testosterone replacement

- Should not be used if interested in fertility in **near** future
- Controlled substance: Schedule III
  - refer to your state regulations

Table 7. Conditions in Which T Administration Is Associated With a High Risk of Adverse Outcomes and for Which We Recommend Against Using T

Very high risk of serious adverse outcomes
Metastatic prostate cancer
Breast cancer
Moderate to high risk of adverse outcomes
Unevaluated prostate nodule or induration
Unevaluated PSA > 4 ng/mL (>3 ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
Hematocrit > 48% (>50% for men living at high altitude)
Severe LUTS associated with benign prostatic hypertrophy as indicated by AUA/IPSS > 19
Uncontrolled or poorly controlled congestive heart failure
Desire for fertility in the near term

Adapted with permission from Bhasin *et al.* (7).

Abbreviations: AUA, America Urological Association; IPSS, International Prostate Symptom Score. LUTS: Lower Urinary Tract Symptoms

+ MI/stroke within 6months

+ Thrombophilia

Endocrine Society Guideline (2018)

Table 8. Potential Adverse Effects of T Replacement

Adverse events for which there is evidence of association with T administration
Erythrocytosis
Acne and oily skin
Detection of subclinical prostate cancer
Growth of metastatic prostate cancer
Reduced sperm production and fertility
Uncommon adverse events for which there is weak evidence of association with T administration
Gynecomastia
Male pattern balding (familial)
Growth of breast cancer
Induction or worsening of obstructive sleep apnea

Endocrine Society Guideline (2018)

Monitoring

- CBC: baseline-3months-annual (stop if hct>54%)
- Gynecomastia/breast mass: aromatization of testosterone to estradiol
- BMD: 1-2years post treatment in men with osteoporosis or low trauma fracture
- Sleep apnea symptoms

TRT and Prostate Cancer

- Meta-analyses found no significant association between TRT and the risk of prostate cx

*exception: metastatic prostate cx, breast cx

- Risk and benefit of prostate monitoring
  - Increases the risk of detecting subclinical cancers due to increased surveillance
  - Adverse effects of prostate bx and cx treatment

Endocrine Society Guideline (2018)

TRT and Prostate Cancer

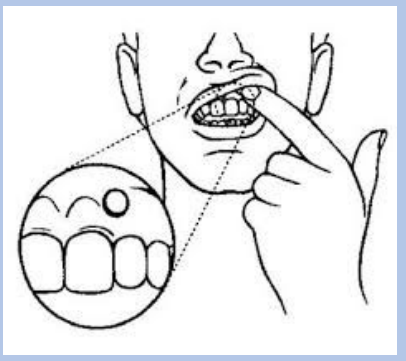
- Explain potential benefit/risk of monitoring prostate cx (shared decision making)
- Patients who choose to monitor and is 55-69yo (40yo for high risk: 1st degree relative, African-Americans)
  - Get baseline PSA/DRE and again in 3-12mo, and according to guideline thereafter
- Urology consult:
  - PSA increase >1.4 ng/mL within 12mo
  - Confirmed PSA > 4ng/mL
  - Abnormal DRE
  - Substantial worsening of LUTS

Take Home Message

- Differentiating organic hypogonadism and LOH is of utmost importance to prevent long-term complication of “true” hypogonadism.
  - Benefit clearly outweighs risk in organic hypogonadism
  - Unknown/unclear benefit-risk ratio in LOH
  - If doing TRT in LOH, do it safely
    - “reasonable” testosterone ranges (350-700 ng/dL)
    - Close monitoring in levels/symptoms/signs

Treatment options

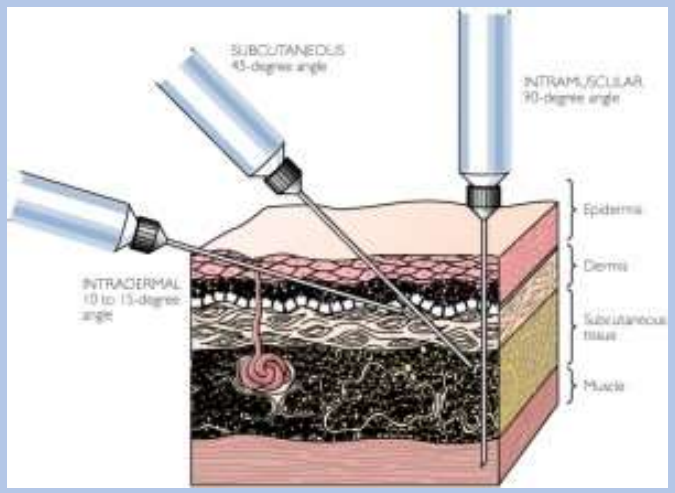
- Which ones to choose from:
  - Injection (IM/SC)
  - SC Pellets
  - Transdermal (gel/patch)
  - Nasal gel
  - Oral tab
  - Buccal tab

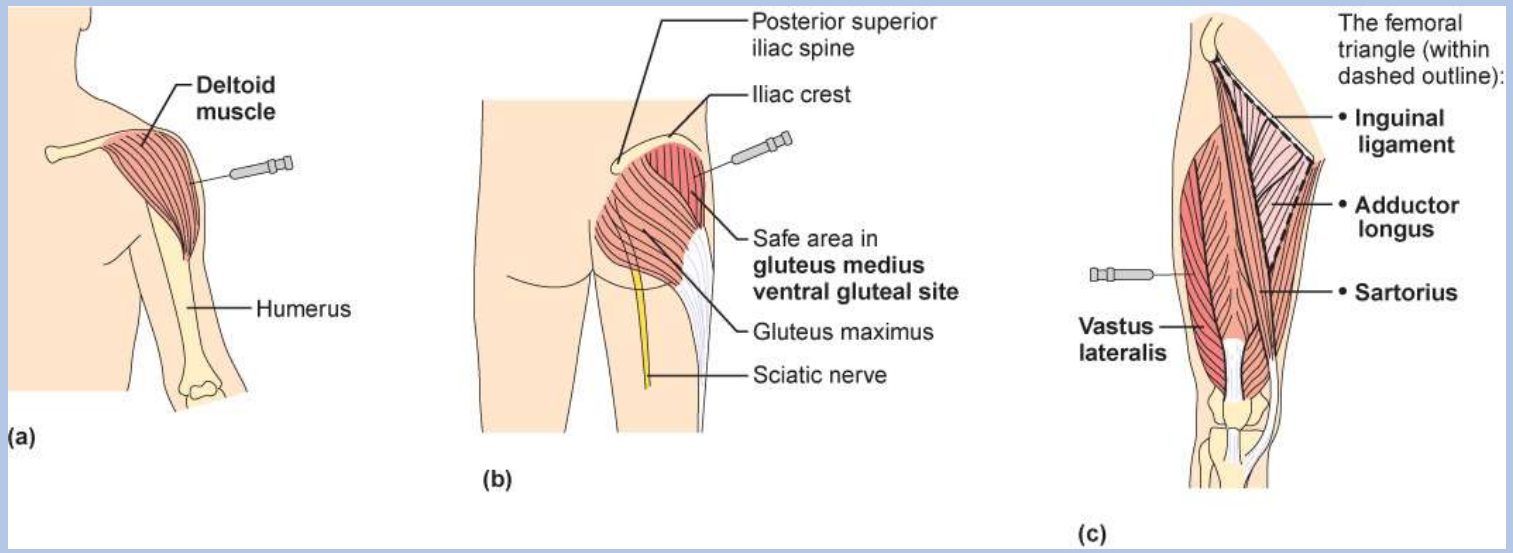


IM/SC injection

- Short acting (trough 2-3 days): IM proprionate
- Intermediate acting (trough 2-3weeks): IM/SC enanthate, IM cypionate
- Long acting (troughs 10-12weeks): IM undecanoate

IM injection





SC injection (autoinjector)

Figure 4:

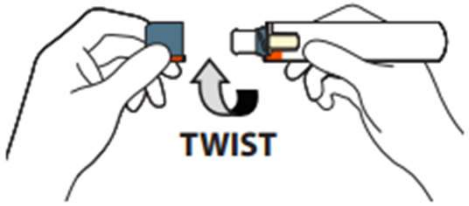


Figure 5:

Figure 6:

Figure 7:

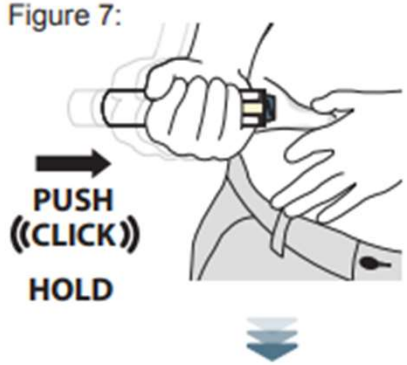


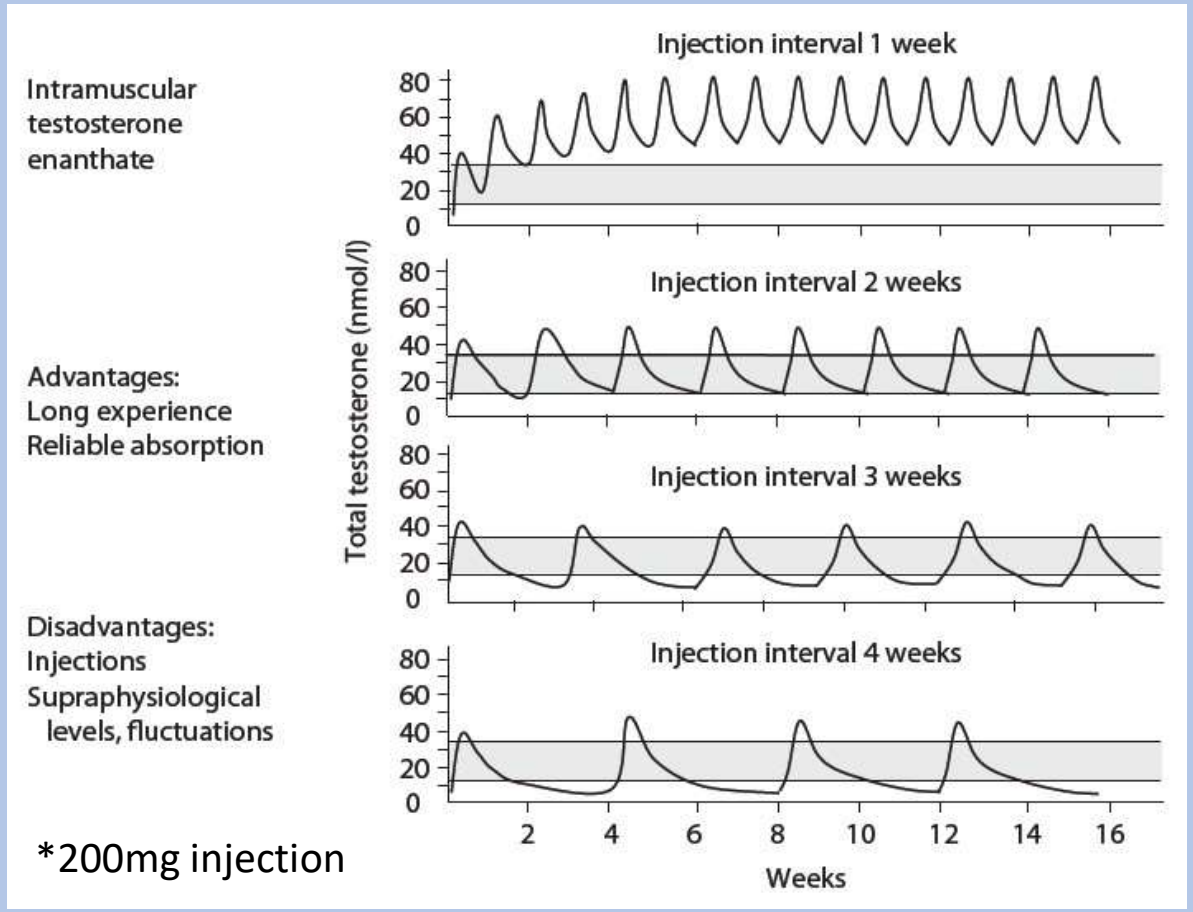
Figure 8:

IM/SC injection

- IM Dosing:
  - 100mg (0.5mL of 200mg/mL) q1week
  - **200mg (1mL of 200mg/mL) q2week**
  - 300mg (1.5mL of 200mg/mL) q3week
  - 400mg (2mL of 200mg/mL) q4week
- Testosterone enanthate SC (autoinjector) dosing
  - Available as 50 mg/0.5 mL, 75 mg/0.5 mL, 100 mg/0.5 mL
  - Starting dose: 75mg/0.5 mL q1week

IM injection

- Peak: 2-3days
- Trough: 2-3weeks
- Check before next injection



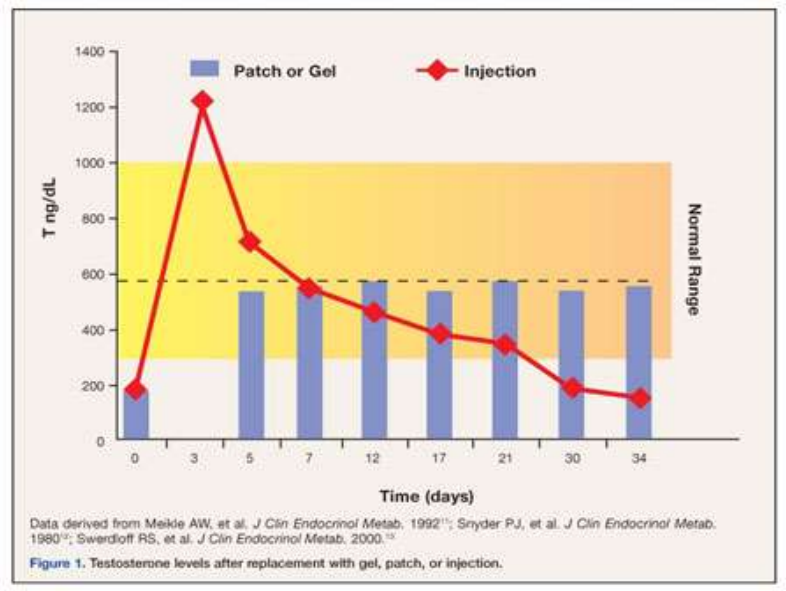
*200mg injection

Behre HM, Wang C, Handelsman DJ, Nieschlag E: Pharmacology of testosterone preparations; in Nieschlag E, Behre HM, Nieschlag S (eds): Testosterone, Action, Deficiency, Substitution, 3rd edition. Cambridge, Cambridge University Press, 2004.

IM injection

- Advantage: less expensive, less frequent dosing, higher levels
- Disadvantage: pain, frequent office visits, trough and nadir (fluctuating levels with supraphysiologic levels, mood, sebum production, adverse events),

  risk of injection site bleeding

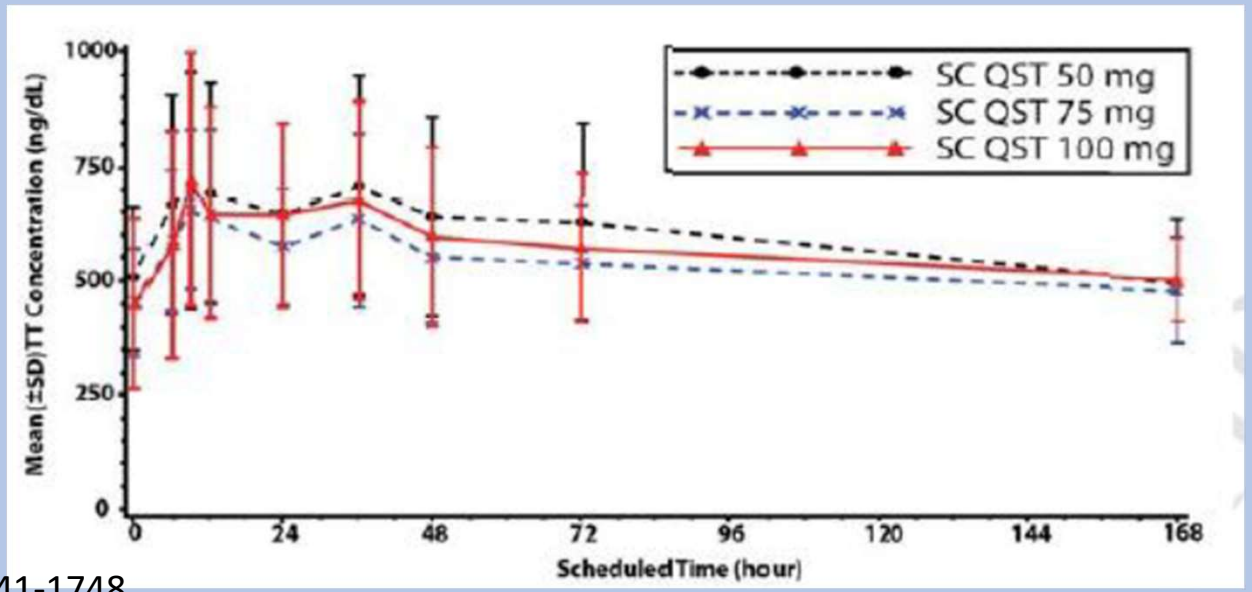


Data derived from Meikle AW, et al. *J Clin Endocrinol Metab.* 1992[11]; Snyder PJ, et al. *J Clin Endocrinol Metab.* 1980[12]; Swerdloff RS, et al. *J Clin Endocrinol Metab.* 2000.[13]

Figure 1. Testosterone levels after replacement with gel, patch, or injection.

SC Testosterone enanthate (autoinjector)

- Advantage: Easier self-injection, more frequent dosing with lower dose → less peak/trough
- Disadvantage: cost



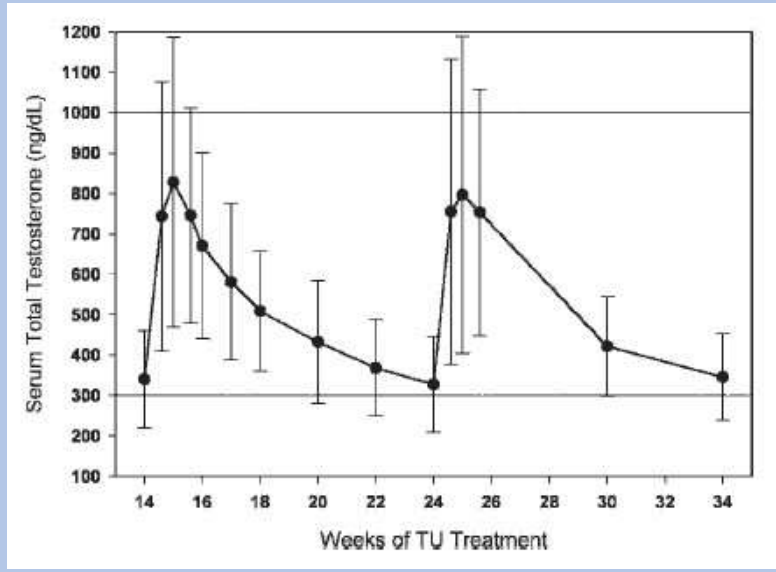
Gittelman et al. J Sex Med 2019;16:1741-1748

Longer acting IM injection

Testosterone undecanoate

- Comes in 750mg/3cc vial
- Dosing: 3mL (750mg) IM, followed by 3mL after 4weeks, then 3mL q10weeks thereafter

- Peak: 7-10 days
- Trough: 10weeks
- Check levels: before next injection



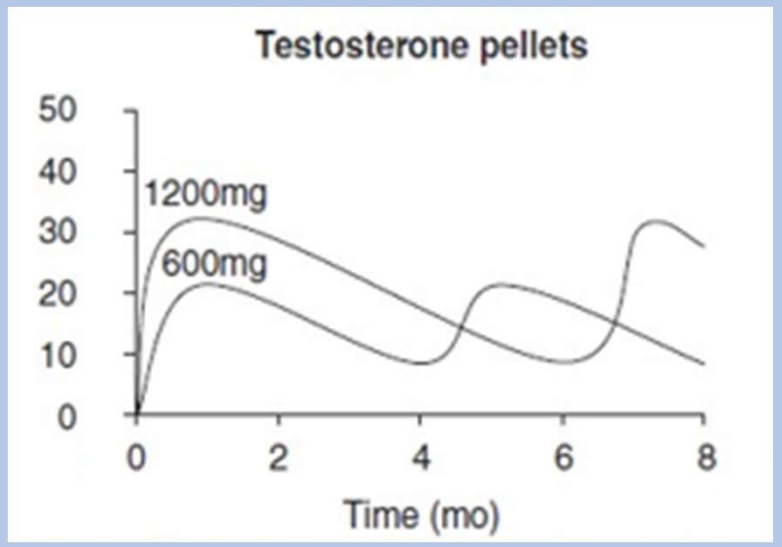
Wang C, Harnett M, Dobs A, Swerdloff R: Pharmacokinetics and Safety of Long-Acting Testosterone Undecanoate Injections in Hypogonadal Men: 84-Week Phase III Clinical Trial. Journal of Andrology, Vol. 31, No.5, Sep/Oct 2010

IM Testosterone Undecanoate

- Advantage: long acting (less frequent dosing), higher levels
- Disadvantage: high cost, pain, **REMS controlled** (only in certified facility by certified prescriber)
- Boxed warning: Serious pulmonary oil microembolism (POME) reactions and anaphylaxis
  - Urge to cough, dyspnea, throat tightening, chest pain, dizzness, and syncope (8/3556; 9cases)
  - Life threatening anaphylactic reactions during or immediately after the injection (2/3556)
  - observe pt in healthcare setting for 30min post injection

Subcutaneous implants (pellet)

- Available in 100mg (0.6cm) and 200mg (1.2cm) dose
- Dosing: 600-1200mg (3-6 200mg pellets) inserted q4-6months
- Mechanism: Slowly release with surface erosion which maintains stable range over long period of time.

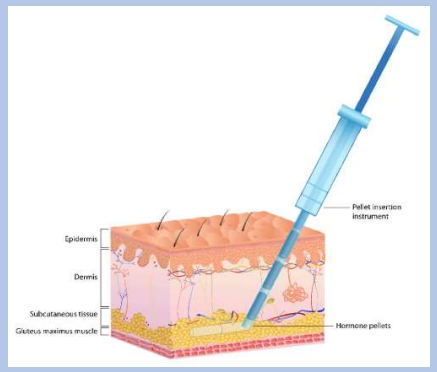


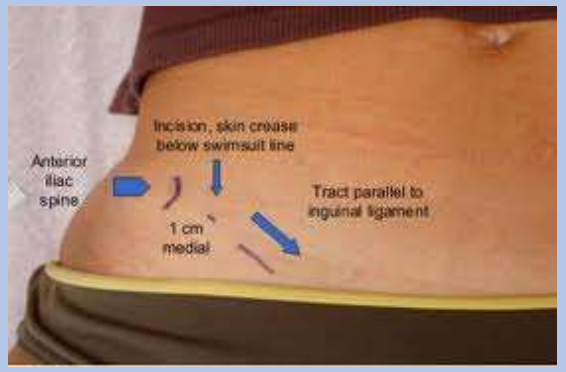
- Residence time 87days, half life 70.8days
- Check before next implantation

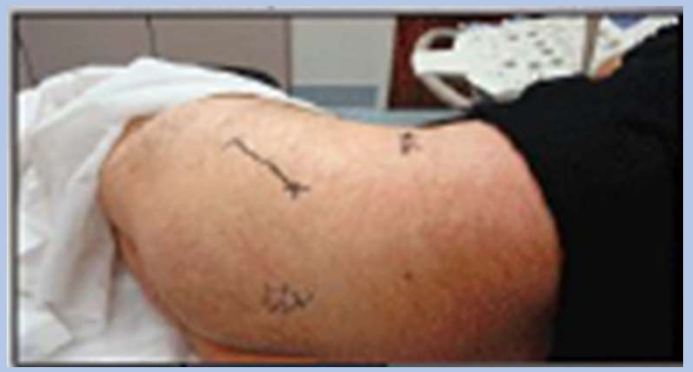
Louis Gooren and Mathijs Bunck: Androgen Replacement Therapy. Present and future. Drugs 2004;64(17): 1861-1891

Subcutaneous implants (pellet)

- Placed in the periumbilical area or buttocks under local anesthesia with a trocar







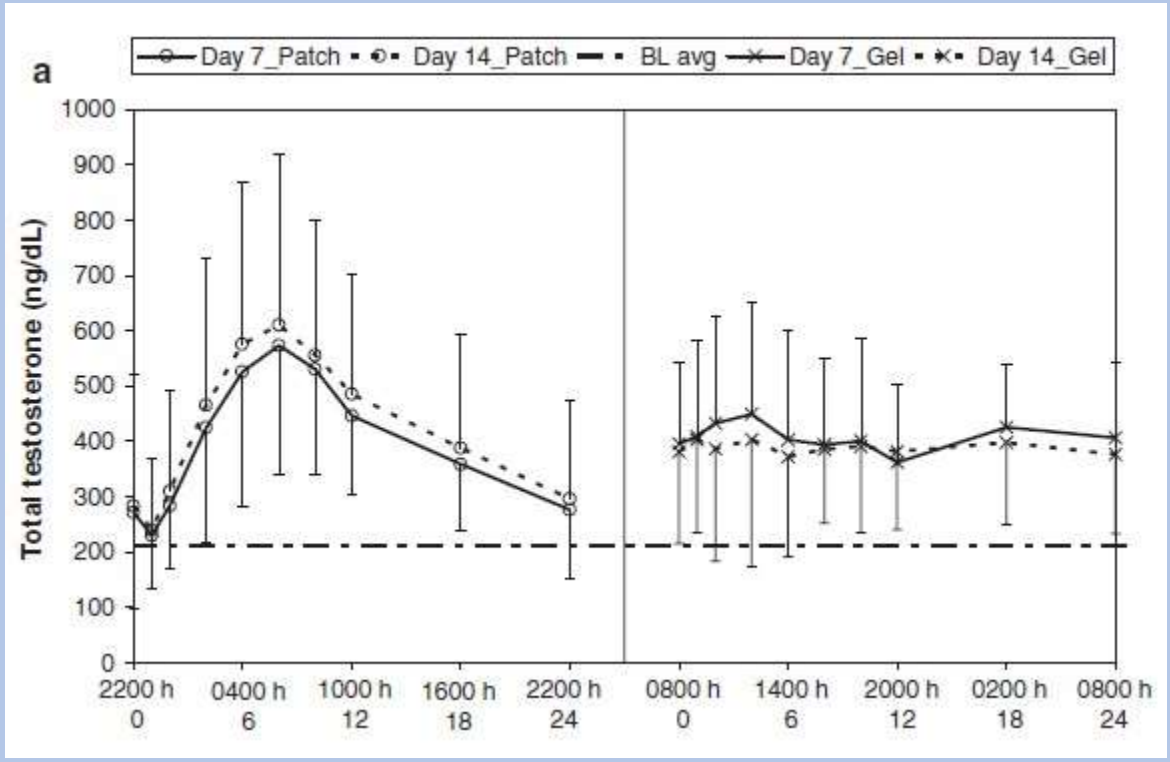
- Advantage: less frequent dosing, Stable level
- Disadvantage: procedure, risk of infection, extrusion with vigorous exercise. Long residence time, bleeding, subdermal fibrosis

Transdermal Gel

- Dosing:
  - 1%: starting dose: 50mg / max dose: 100mg
  - 1.62%: starting dose: 40.5mg / max dose: 81mg
  - 2%: starting dose: 40mg / max dose: 70mg
- Advantage: painless, steady levels (?)
- Disadvantage: potential transfer, cost, daily usage, skin irritation (5-7%), odor
- Apply daily to designated area and wait 5-10min to dry. Avoid showering, swimming, physical contact within 5h (due to left over residue)

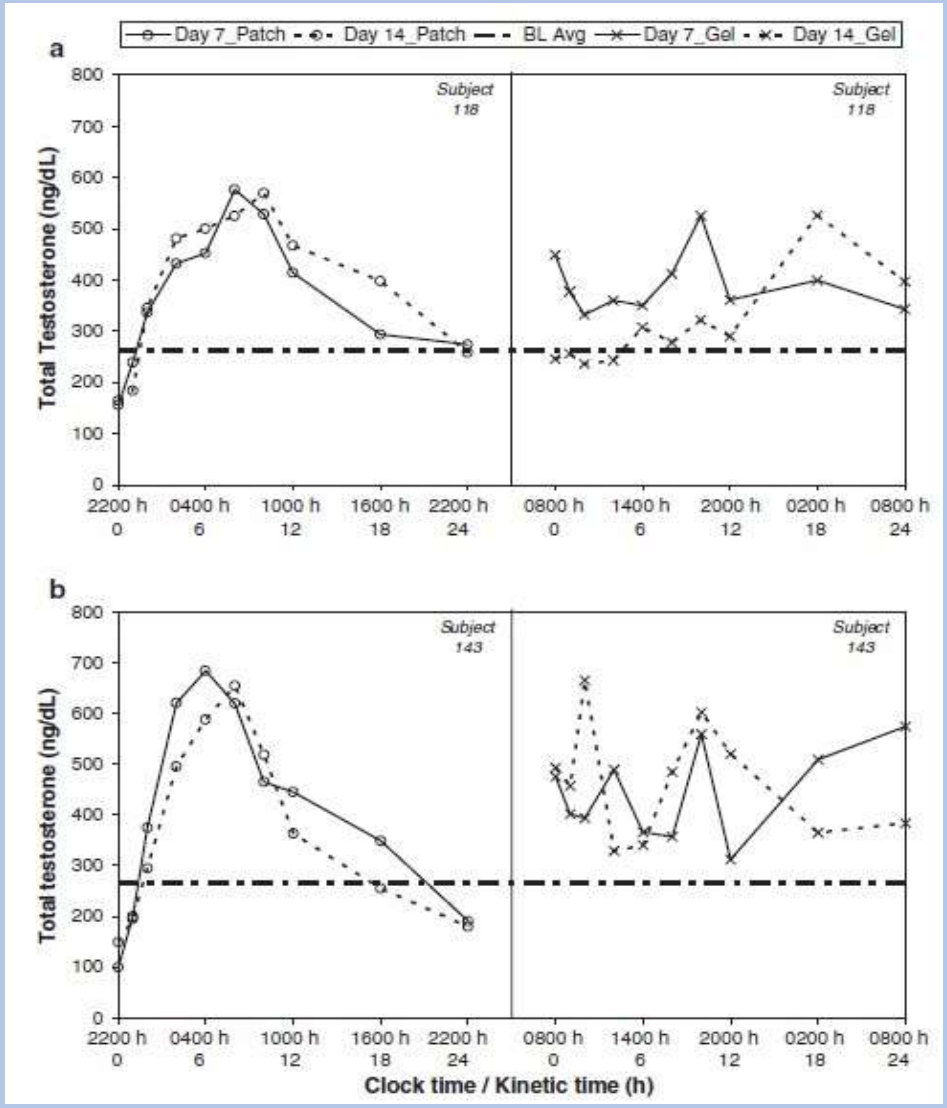
Transdermal Gel

- Peak: 2-4h
- Trough: 24h
- Steady state reached at 1-3 days
- Check: anytime after 1week



Mazer N, Bell D et al: Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. J Sex Med 2005;2: 213-226

- Steady level?



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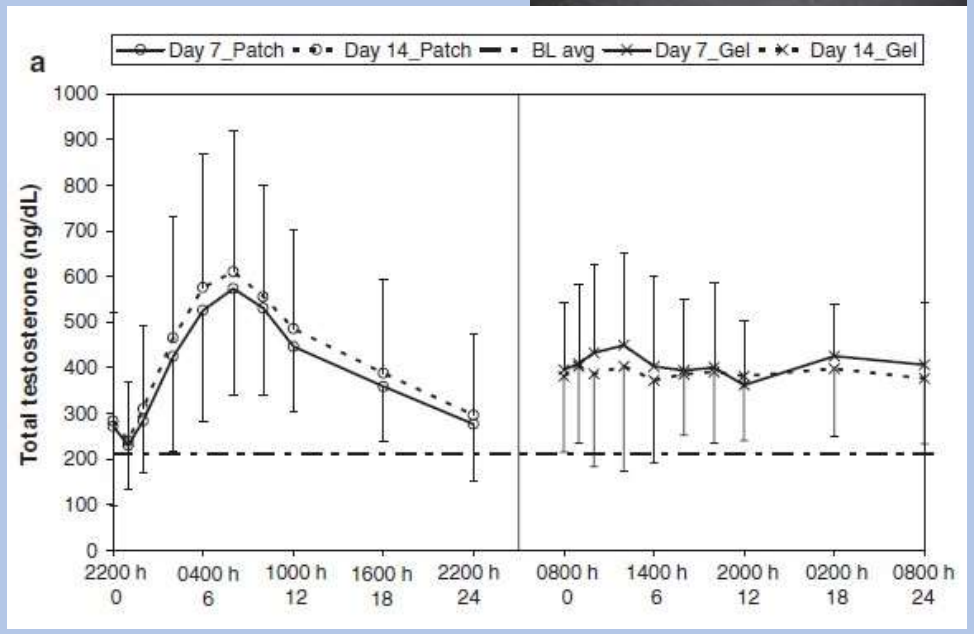
Transdermal patch

- Dose:
  - Available in 2mg and 4mg
  - Starting dose: 4mg
  - max dose: 8mg
- Peak: 3-10h (mimic physiologic level if applied at bedtime)
- Trough: 24h
- Check level 3-12h after application



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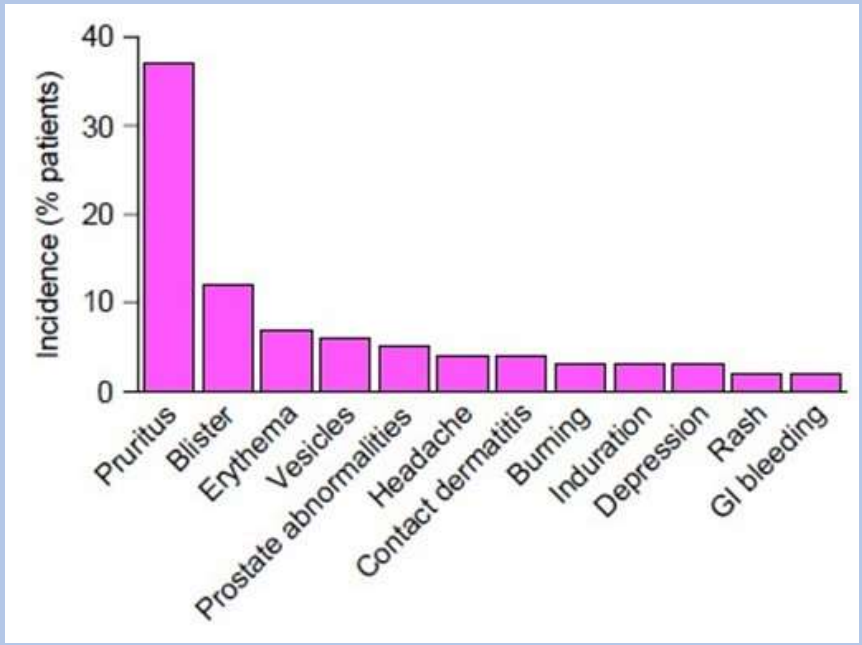
Transdermal patch

- Advantage: stable level, only transdermal option without risk of transference



- Disadvantage: rash (30-60%), cost, daily use

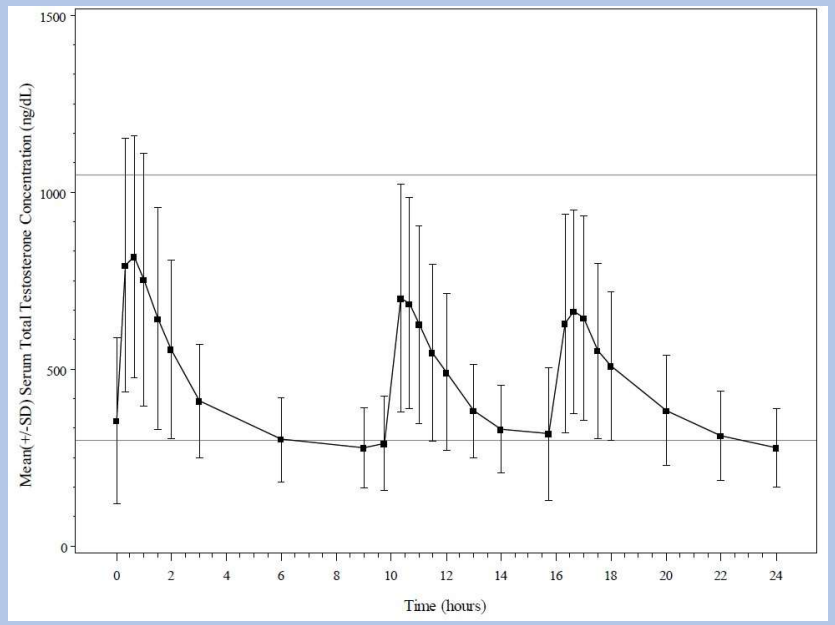
*Avoid bony prominences and pressure area

*May pre-apply 0.1% triamcinolone cream

Karen McClellan and Karen Goa: Tansdermal Testosterone. Drugs 1998 Feb; 55 (2): 253-258

Testosterone Nasal Gel

- Dosing: Metered pump (1 pump actuation=5.5mg)
  - 2 pumps (11mg) TID (about 6-8hrs apart)
  - Aim to the lateral wall of the nostril
  - Blow the nose before application and refrain from blowing the nose or sniffing for 1hr post application
- Peak: 40min / Trough: 8hrs
- Check: prior to each application



Testosterone Nasal Gel

- Advantage: physiologic level, easy to use
- Disadvantage: nasal discomfort (rhinorrhea, epistaxis, nasal scab, parosmia), cannot use in nasal disorders/decongestants, frequent dosing (TID), cost

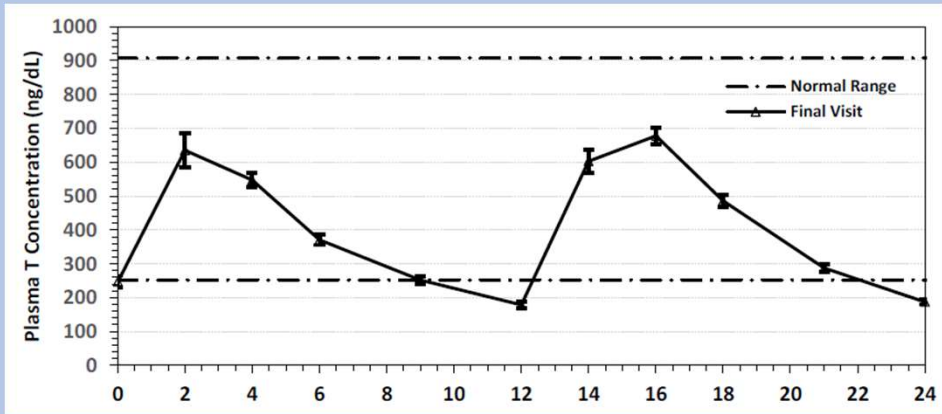
Nasopharyngitis	6 (8.7)
Rhinorrhea	5 (7.2)
PSA increased	4 (5.8)
Parosmia	4 (5.8)
Nasal discomfort	4 (5.8)
Nasal Scab	4 (5.8)
Upper respiratory tract infection	3 (4.3)
Bronchitis	3 (4.3)
Procedural pain	3 (4.3)
Pain in extremity	3 (4.3)
Headache	3 (4.3)
Epistaxis	3 (4.3)

Oral tab

Testosterone undecanoate

- Dose:
  - Jatenzo: 158/198/237mg. Start: 237mg BID / max: 396mg BID
  - Kyzatrex: 100/150/200mg. Start: 200mg BID / max: 400mg BID
  - Tlando: 112.5mg. Start/max: 225mg BID (no titration needed)
- Must be taken with food
- Peak: 2-5hrs / Trough: 2-8hrs
- Check: 3-6hrs after morning dose

  (After 1 week of therapy)



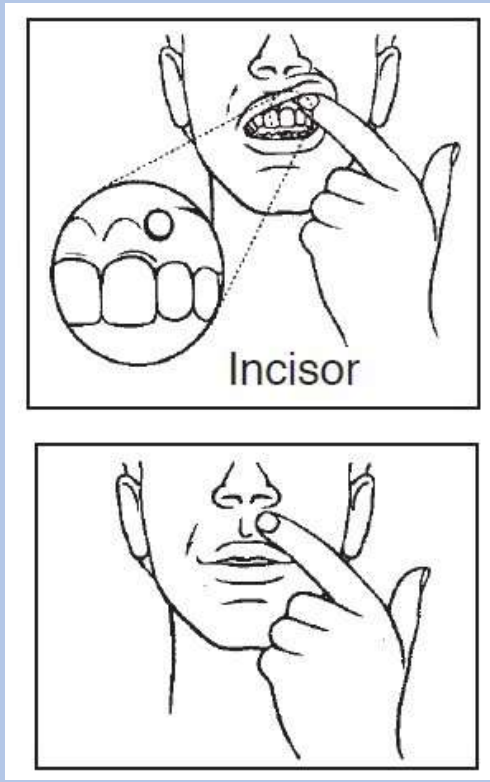
Oral Tab

- Advantage: oral (easy to use)
- Disadvantage: Headache, increase in BP, decrease in HDL, nausea, cost

Preferred Term	Overall (N = 166) n (%)
Headache	8 (4.8)
Hematocrit increased	8 (4.8)
Hypertension	6 (3.6)
High-density lipoprotein decreased	5 (3.0)
Nausea	4 (2.4)

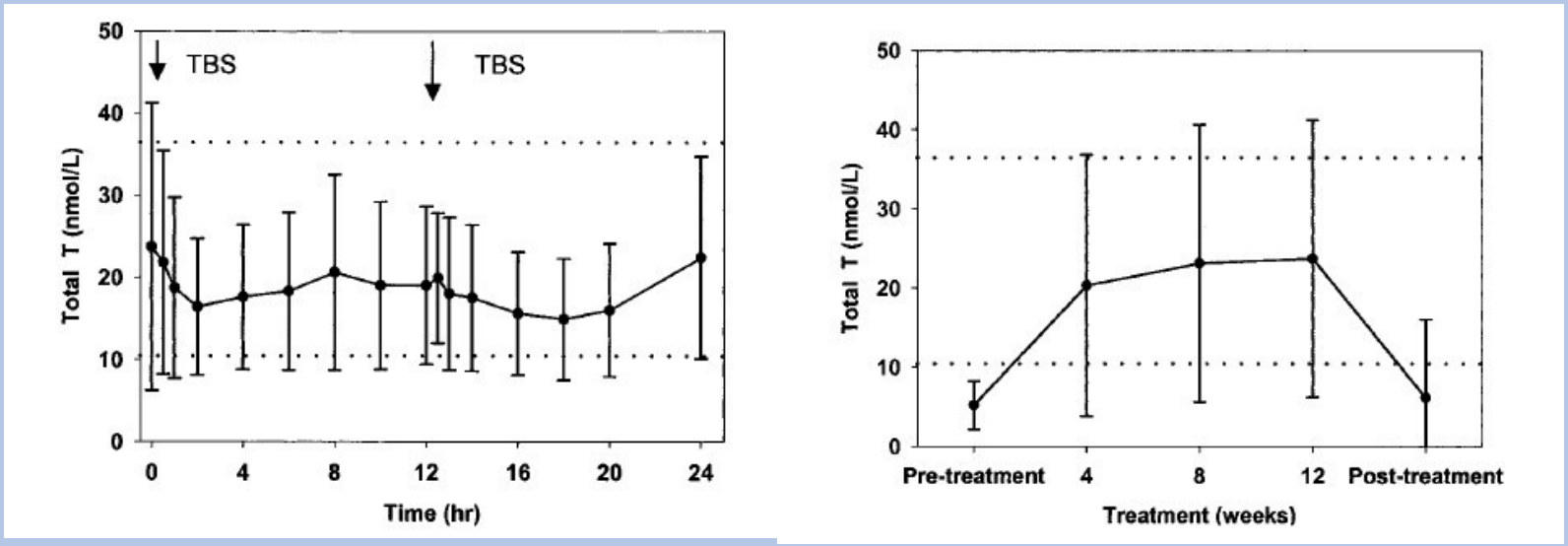
Buccal tab

- Dose: 30mg buccal ER tab
- Apply at depression in gum above the incisor (do not chew or swallow)
- Avoid first-pass liver metabolism via superior vena cava. (avoid liver toxicity)



Buccal tab

- Dosing: 30mg tab buccally q12h
- Check level: immediately before or after application



Wang C, Swerdloff R et al: New testosterone buccal system (Striant) delivers physiological testosterone levels: Pharmacokinetics study in hypogonadal men. J Clin Endocrinol Metab, August 2004, 89(8):3821–3829

Buccal tab

- Advantage: steady level
- Disadvantage: gum irritation (16%), altered taste, frequent dosing (q12h), cost

AE	Incidence, % N = 98
Gum or mouth irritation	9.2
Taste bitter	4.1
Gum pain	3.1
Gum tenderness	3.1
Headache	3.1
Gum oedema	2.0
Taste perversion	2.0

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Summary

- Understanding the differences between various routes of delivery is essential for right dosing and monitoring.
- Each has its own advantages and disadvantages/risks compared to other options. Clinicians have to be familiar with each option to be able to choose the most appropriate (the safest, most effective and affordable) option for each patient.