Testosterone Therapy (TTh) in Males: Best Practice

Doreen Saltiel, MD JD FACC

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Disclaimer

This lecture and the cited scientific literature, when referring to men/males, are referring to individuals born biological males.

Objectives

- Define testosterone deficiency (TD) and its diagnostic criteria
- Debunk the testosterone, prostate cancer (PC), and cardiovascular disease (CVD) myths
- Determine what else needs to be considered before initiating TD treatment
- Discuss treatment options

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What Do The Guidelines Say?

- American Urological Association (AUA): TT < 300ng/dL
- British Society for Sexual Medicine (BSSM): TT < 230ng/dL
- Canadian Medical Association Journal (CMAJ): TT No specific cutoff
- International Society for Sexual Medicine (ISSM): TT < 230ng/dL
- European Association of Urology (EAU): TT < 231ng/dL
- Endocrine Society Practice Guidelines: TT < 300ng/dL
- European Menopause and Andropause Society (EMAS): TT < 350ng/dL

TD: Making the Diagnosis

- In healthy males, testosterone decreases by ~ 1-2% per year
- The most common and reliable symptoms are sexual symptoms
  - Decreased libido is a primary TD symptom and may occur without any other symptoms
  - In men > 50 decreased libido strongly suggests TD, without other obvious causes
  - Other sexual symptoms include erectile dysfunction, difficulty achieving or maintaining an erection, etc.
- Non-sexual TD symptoms include
  - Fatigue, decreased energy, decreased vitality, depressed mood, irritability, “brain fog,” decreased motivation, etc.

Morgentaler A, et al. J Sex Med. 2014; 11(7): 1636-1645.
Morgentaler A, et al. Mayo Clin Proc. 2016; 91(7): 881-896.
Bhasin S, et al. J Clin Endocrinol Metab. 2018; 103(5): 1715-1744.
Morgentaler A, Traish AM. Sex Med Rev. 2020; 8(2): 286-296.

TD: Making the Diagnosis

- TD signs include
  - Loss of muscle mass, decreased BMD, and/or anemia
  - Decreased testicular volume (< 10mL)
- Laboratory Testing
  - Total Testosterone < 300-350ng/dL is a reasonable threshold, but not absolute
    - Multiple cofounding factor including SHBG level and androgen receptor sensitivity as measured by CAG repeats (> 24 repeats = decreased AR sensitivity, genedx.com)
      - CAG = cytosine, adenine, guanine; mean #: AA ~ 18-20, Caucasians ~ 21-23, East Asians ~ 22-23
  - Calculated Free T (FT-C) or equilibrium dialysis FT threshold levels of < 65-100pg/mL have been recommended
  - A TT < 200-250ng/dL is associated with adverse health outcomes, to include decreased BMD

Morgentaler A, et al. J Sex Med. 2014; 11(7): 1636-1645.
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TD: Making the Diagnosis

- Testosterone should be measured in the AM
  - Always measure a morning specimen x 2
  - In healthy young males, T has a diurnal pattern
  - In males > 40, this diurnal pattern may be lost
- Optimal total testosterone levels
  - > 500ng/dL to < 1,000ng/dL, with a goal of > 500ng/dL to 900ng/dL

Morgentaler A, et al. J Sex Med. 2014; 11(7): 1636-1645.
Morgentaler A, et al. Mayo Clin Proc. 2016; 91(7): 881-896.
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TD: Making the Diagnosis

- Testosterone should be measured in the AM
  - Always measure a morning specimen x 2

Clinical Pearl: A TD diagnosis requires a TT < 300-350ng/dL and sexual symptoms/signs

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Morgentaler A, et al. Mayo Clin Proc. 2016; 91(7): 881-896.
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What Tests Do We Do?

Serum is the gold-standard for testosterone testing and monitoring, DUTCH adds comprehensiveness

What Tests Do We Do?

- Serum laboratory testing
  - CBC, CMP, SHBG
    - 1st year: baseline, 1, 3, 6, 12 months
    - Ongoing: 2-3x year
  - Total testosterone (TT), free T (FT), E2 (LC-MS/MS)
    - 1st year: baseline, 1, 3, 6, 12 months
    - Ongoing: 2-3x a year
  - FSH, LH, prolactin
    - Prolactin: baseline
    - FSH, LH: baseline, 1, 3, 12 months, prn
  - Other
    - TFT's, vitamin D, etc.
    - Glycemic parameters
- PSA, DRE, testicular exam
  - PSA and DRE
    - 1st year: baseline, 3, ± 6, 12 months, at least yearly
  - Testicular exam
    - Baseline, at least yearly
    - Ultrasound: if diagnosis is unsure (< 10mL is abnormal)
- DUTCH testing
  - 1st year: baseline, 6, 12 months, 2-3x year
  - HPA axis: saliva or urine
  - Hormones
    - To evaluate hormone metabolism
    - Evaluate total androgen production and activity
    - To optimize detoxification pathways

ADAM Questionnaire

Check if you have any of the following:

- ❑ *1. Do you have a decrease in libido (sex drive)?*
- ❑ *2. Do you have a lack of energy?*
- ❑ *3. Do you have a decrease in strength and/or endurance?*
- ❑ *4. Have you lost height?*
- ❑ *5. Have you noticed a decreased "enjoyment of life"?*
- ❑ *6. Are you sad and/or grumpy?*
- ❑ *7. Are your erections less strong?*
- ❑ *8. Have you noticed a recent deterioration in your ability to play sports?*
- ❑ *9. Are you falling asleep after dinner?*
- ❑ *10. Has there been a recent deterioration in your work performance?*

If you checked question **1** or **7** or ***any 3 other questions***, you may have low testosterone. A simple blood test can determine your testosterone level. **Talk with your doctor to see if you should be tested.**

Morley JE, et al. Metabolism. 2000; 49(9): 1239-1242.

IIEF-5 Questionnaire

The IIEF-5 Questionnaire (SHIM)

Please encircle the response that best describes you for the following five questions:

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never of never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5

Rosen RC, et al. Int J Impot Res. 1999; 11(6): 319-326.

IIEF-5 scoring

- Severe: 1-7
- Moderate: 8-11
- Mild-Moderate: 12-16
- Mild: 17-21
- No ED: 22-25

Key Points

- A TD diagnosis requires both a TT < 300-350ng/dL and sexual symptoms/signs
  - Example: TT < 350ng/dL with a FT 75pg/dL (LC-MS/MS) and sexual symptoms
  - Example: TT < 300ng/dL with a FT ~ 75pg/mL (LC-MS/MS) and sexual symptoms
- In a male > 50 years old, with SS consistent with TD (ADAM, IIEF-5), low TT and/or FT-C, evaluate and treat all underlying etiologies, and consider TTh
- In a male < 50 years old, with SS consistent with TD (ADAM, IIEF-5)
  - **Primary TD** (elevated LH and low TT and/or FT-C), after ruling out other possible etiologies, TTh is the treatment of choice
  - **Secondary TD** (low or normal LH, low TT and/or FT-C), evaluate and treat all underlying etiologies and recommend against TTh as the first choice, use other options: peptides (kisspeptin, gonadorelin) clomid, nutraceuticals

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  - Discuss treatment options

TTh in Males (> 50 years old) with TD

TTh benefits

- Sexual signs and symptoms
- Body composition
- Bone mineral density

TTh risks

- Prostate cancer
- Cardiovascular disease

How do we optimize these,
While minimizing these

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TTh Benefits in Males with TD

- Regardless of delivery, a serum TT level > 500ng/dL improves sexual function, body composition, BMD, CV outcomes, and does not increase PC
  - AndroGel: 50-100mg/d; T pellets: average dose 750mg; T creams: 50-100mg/d
  - Testosterone Undecanoate: 750-1000mg initially, then at 6-weeks, then Q10-12 weeks
- Serum total E2 levels should be maintained between 20-40pg/mL (LC-MS/MS), goal 30-35pg/mL for optimum benefit
  - Sexual function, BMD, etc.
- Young males on clomid, gonadorelin, kisspeptin
  - After treatment for 6 months to 1 year + lifestyle changes, there will be a percentage of males who no longer require therapy
  - Stop treatment for 3 months and re-evaluate patient

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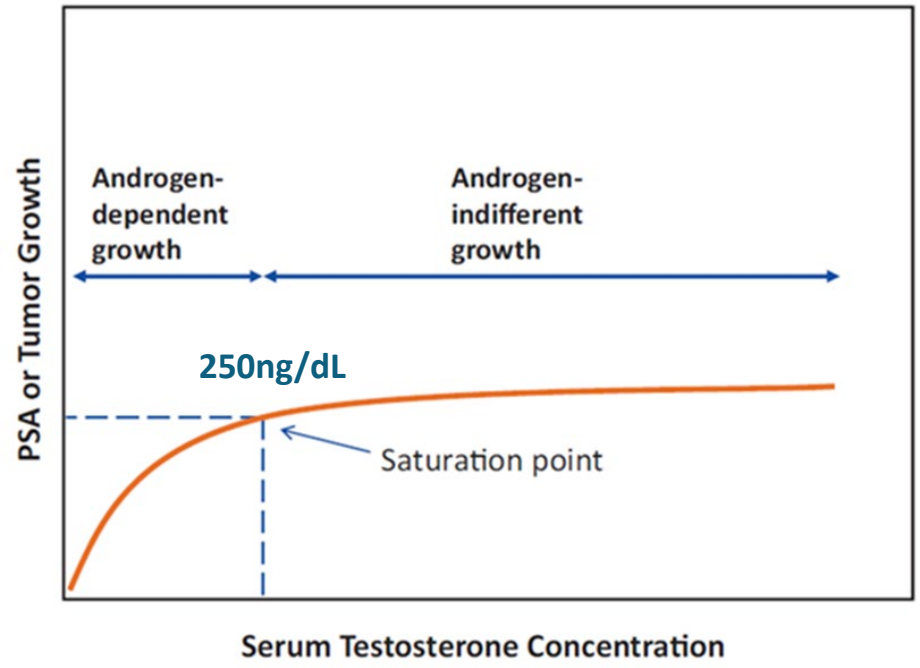
TTh Does Not Increase PC

- Rhoden and Morgentaler literature review (2004)
  - No compelling evidence that higher endogenous TT levels or TTh was associated with PC risk
- Roddam, et al. 18 prospective study collaborative analysis (2008)
  - No association between PC risk and serum TT or DHT

Rhoden EI, Morgentaler A. N Engl J Med. 2004; 350(5): 482-492.
Roddam AW, et al. J Natl Cancer Inst. 2008; 100(3): 170-183.
Muller RL, et al. Eur Urol. 2012; 62(5): 757-764.

TTh Does Not Increase PC



- The Saturation Model (2009)
  - T has a limited ability to stimulate prostate growth
  - Prostate tissue is exquisitely sensitive to changes in serum TT at low concentrations, but becomes indifferent to changes at higher TT concentrations
  - The saturation point, the TT concentration at which androgen binding to the androgen receptor is maximal, is approximately 250ng/dL
  - A threshold effect occurs, in which increasing TT levels reach a limit (the saturation point) beyond which there is no further ability to induce androgen-driven changes in prostate tissue growth

- With a TT < 250ng/dL, expect PSA to increase as TT levels increase
- With a TT > 250ng/dL, typically there is minimal PSA increase as TT levels increase

Morgentaler A, Traish AM. Eur Urol. 2009; 55(2): 310-320.
Morgentaler A. Eur Urol. 2012; 62(5): 765-767.
Khera M, et al. Eur Urol. 2014; 65(1): 15-23.

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TTh Does Not Increase PC

- Muller, et al. REDUCE trial's placebo arm (2012)
  - Randomized, double-blind, placebo-controlled, parallel-group study
  - Assessed dutasteride's effect on incident PC
    - The study found that dutasteride did decrease incident PC risk (biopsy diagnosis) and prostate hyperplasia
  - Placebo arm results
    - PC risk is unrelated to serum androgen concentrations
    - Higher TT levels do NOT predispose to PC and low TT levels are not protective
  - Lays to rest the false belief that T increases PC risk

- Endogenous T and/or TTh DOES NOT increase PC risk

Rhoden EI, Morgentaler A. N Engl J Med. 2004; 350(5): 482-492.
Roddam AW, et al. J Natl Cancer Inst. 2008; 100(3): 170-183.
Muller RL, et al. Eur Urol. 2012; 62(5): 757-764.

TTh Does Not Increase PC

Author/Date	Study Design	Results
Testosterone Therapy Does NOT Increase Prostate Cancer		
Cui, 2014	• Metanalysis: 22 RCTs	• Males treated with TTh, regardless of duration, dose, or delivery method had no increased PC risk when compared to placebo
Loeb, 2015	• Nested case-control study	• In males treated with TTh, there was no association between TTh and PC • T-treated males, if developed PC, had more favorable and less aggressive disease
Baillargeon, 2015	• Long-term observational study	• TTh exposure did not increase high grade PC risk • High-grade PC did not increase as the number of T injections increased • In TTh treated males, those who did develop PC did not necessitate ADT (more favorable disease)
Schenk, 2016	• PCPT's placebo arm analysis	• Prostate Cancer Prevention Trial (PCPT) • Similar results to Muller: males with high TT and/or DHT levels had no greater PC risk than males with the lowest concentrations
Wallis, 2016	• Population-based retrospective matched cohort	• Confirmed Baillargeon's results: Long-term TTh was associated with reduced PC risk

TTh in Males (> 50 years old) with TD

TTh benefits

- Sexual signs and symptoms
- Body composition
- Bone mineral density
- Prostate health

TTh risks

- Prostate cancer
- Cardiovascular disease

How do we optimize these,
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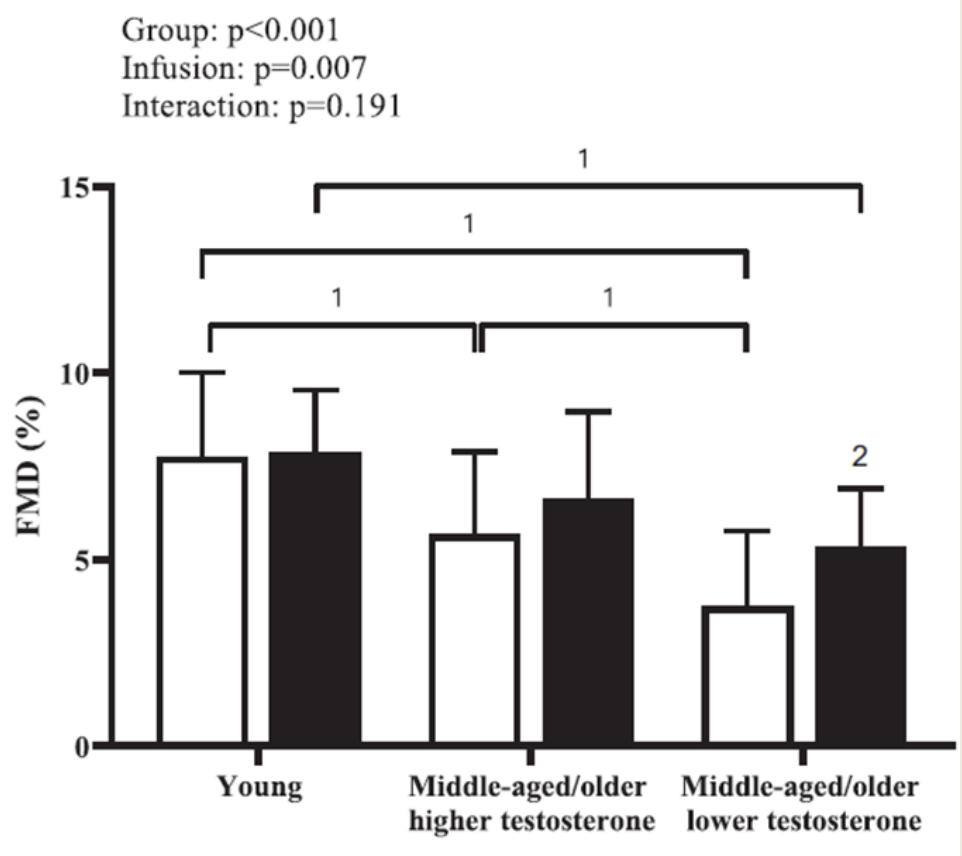
Testosterone, TTh, and CVD

- Testosterone's endothelial effects
  - Testosterone is an independent determinant of endothelial function
  - Testosterone deficiency (TD) leads to endothelial dysfunction
    - TD decreases NO production
    - TD increases ADMA expression (competitive inhibitor of eNOS)
      - Nitric oxide synthase is the enzyme responsible for converting arginine to NO
    - TD decreases endothelial progenitor cells (involved in endothelial repair)
  - TD increases proinflammatory cytokines (IL-6, IL-1β, TNF-α)
  - Testosterone therapy (TTh) decreases proinflammatory cytokines and increases anti-inflammatory cytokines, i.e., IL-10

Hotta Y, et al. Sex Med Rev. 2019; 7(4): 661-668.
Moreau KL, et al. Biol Sex Differ. 2020; 11(1): 18.
Babcock MC, et al. J Clin Endocrinol Metab. 2021; dgab175.

TD Associated Endothelial Dysfunction is Related to Inflammation and Oxidative Stress



- Objective: Determine if middle-age/older males with low TT would have greater age-associated endothelial dysfunction, related to inflammation and oxidative stress
- Study: Cross-sectional study; 58 healthy males: 20 younger, 20 middle-age/older higher TT, 20 middle-aged/older lower TT
  - Younger (20) TT: 500 ± 58ng/dL
  - Middle-aged/older higher TT (20): 512 ± 115ng/dL
  - Middle-aged/older lower TT (18): 269 ± 48ng/dL

Babcock MC, et al. J Clin Endocrinol Metab. 2021; dgab715.

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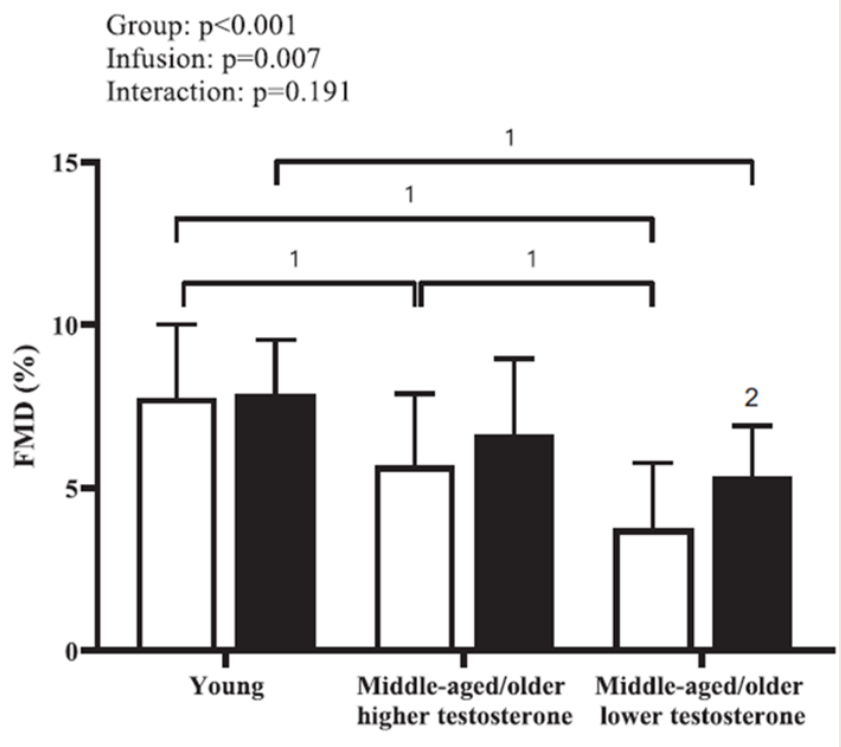
TD Associated Endothelial Dysfunction is Related to Inflammation and Oxidative Stress



- Results:
  - Middle aged/older high TT vs control (young males normal TT)
    - SS decreased endothelial function when compared to young
    - After vitamin C, no longer SS
  - Middle aged/older lower TT vs control vs higher TT
    - SS decreased endothelial function when compared to higher TT and young
    - Vitamin C
      - SS improvement when compared to baseline
      - Improved endothelial function, no longer SS different than high TT, but still SS different than young

- Lower TT may be associated with accelerated vascular aging 2^0 endothelial dysfunction, in part due to increased inflammation and oxidative stress
- Physiologic TT levels may attenuate age-related endothelial dysfunction, by decreasing inflammation and oxidative stress

Babcock MC, et al. J Clin Endocrinol Metab. 2021; dgab715.

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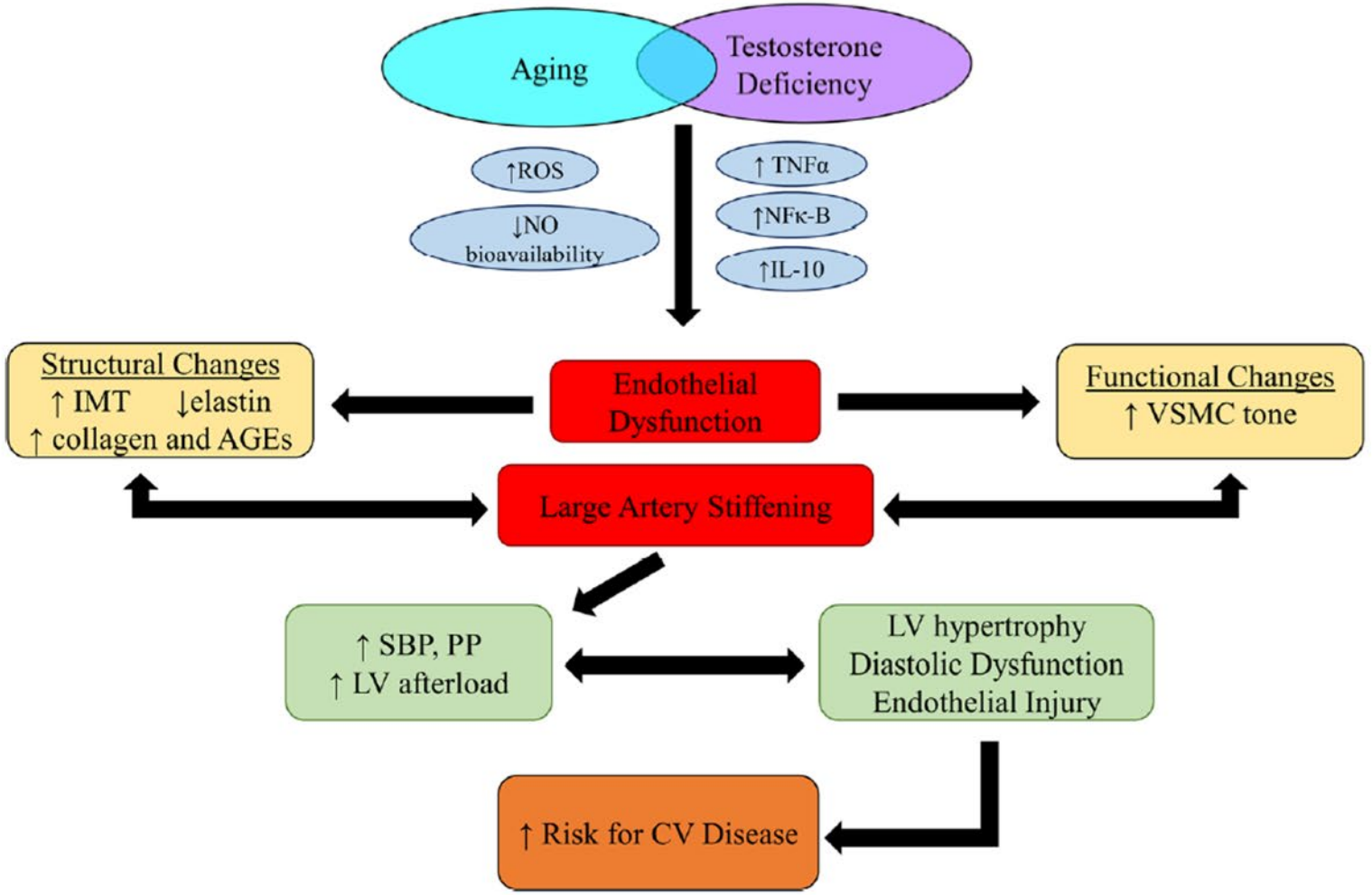
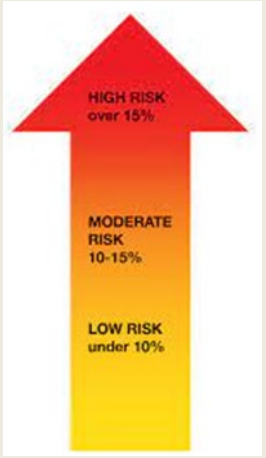


Fig. 1 Hypothesized mechanisms by which testosterone deficiency may contribute to vascular aging in women and men. AGEs, advanced glycation end products; CV, cardiovascular; IL-10, interleukin-10; IMT, intima-media thickness; LV, left ventricle; NFκ-B, nuclear factor κ-B; NO, nitric oxide; PP, pulse pressure; SBP, systolic blood pressure; ROS, reactive oxygen species; TNFα, tumor necrosis factor-α, VSMC, vascular smooth muscle cell

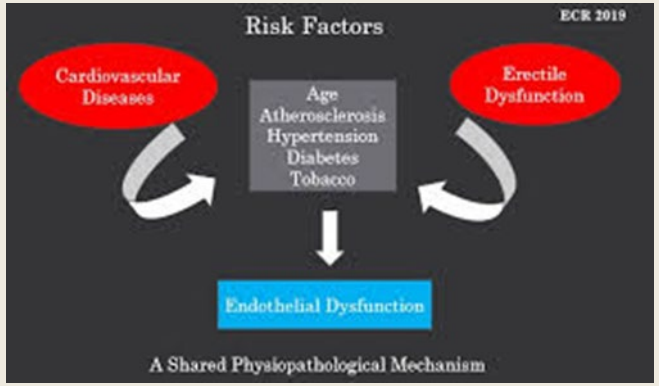
Moreau K, et al. Biol Sex Differ. 2020; 11(1): 18.

Question

In males, what else do we need to think about when considering CVD risk stratification?



cvdcheck.org.au



epos.myesr.org

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Males

"Erectile dysfunction should be considered a vascular disease until proven otherwise."

Graham Jackson, MD

Jackson G, et al. Int J Clin Pract. 2013; 67(11): 1163-1172.

Erectile Dysfunction and CVD Link

- EGX degradation and endothelial dysfunction are common links between erectile dysfunction and CVD
  - Erectile dysfunction and CVD share the same set of CVD risk factors
  - Vascular erectile dysfunction is an independent CVD risk marker
  - Erectile dysfunction may indicate subclinical vascular disease in an otherwise asymptomatic male, especially 40-60 years old
  - CVD patients are more likely to have erectile dysfunction, and erectile dysfunction patients are more likely to develop CVD in the future

Jackson G, et al. Int J Clin Pract. 2013; 67(11): 1163-1172.
Miner M, et al. Sex Med Rev. 2019; 7(3): 455-463.

Erectile Dysfunction and CVD Link

- Erectile dysfunction symptoms and CVD
  - There is a 2-5-year interval between erectile dysfunction onset and CVD events
  - Erectile dysfunction severity is correlated with coronary disease burden
  - Erectile dysfunction has been independently associated with CVD events

Jackson G, et al. Int J Clin Pract. 2013; 67(11): 1163-1172.
Miner M, et al. Sex Med Rev. 2019; 7(3): 455-463.

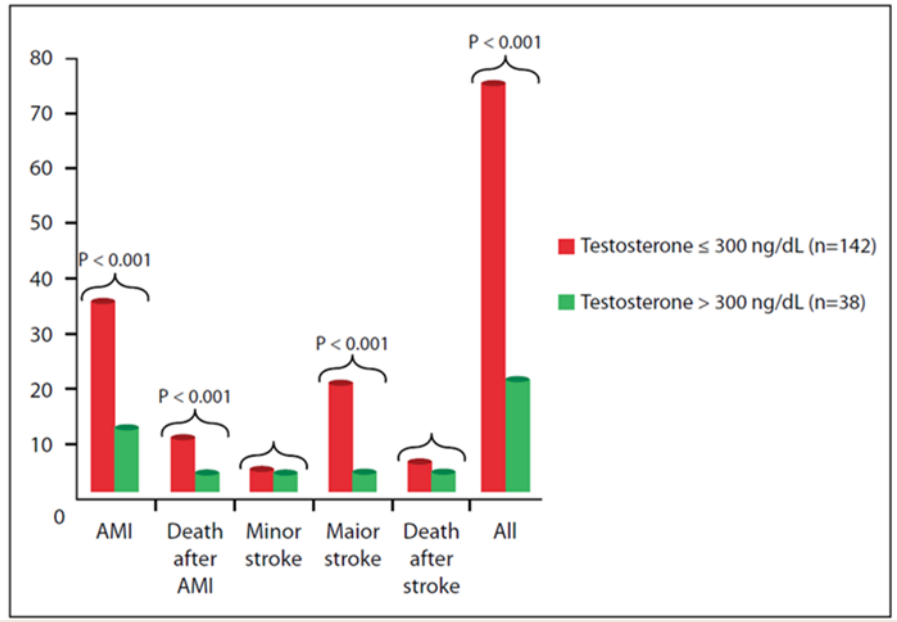
Males, Erectile Dysfunction, and CVD Events

- Zhao, et al. Erectile dysfunction predicts CV Events (2018)
  - Comprehensive literature review and meta-analysis
  - Objective: assess whether erectile dysfunction was an independent risk factor for CV events
  - Study: 154,794 males
  - Results: Severe erectile dysfunction predicted higher CVD and all-cause mortality risk
    - When compared to males without erectile dysfunction, males with erectile dysfunction had a SS increase in CVD by 43%, CAD by 59%, stroke by 34%, and all-cause mortality by 33%
    - Older males (≥ 55 years old), males with erectile dysfunction for a shorter duration (≤ 7 years), and males with DM and smoking history, were more prone to develop CVD

- CVD, CAD, stroke, and all-cause mortality may be significantly increased in males with erectile dysfunction, especially severe erectile dysfunction

Zhao B, et al. J Sex Med. 2019; 16(7): 1005-1017.

Males, Erectile Dysfunction, TD, and CVD Events



- Objective: Assess the testosterone's prognostic significance on CV outcomes
- Study: 5-year prospective study assessing CVD in males with erectile dysfunction and TD
  - 802 males, 40-80 years old at intermediate CV risk
    - Framingham 10-year CAD event: 10-20%
  - TT levels > 300ng/dL considered normal
  - FMD and IIEF-5 questionnaire administered

Iacona R, et al. Arch Ital Urol Androl. 2017; 89(4): 313-315.

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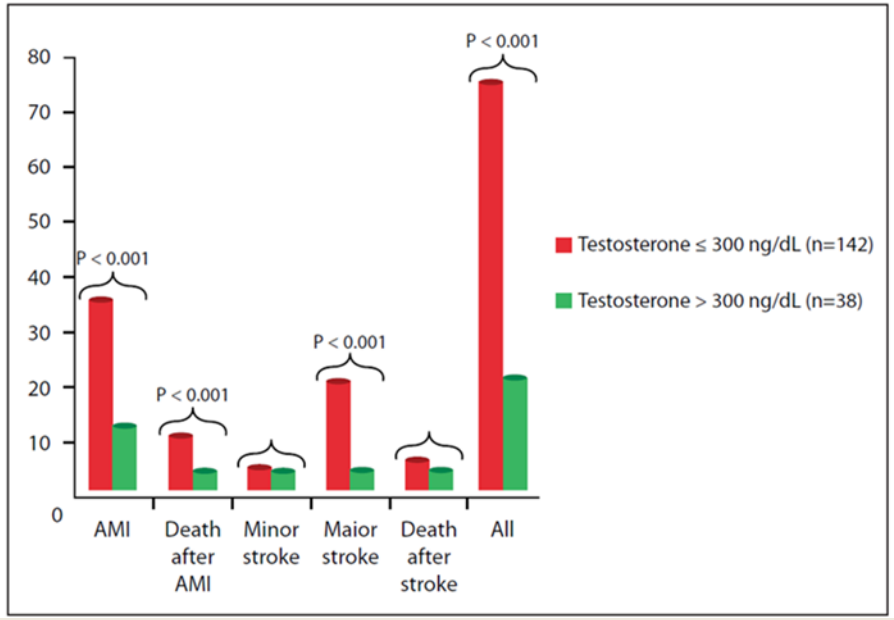
Males, Erectile Dysfunction, TD, and CVD Events



- Results:
  - TT < 300ng/dL had SS higher prevalence of
    - HTN, DM, hyperlipidemia, obesity, endothelial dysfunction
  - TT < 300ng/dL SS more frequent
    - AMI, death post-MI, major stroke, and the composite of all MACE
  - Future CV event independent predictors
    - Dyslipidemia, obesity, TT < 300ng/dL, and erectile dysfunction

- Males with CVD risk factors and erectile dysfunction should have TT levels checked
- TTh may prevent future CV events

Iacona R, et al. Arch Ital Urol Androl. 2017; 89(4): 313-315.

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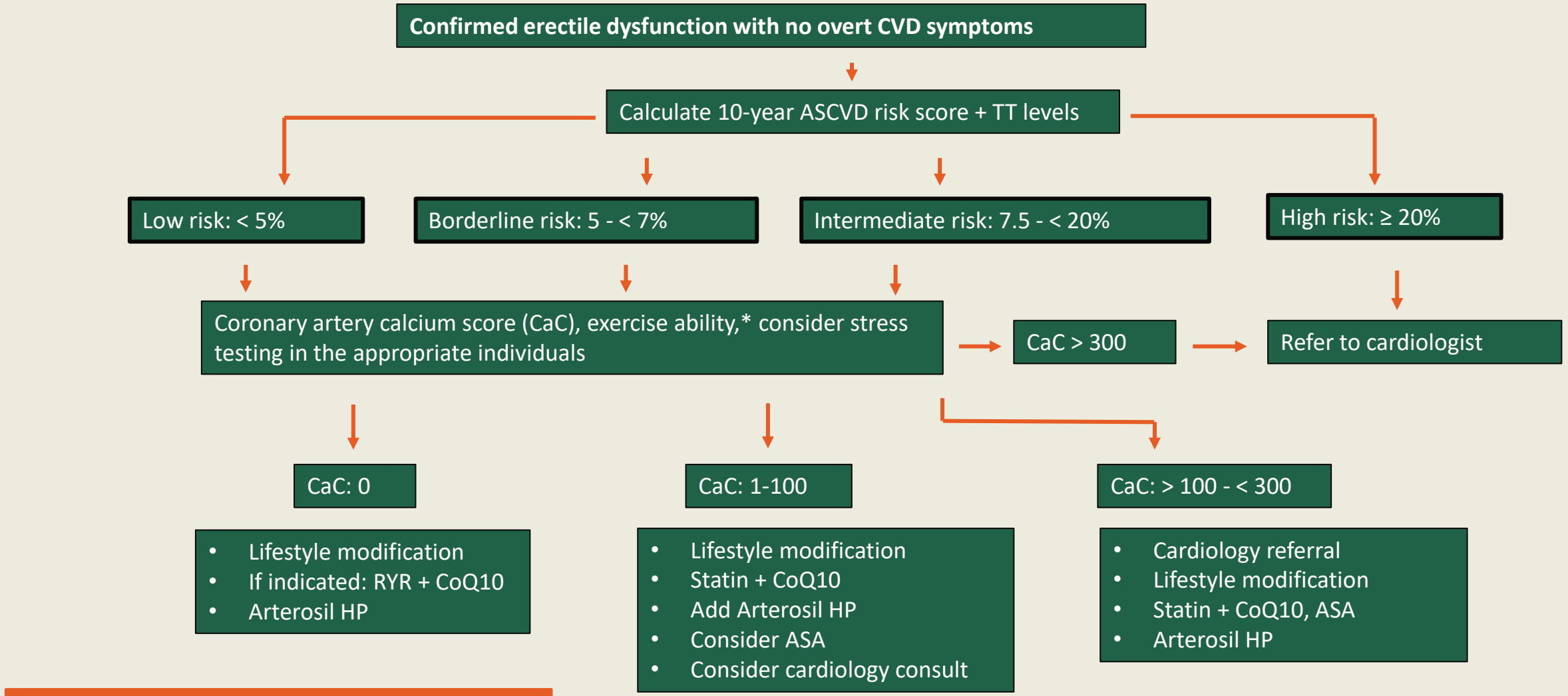

- Sexual activity = walking 1 mile on a flat surface in 20 minutes, briskly climbing 2 flights stairs in 10 sec, or walking 4 min using the Bruce treadmill protocol

Adapted from: Miner M, et al. Sex Med Rev. 2019; 7(3): 455-463.
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

Key Points and Clinical Pearls

- Erectile dysfunction is common and shares the same risk factors and pathophysiology with CVD
  - All males with erectile dysfunction should undergo CV risk stratification
- Erectile dysfunction is commonly associated with TD
  - All males with erectile dysfunction should have 2 AM TT levels checked on separate days, improving TT levels may decrease major CV events
- Erectile dysfunction is a general vascular disease marker and precedes a CV event by 2-5 years
- Erectile dysfunction is highly prevalent in CAD patients and is associated with increased all-cause mortality

Question

Why is there a black-box warning on all testosterone prescriptions regarding possible increase in CVD; when we know that TTh improves endothelial function, and TD leads to endothelial dysfunction, inflammation, and oxidative stress?

Question

Why is there a black-box warning on all testosterone prescriptions re: possible increase in CVD?

4 studies, whose accuracy, validity, and credibility are questioned by experts all over the world, as well as the FDA, prompted the mandated warning

Study	Design/Drugs	Results
Studies suggesting increased CV risk		
Basaria, 2010	• TOM Trial; 6-month RCT, older frail males • Mean age 74 years old • Maintain TT levels > 500 to < 1,000ng/dL • Not a CV study • Primary objective: assess whether T gel increased muscle strength and physical function in elderly frail males	• T significantly improved leg press muscle strength, chest press strength, and stair climbing power • Increased "CV events" stopped study early • Most CV events were not clinically significant: palpitations, PVCs, NS EKG changes, pedal edema • 4 clinically significant events occurred in males with higher TT levels (> 1000ng/dL) who were given higher than recommended T doses
Vigen, 2013	• Retrospective 3-year, VA observational study • No TTh mean age 63.8 years, TTh mean age 60.6 years • Males with TD, undergoing coronary angiography • Compared those who received T prescriptions with those who did not	• Initial results: 3-years after angiography, T prescriptions were associated with increased CV events • However, data flawed and contaminated (10% females) • Reanalysis documented a 10.1% absolute event rate in T prescriptions vs 21.1% events in the non-T group
Finkle, 2014	• Retrospective, observational study of a health insurance database • Grouped as males ≥ 65 years or ≤ 65 years • Assessed nonfatal MI rates up to 90 days after a T prescription	• Compared post-prescription MI rates to pre-prescription MI rates, which are unrelated • No validation of actual events, only used ICD codes • No control group, important data points, i.e., TT levels, risk factors, etc. were unknown • T-related events were low and lower than that expected in the general population

Xu, 2013	• Metanalysis 27 RCTs
	• Copenhagen study: mean age 53 years old
	• TOM trial: mean age 74 years old
	• Assessed CV events and TTh
		• 2 studies made up 35% CV events
		  • Basaria (TOM) 2010 study; events of questionable clinical significance
		  • Copenhagen study involving high dose oral T resulting in supraphysiologic TT levels in males with cirrhosis; most common CV adverse event was esophageal variceal bleeding
		• When 2 studies removed: no SS difference in event rates between T-treated males and the placebo group

Study	Design/Drugs	Results
Studies suggesting decreased CV risk		
Basaria, 2015	• TEAAM Trial, 3-year RCT • Determined if increasing TT levels into the mid-normal range (500-900ng/dL) would affect CIMT or CaC • Same authors as TOM study	• No increase in CIMT or CaC in T-treated when compared to placebo
Snyder, 2016	• Testosterone Trials (T Trials) • 1-year RCTs with a 2nd year safety follow-up • 3 main studies with 4 additional studies	• Intervention trials: MACE rates were identical when comparing TTh vs placebo groups • Second year (safety data): T-treated males with fewer CV events, hospitalizations, or deaths than placebo
Budoff, 2017	• T Trial: CV study • 1-year RCT, 2nd year follow-up • 138 men at moderate to high risk for a CV event • Assessed noncalcified plaque volume, CaC	• T-treated males had higher non-calcified coronary plaque volume; unclear how translates clinically • No increase in CaC or calcified plaque when T-group compared with placebo • No difference in MACE between T-treated and placebo
Sharma, 2015	• Large, retrospective, observational study • Compared TTh resulting in normal TT levels (TTh-normal) vs TTh resulting in persistently low TT (TTh-low) vs no TTh (no-TTh) • Study objective was to evaluate TTh's association with all-cause mortality, MI, and stroke • Study duration 4.6-6.2 years	• Compared to no-TTh, TTh-normal levels had a 56% reduction in death, 24% reduction in MI, and a 35% reduction in stroke • Compared to TTh-low, TTh-normal had a 37% reduction in death, 18% reduction in MI, and a 30% reduction in stroke • Compared to no-TTh, TTh-low had a decreased mortality • Adverse events similar between the 2 groups
Anderson, 2016	• 3-year, retrospective observational study • Compared males with low serum TT levels who received TTh and either had low, normal, or high T levels • MACE: nonfatal MI, stroke, death	• Confirmed Sharma's 2015 study results • Males who achieved normal TT levels, 3-year MACE rates were significantly lower than males with low TT • MACE rates similar in males with normal TT and high TT • However, males in high TT-group trended toward increasing stroke rates
Wallis, 2016	• Retrospective, population-based, cohort observational study • Follow-up duration ~ 5.3 years in the TTh group and 5.1 years in the control group	• TTh was associated with decreased mortality • Longer the TTh, greater the risk reduction
Cheetham, 2017	• Retrospective, cohort study • Evaluated the association between TTh and CV outcomes • Composite outcome: AMI, coronary revascularization, unstable angina, stroke, transient ischemic attack (TIA), and sudden cardiac death (SCD) • Follow-up 3.4 years	• T treatment was associated with decreased CV adverse outcomes after a median follow-up of 3.4 years • The hazard ratio for adverse CV events was one-third lower in the TTh group when compared to the non-treated group

Question

Should there be a black-box warning on T prescriptions?

Probably Not!

CVD Summary

- Testosterone is an immune modulator
- TD is associated with increased CV events
- Erectile dysfunction is an independent CV disease marker in males with and without TD
- In males with TD, screen for erectile dysfunction and CVD
- In males with erectile dysfunction, screen for TD and CVD
- In males with and without premature CVD, screen for TD and erectile dysfunction

TTh in Males (> 50 years old) with TD

TTh benefits

- Sexual signs and symptoms
- Body composition
- Bone mineral density
- Prostate health
- CVD

TTh risks

- Prostate c
- C ase

How do we optimize these,
While minimizing these

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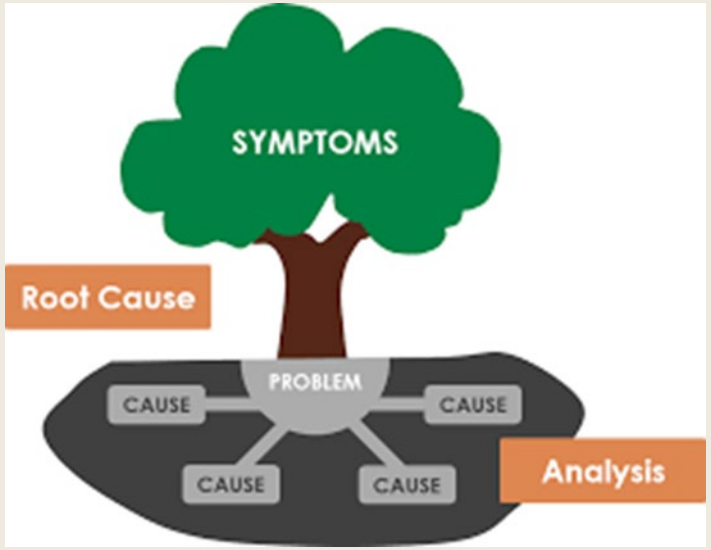
Objectives

- Define testosterone deficiency (TD) and its diagnostic criteria
- Debunk the testosterone, prostate cancer (PC), and cardiovascular disease (CVD) myths
- Determine what else needs to be considered before initiating TD treatment
- Determine treatment options

Root Cause Analysis



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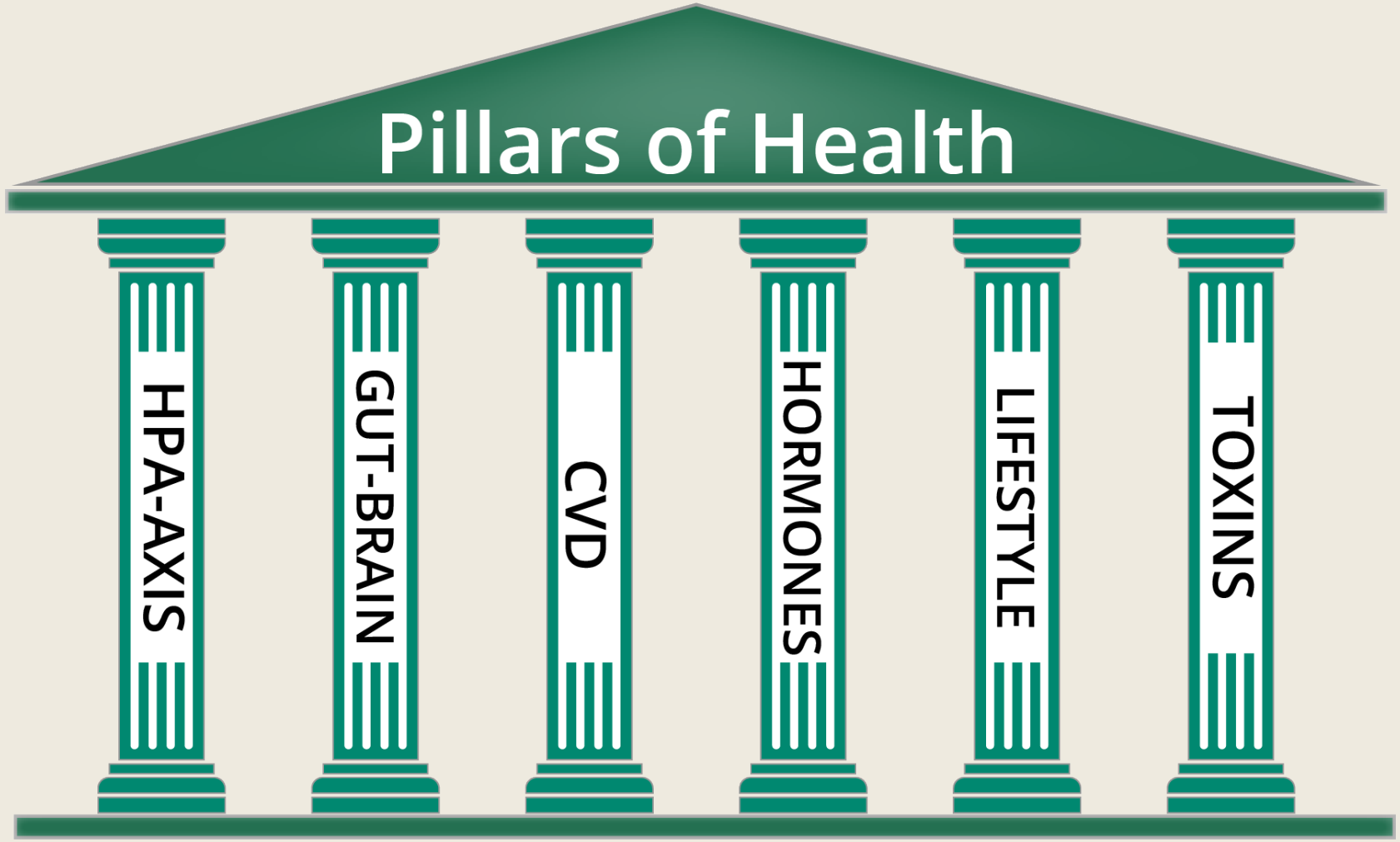
Risk Factors Matter



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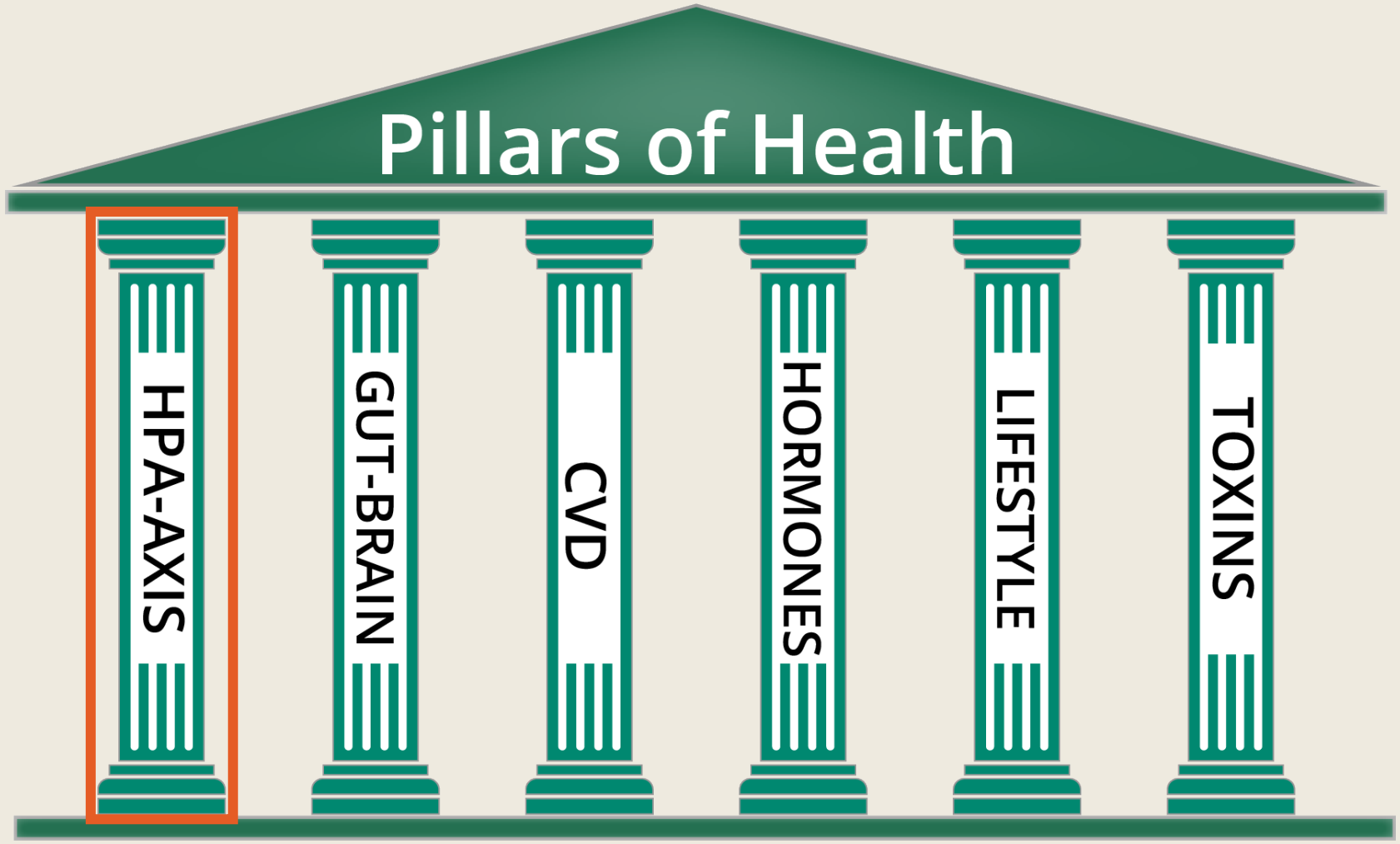

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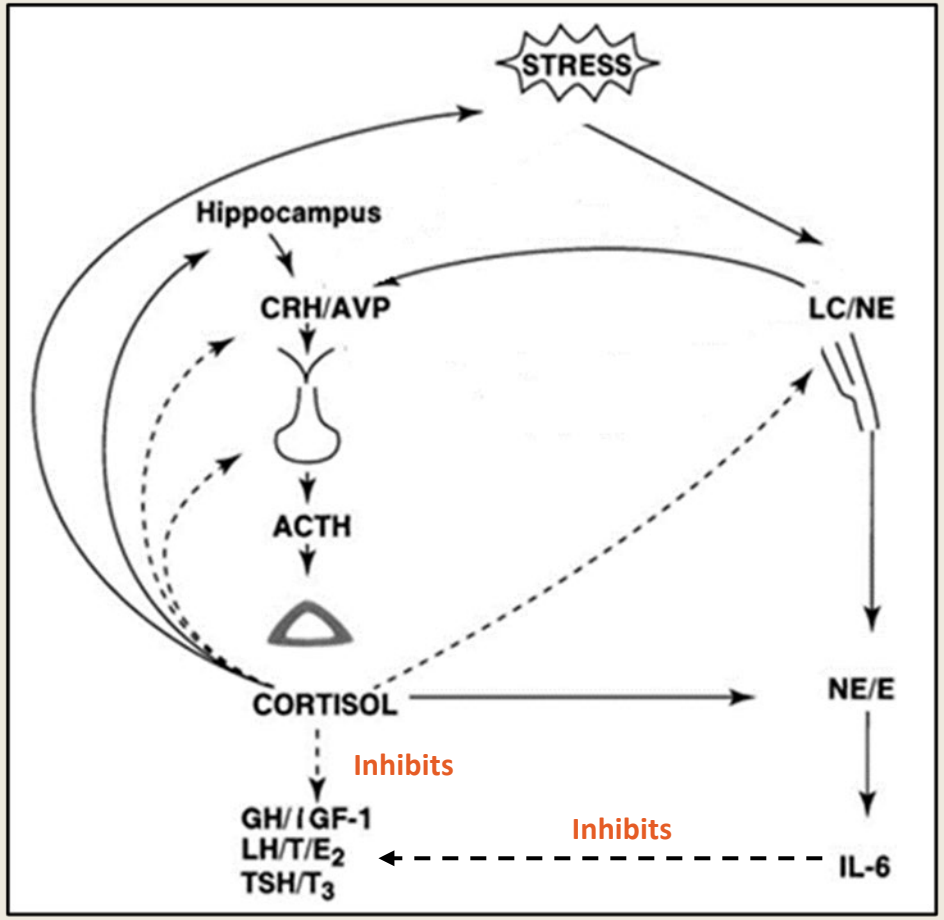
HPA and HPG Axes



- Chronic Stress, HPA axis dysfunction, and the HPG axis
  - Stress → ↑CRH, which suppresses gonadotrophin releasing hormone (GnRH), FSH, and LH
  - Elevated cortisol inhibits FSH, LH, and leads to gonadal tissue receptor resistance, thus decreasing TT levels, and T's effectiveness
  - Chronic stress increases inflammation, which also effects testicular function, decreasing LH and T

Tsigos C, Chrousos GP . J Psychosom Res. 2002; 53(4): 865-871.
Pasquali R. Ann N Y Acad Sci. 2012; 1264(1): 20-35.

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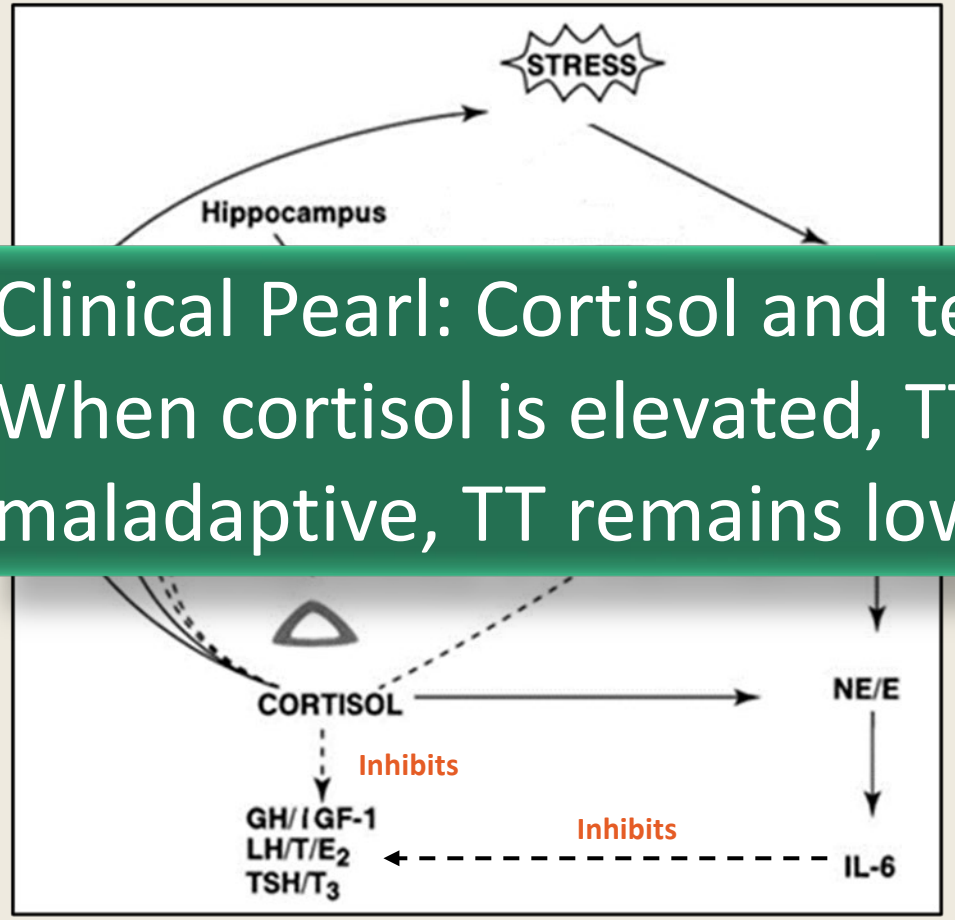
HPA and HPG Axes



- Chronic Stress, HPA axis dysfunction, and the HPG axis
  - Stress → ↑GRH, which suppresses gonadotrophin
  - Chronic stress increases inflammation, which also effects testicular function, decreasing LH and T

Clinical Pearl: Cortisol and testosterone have an inverse relationship. When cortisol is elevated, TT decreases. When this becomes maladaptive, TT remains low.

Tsigos C, Chrousos GP . J Psychosom Res. 2002; 53(4): 865-871.
Pasquali R. Ann N Y Acad Sci. 2012; 1264(1): 20-35.

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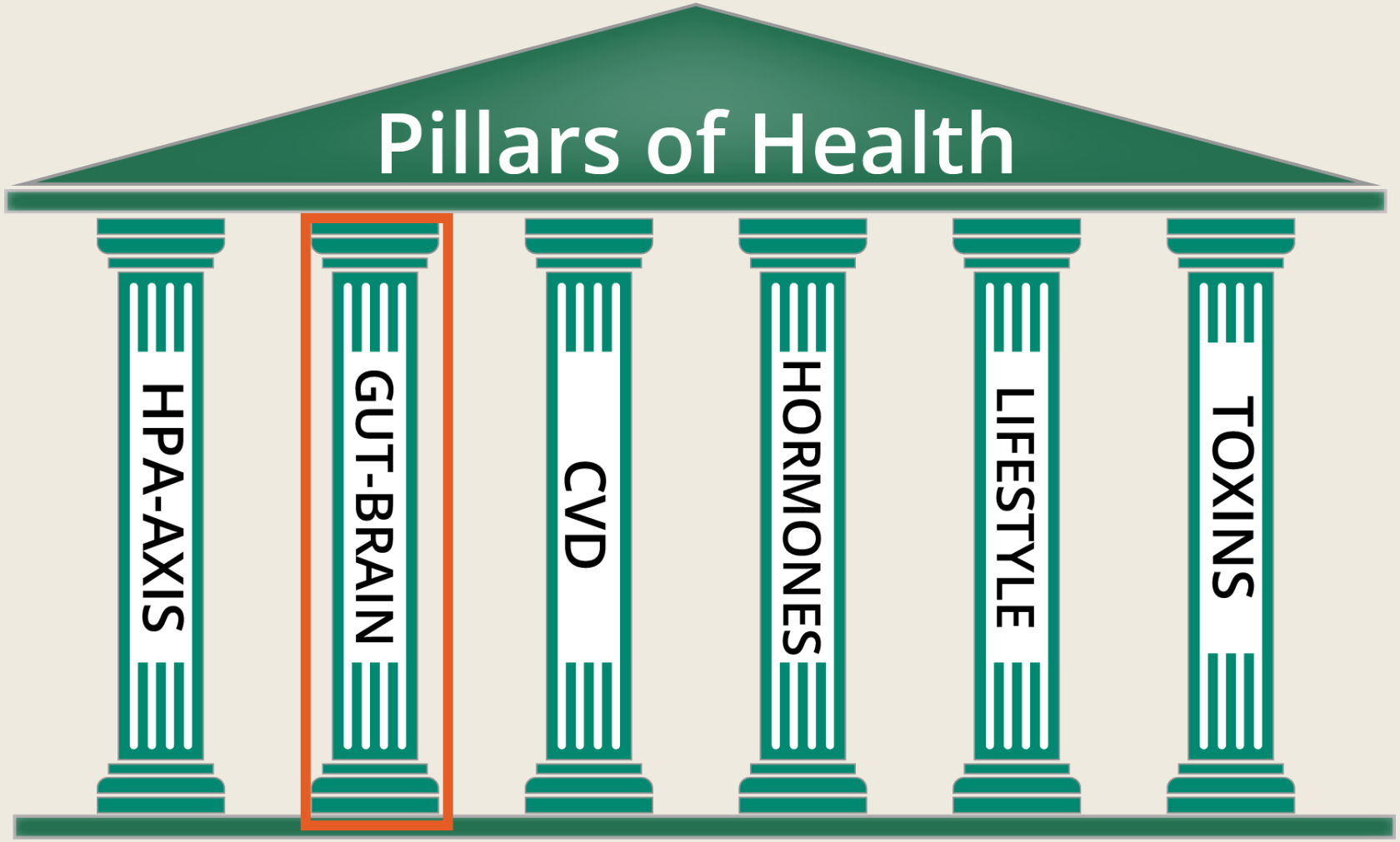
Risk Factors Matter



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GUT and Sex Hormones

- The gut mediates hormone metabolism and hormone-related diseases
  - A balanced microbiome is diverse, with > 90% of species within the Firmicutes and Bacteroidetes phyla, and has a lower F/B ratio
  - β-glucuronidase secreting microbes modulate systemic E and T levels
  - Dysbiosis reduces bacterial diversity, increases the F/B ratio, decreases or increases β-glucuronidase
    - Low β-glucuronidase secreting bacteria may lead to low T states
    - High β-glucuronidase secreting bacteria may lead to estrogen-dominant states
      - Females: Endometriosis, uterine fibroids, endometrial hyperplasia and cancer
      - Males: elevated SHBG, prostate cancer
  - Gut's 5α- and 5β-reductase activity impacts Pg and androgen metabolism

Baker J, et al. 2017; 103: 45-53.
Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

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Inflammation, Metabolic Endotoxemia, and TD

Gut Endotoxin Leading to a Decline IN Gonadal Function (GELDING) theory for obesity related male hypogonadism

- First theory linking obesity, endotoxemia, and TD
- There is minimal supporting human male data; however, there is abundant animal data and data in females supporting this theory

Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

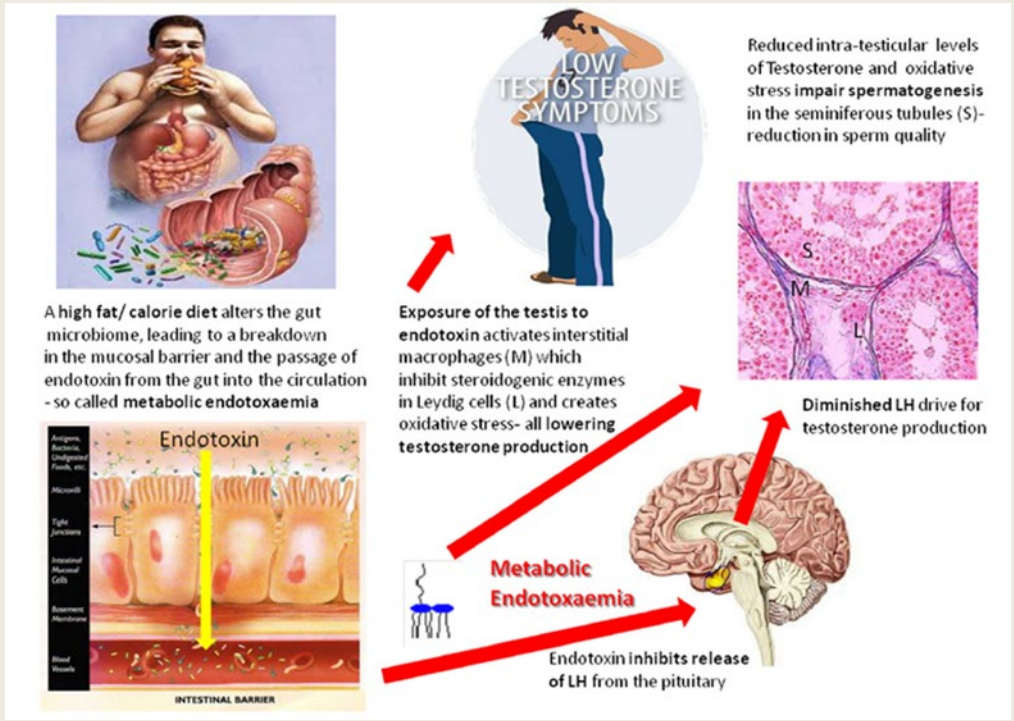
Gut Endotoxin Leading to a Decline IN Gonadal Function (GELDING) Theory

- Theory posits that obesity, a poor diet ⇨ increased gut permeability and chronic low-grade inflammation ⇨ impaired testicular function
  - It is not low T's decreased immunosuppressive effects that increases inflammation
- Mechanism
  - Gut permeability facilitates LPS translocation to systemic circulation
    - May be the key inflammatory trigger
  - LPS decreases testicular T production, both directly and indirectly
    - Direct: inhibits Leydig cell steroidogenesis
    - Indirect: decreases both LH (T) and FSH (spermatogenesis) drive

Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

GELDING Theory, a Root Cause

High saturated fat diet and chronic stress are triggers



- Under normal conditions, macrophages necessary for Leydig cell development, provide growth and differentiation factors
- With inflammation
  - Macrophages produce proinflammatory cytokines: IL-1β, IL-6, and TNF-α, and ROS
  - Leydig cells also produce proinflammatory cytokines: IL-1β, IL-6, and TNF-α
  - Leydig cells have TLR4 receptors
    - TLR4 bind LPS, bind to Leydig cell TLR4 receptors and directly inhibit T production

- Increased gut permeability and chronic low-grade inflammation leads to TD

Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

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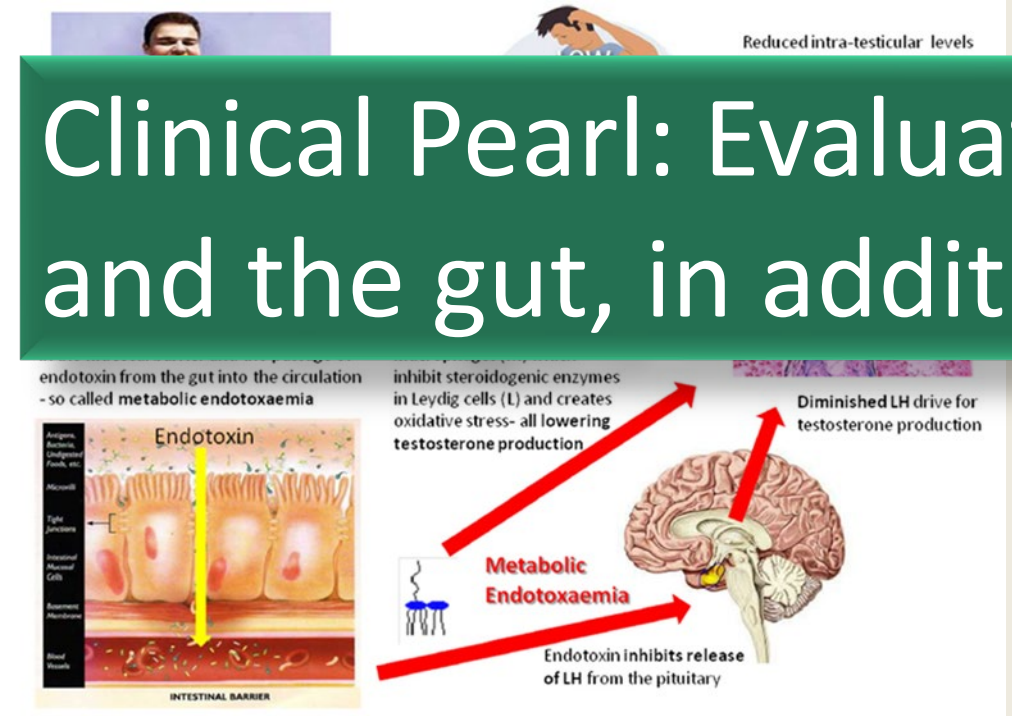

- Under normal conditions, macrophages necessary for Leydig cell development, provide growth and differentiation factors

Leydig cells have TLR4 receptors

- TLR4 bind LPS, bind to Leydig cell TLR4 receptors and directly inhibit T production

- Increased gut permeability and chronic low-grade inflammation leads to TD

Clinical Pearl: Evaluate and treat the HPA axis and the gut, in addition to TD

Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

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Endocrinopathies Associated with TD and Male Infertility

- Central endocrinopathies
  - Hyperprolactinemia
    - Pituitary adenomas, antipsychotic drugs, opioids, hypothyroidism, chronic renal failure, and high estrogens
  - Hypogonadotropic Hypogonadism (HH)
    - Classic forms uncommon: Kallmann syndrome (impaired smell, delayed or absent puberty, missing X chromosome KAL1 gene, early presentation)
      - Definition: LH < 2.5IU/L + hypogonadism
    - Common form idiopathic HH: post puberty
      - Present as a young male with decreased libido and difficulty conceiving
      - Definition: low bioavailable T: < 155ng/dL + inappropriately low LH (< 5 IU/L)
      - Note: 1/3 of obese, IR/DM males have HH and low estrogens

Patel DP, et al. Curr Urol Rep. 17(8): 56.

Endocrinopathies Associated with TD and Male Infertility

- Peripheral endocrinopathies
  - Obesity with TD and elevated estrogens
    - Decrease optimal T: E ratio of > 10: 1
  - Thyroid dysfunction: very rare sole cause of infertility and/or TD
- Congenital adrenal hyperplasia
  - High adrenal androgens with increased negative HPG feedback ➔ decreased LH
- Exogenous TTh or anabolic steroid use
- Partial androgen insensitivity
  - Androgen receptor mutations, i.e., high CAG repeats

Patel DP, et al. Curr Urol Rep. 17(8): 56.

Key Points and Clinical Pearls

- In males, especially young males with TD, evaluate and treat all underlying etiologies
- HPA axis dysfunction impacts testosterone production
- Gut dysbiosis, obesity, or any stressor impacts testosterone production
- Address all endocrinopathies
- In younger males, TTh should not be the first treatment choice for TD
- Treatment decisions should be based on the desire to maintain fertility

Objectives

- Define testosterone deficiency (TD) and its diagnostic criteria
- Debunk the testosterone, prostate cancer (PC), and cardiovascular disease (CVD) myths
- Determine what else needs to be considered before initiating therapy
- Determine treatment options

Approach to Treatment

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Age, LH, Prolactin

- Primary Hypogonadism
  - T Replacement
- Secondary Hypogonadism

LH RR (1.5-9.3mIU/mL) **LH**

Above the upper limits of RR

Typically, at the lower end of the RR

Low TT level

3 - 18 → Normal

Prolactin

> 18 → High

- **Work-up**
  - MRI Brain to rule out prolactinoma
    - Cabergoline (dopamine agonist)
  - Chronic renal?
  - Hypothyroid?
  - Cortisol?

Lifestyle

- 8-hours restful sleep, movement
- Higher protein, Mediterranean eating

Nutraceuticals

- Eurycoma, Tribulus, Testofen, Thai Ginseng, Zinc

Age < 50-55

- Clomid: 25mg QD to QOD, most common
- HCG: 1000 IU 2x week x 6-8 weeks
  - 250 IU 6 x 6-8 weeks
  - 500 IU d/w 3 weeks, then 500 IU 2d/w x 3 weeks
- Kisspeptin: 100-200mcg at HS 1-2 days/week (modulates GNRH)
- Gonadorelin: 100mcg 1-2 days/week (GnRH analog)
- TTh + Gonadorelin (maintain testicular size and fertility [?])

Age > 50-55

- Testosterone therapy (TTh) ± gonadorelin

Formulation	Typical Starting Dose	Advantages	Disadvantages
Patch	• Available in 2.5 and 5mg • Typical starting dose is 5mg • Apply to clean dry area • Rotate areas	• Re-creates circadian rhythm	• Skin irritation, contact dermatitis
Gel or cream	• Available as FDA-approved or compounded products • **Initial T gel dose: 50mg/d** • Consider adding Chrysin 2.5-4% to start (an aromatase inhibitor)	• Dosing flexibility • Application is easy • Well tolerated • Erythrocytosis < than with injections and pellets	• Potential transference • Creams – decreased absorption with common versa base • Increase absorption using an atrevis base
Intranasal gel (Natesto)	• **11mg total** (2 pumps, one in each nostril [5.5mg each]) **3 times a day** (6-8 hours apart)	• **Daily dose is 33mg/d** • Minimal transfer risk	• 3 times a day application inconvenient • Nasal issues limit its use
Oral capsule (Jatenzo)	• Available as FDA-approved • Initial dose: **237mg BID with food** • Dose range: 158-396mg BID	• Lipophilic and absorbed through the lymphatics • Bypasses first-pass metabolism	• May increase BP and possibly CV events • Would avoid in older men
Oral capsule (TLANDO)	• Available as FDA-approved • Initial dose: **225mg BID with food**	• Available as FDA-approved	• May increase BP and possibly CV events • Would avoid in older men

Injections: SQ* or IM
*SQ delivery require a lower dose than IM
	• Cypionate or enanthate: ½ life ~ 12 days
	  ○ 50-100mg weekly
	  ○ **25-50mg 2x week**
	• Propionate: ~ 4.5 days
	  ○ 10-25mg 3x week
		• Inexpensive
		• Bi or Triweekly injections avoids the highs and lows
		• Use enanthate in older males to avoid water retention commonly seen with cypionate
			• Invasive, painful, injection site reactions
			• Highest incidence of erythrocytosis

Pellets	• **Average starting dose is 600-750mg** • Note: for every 75ng/dL increase in TT, insert a 75mg pellet • Baseline TT = 300ng/dL, goal is 900ng/dL, dose 600mg	• Infrequent administration – leave it and forget it for ~ 100-120 days	• Requires understanding of hormone metabolism and detoxification • Requires surgical incision • Pellets may extrude • Rarely: local hematoma, infection

Adapted from Bhasin S, et al. J Clin Endocrinol Metab. 2018; 103(5): 1715-1744.

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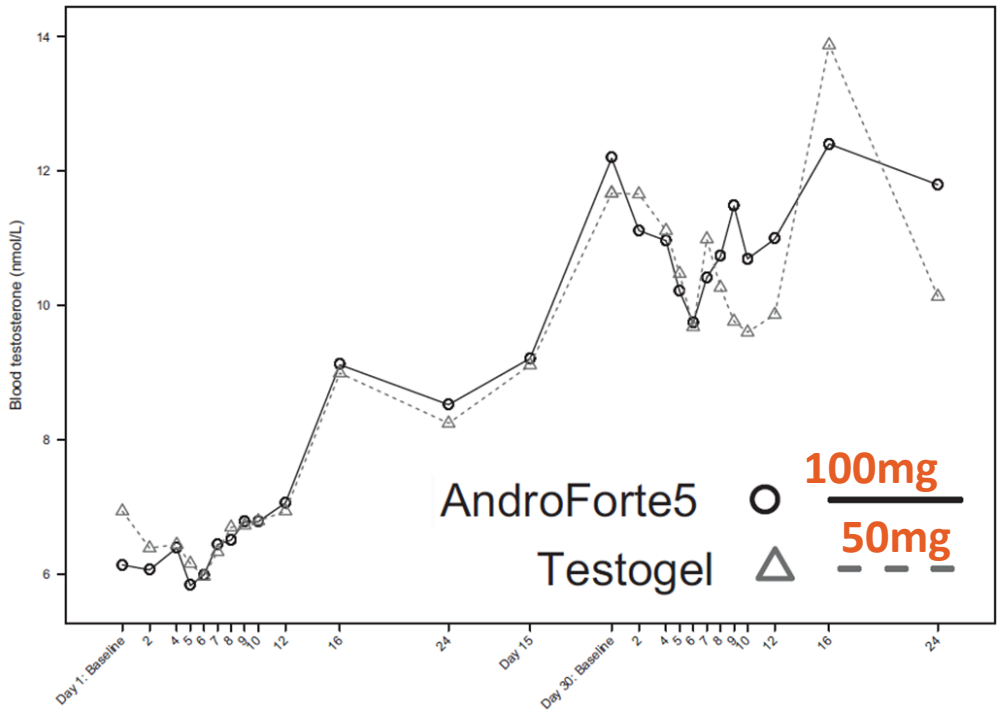
T Gels vs Creams in Males with TD

Figure 3 Mean serum total testosterone levels over 24 h at Day 1 and Day 30 by product.



- Objective: Pharmacokinetic study assessing the bioequivalence of AndroForte 5 cream 100mg vs Testogel 50mg
- Study: open-label crossover study in 16 males with TD; kinetics obtained days 1 and 30

- AndroForte 5 100mg and Testogel 50mg are bioequivalent
- Therefore, it may require 2x the cream dose to improve clinical outcomes like the standard 50mg gel dose

Wittert GA, et al. Andrology. 2016; 4(1): 41-45.

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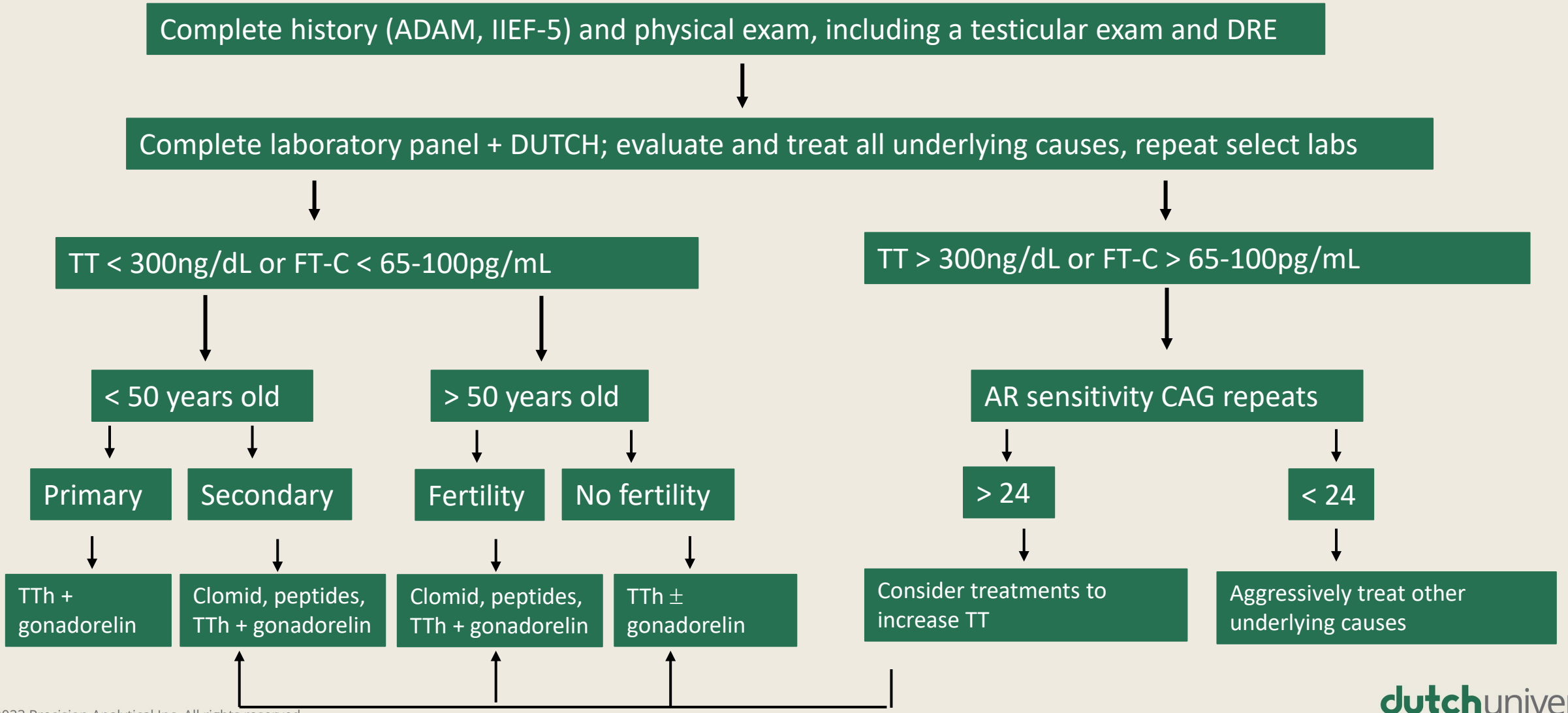
My Approach To Males with Suspected TD



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Question

When deciding on treatments to increase total/free testosterone levels and improve clinical outcomes, the question that needs to be asked and answered: Is fertility desired?

Increasing Total Testosterone Levels

Fertility Desired

- Clomiphene citrate and enclomiphene
  - CC contains both enclomiphene (E antagonist) and zuclomiphene (E agonist)
- HCG (not available)
- Kisspeptin
- Gonadorelin
- Aromatase inhibitors (controversial)
- Testosterone + gonadorelin

Fertility not desired

- Testosterone ± gonadorelin

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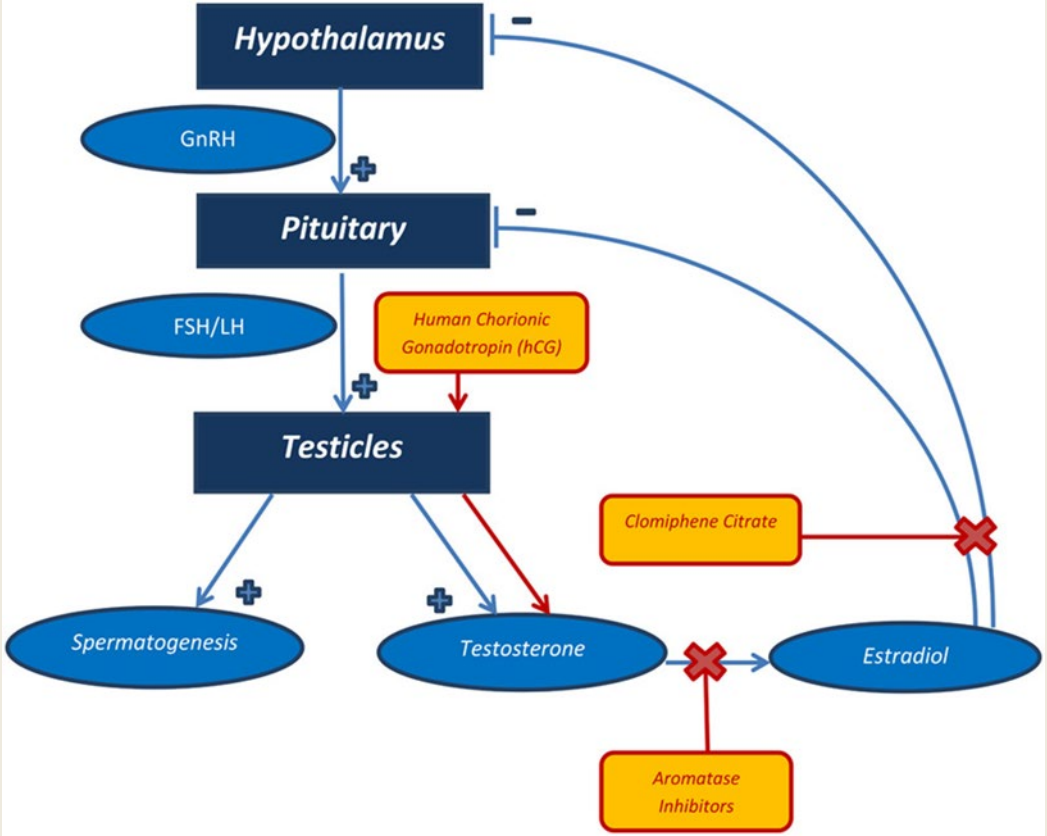
HCG



- There is strong literature support for LH's effect on serum total testosterone, intratesticular total testosterone (ITT), spermatogenesis, and maintaining testicular size
- hCG doses as low as 500-1500IU 2-3x week will preserve testicular size, will increase TT levels, maintain ITT levels, and maintain or improve spermatogenesis
- In males treated with TTh, hCG 500IU 2-3x per week, maintains testicular size, ITT levels, and spermatogenesis, if adequate FSH
- However, cannot be obtained legally

Kim ED, et al. Fertil Steril. 2013; 99(3): 18-24.
Lo EM, et al. Sex Med Rev. 2018; 6(1): 106-113.

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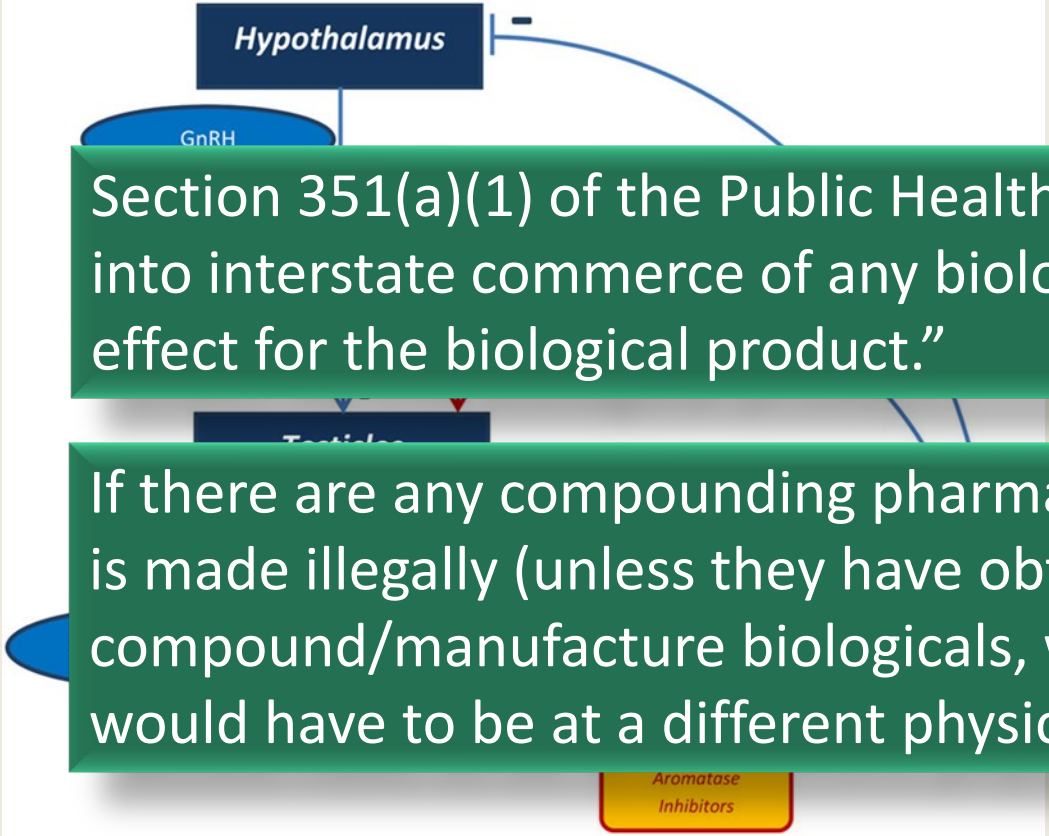
HCG



- There is strong literature support for LH's effect on serum total testosterone, intratesticular total testosterone (ITT),

Section 351(a)(1) of the Public Health Services Act (PHS) prohibits the introduction into interstate commerce of any biological product unless "a biologics license . . . is in effect for the biological product."

If there are any compounding pharmacies still compounding hCG from raw API, yes, it is made illegally (unless they have obtained a separate license to compound/manufacture biologicals, which is very unlikely as a 503A/B pharmacy … would have to be at a different physical address than the 503A/B pharmacy).

Kim ED, et al. Fertil Steril. 2013; 99(3): 18-24.
Lo EM, et al. Sex Med Rev. 2018; 6(1): 106-113.

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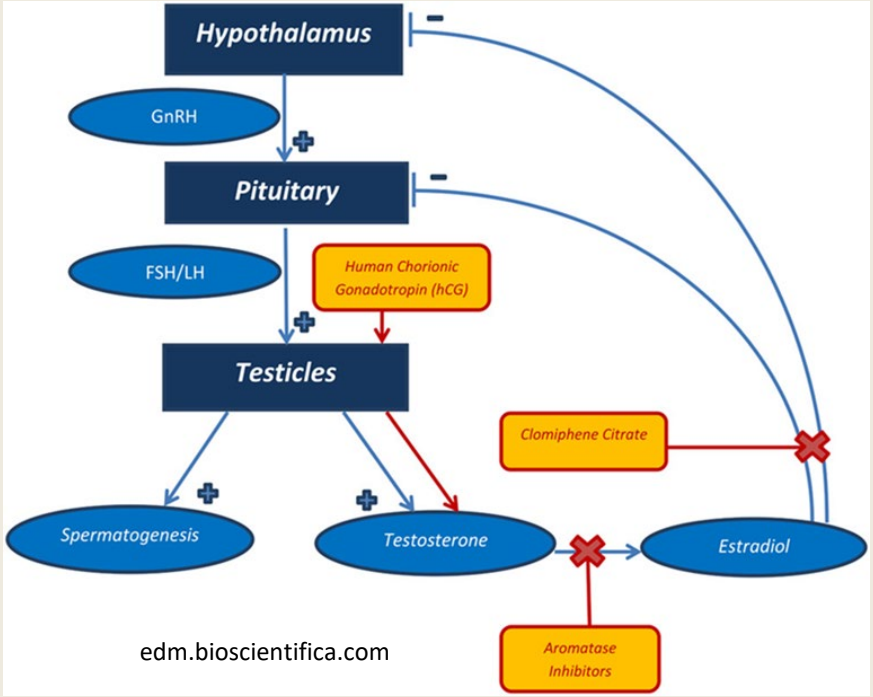
Clomiphene Citrate (CC)



- What is it?
  - CC is a selective estrogen receptor modulator
  - Acts centrally by competitively binding to the hypothalamic and pituitary estrogen receptors, thus antagonizing estradiol's inhibitory effects on gonadotrophin release
- CC binding effects
  - Increases GnRH, FSH, and LH release
  - Increases serum LH, FSH, TT, and estradiol levels
  - Increases intratesticular TT (ITT) levels, which are 100x higher that serum TT levels
  - Increases spermatogenesis (> 20million sperm/mL) and maintains testicular size

Kim ED, et al. Fertil Steril. 2013; 99(3): 18-24.
Lo EM, et al. Sex Med Rev. 2018; 6(1): 106-113.
Huijben M, et al. Andrology. 2022; 10(3): 451-459.

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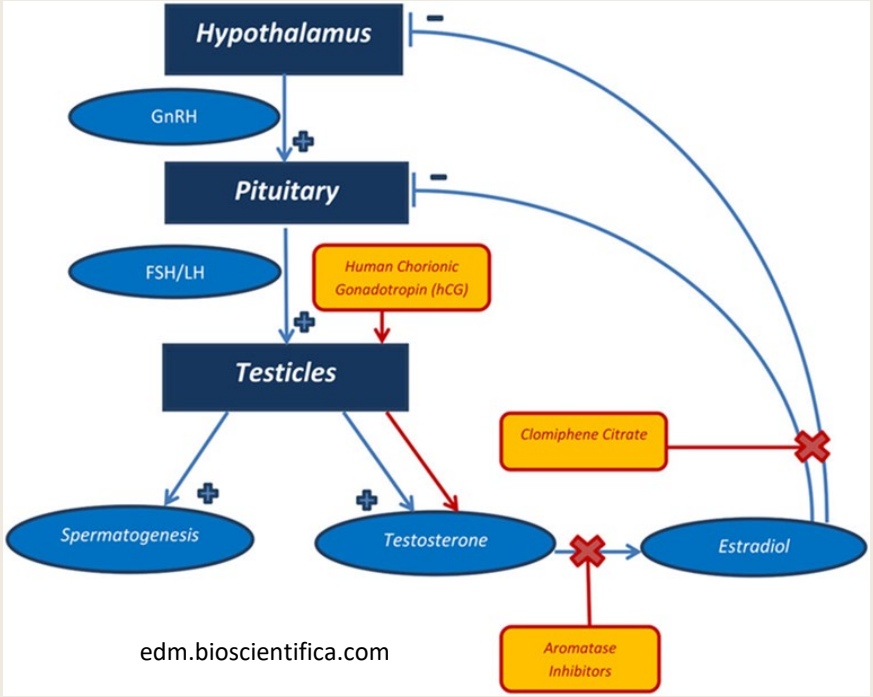
Clomiphene Citrate (CC)



- Concerns
  - Treatment serum E2 levels may increase to > 40pg/mL (LC-MS/MS assay) necessitating anastrozole (dose dependent on E2 levels)
  - Data mixed in older men
  - May be less effective in males with LH levels at the higher end of the LH RR (LH RR: 1.5-9.3mIU/mL)
  - Side effects: gynecomastia, mood swings, headaches

- Typical starting dose: 25mg QOD to QD depending on baseline TT, E2, FSH, and LH
- Anastrozole need dependent on baseline and treatment E2 levels

Kim ED, et al. Fertil Steril. 2013; 99(3): 18-24.
Lo EM, et al. Sex Med Rev. 2018; 6(1): 106-113.
Huijben M, et al. Andrology. 2022; 10(3): 451-459.

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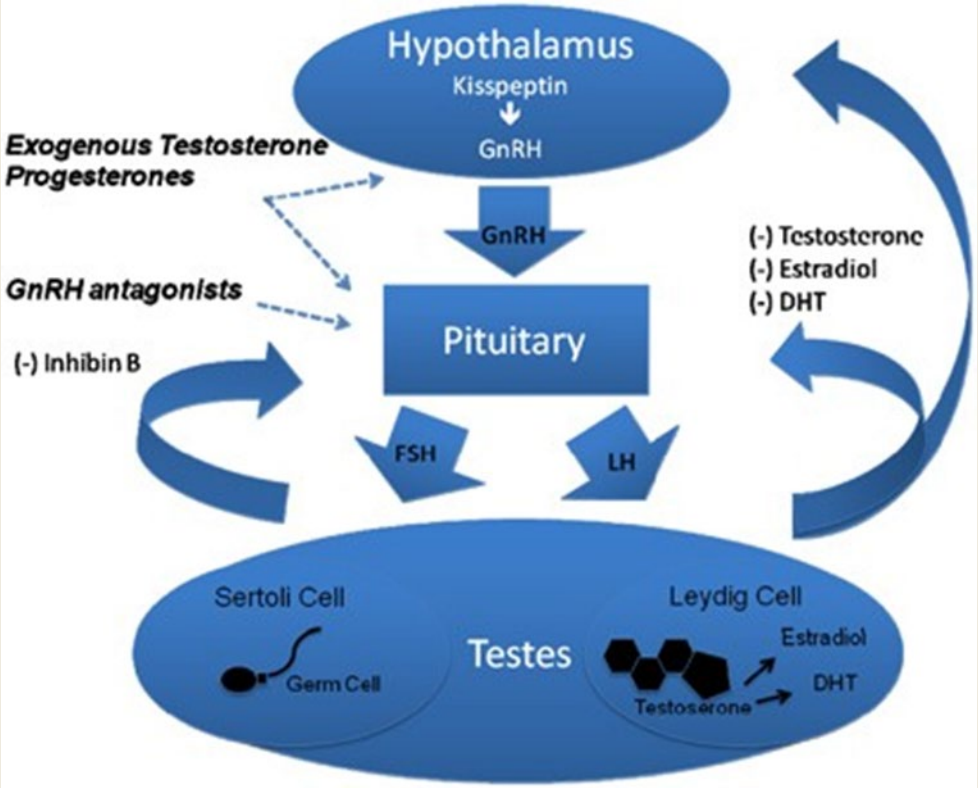
Clinical Pearl: The enemy of good is better and less is more

Kisspeptin



nature.com

endocrinology.org

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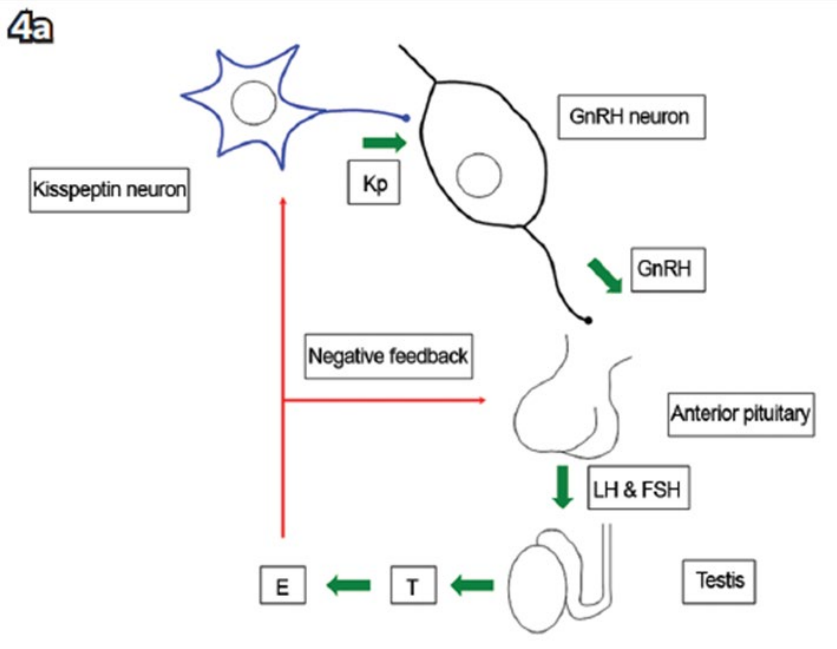
Kisspeptin (KP-10)



Adapted from Tng EL. Singapore Med J. 2015; 56(12): 649-656.

- What are they?
  - Endogenous KP is a 54 amino acid peptide derived from KISS1 gene
  - KP-10, -13, and -14 are peptide fragments derived from KP-54
  - KP's are expressed in the hypothalamus, gonads, placenta, liver, and pancreas
- What do they do?
  - Originally, discovered to inhibit melanoma metastasis
  - KP is the most potent GnRH secretagogue stimulating both LH and FSH, favoring LH >> FSH stimulation
- Mechanism
  - Chronic/continuous KP exposure desensitizes the HPG axis
    - Initial stimulatory effect, with chronic use and high doses leads to a suppressive effect
  - Negative feedback occurs when estradiol binds to hypothalamic and anterior pituitary ER-α receptors

Calley JL, Dhillo WS. Adv Biol. 2014; 2014: 1-10.
Skoropuskaite K, et al. Hum Reprod Update. 2014; 20(4): 485-500.
Anderson RA, Millar RP. J Neuroendocrinol. 2022; 34(5): e13081.
Tng EL. Singapore Med J. 2015; 56(12): 649-656.
George JT, et al. Clin Endocrinol (Oxf). 2013; 79(1): 100-104.

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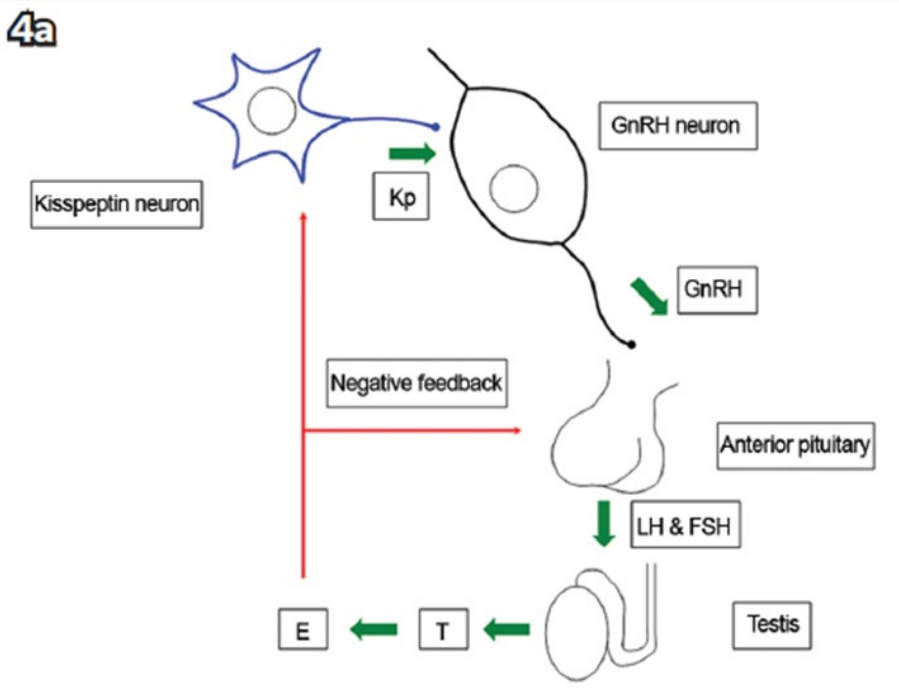
Kisspeptin (KP-10)



Adapted from Tng EL. Singapore Med J. 2015; 56(12): 649-656.

- Kisspeptin signaling is negatively impacted by:
  - Stress
  - Hypoglycemia
  - Starvation
  - Opioids
  - Elevated prolactin
  - Inflammation
- Effectiveness
  - Probably less effective in males with LH levels at the higher end of the LH RR (LH RR: 1.5-9.3mIU/mL)

- Recommended dosing: 100-200mcg 1-2x week

Calley JL, Dhillo WS. Adv Biol. 2014; 2014: 1-10.
Skoropuskaite K, et al. Hum Reprod Update. 2014; 20(4): 485-500.
Anderson RA, Millar RP. J Neuroendocrinol. 2022; 34(5): e13081.
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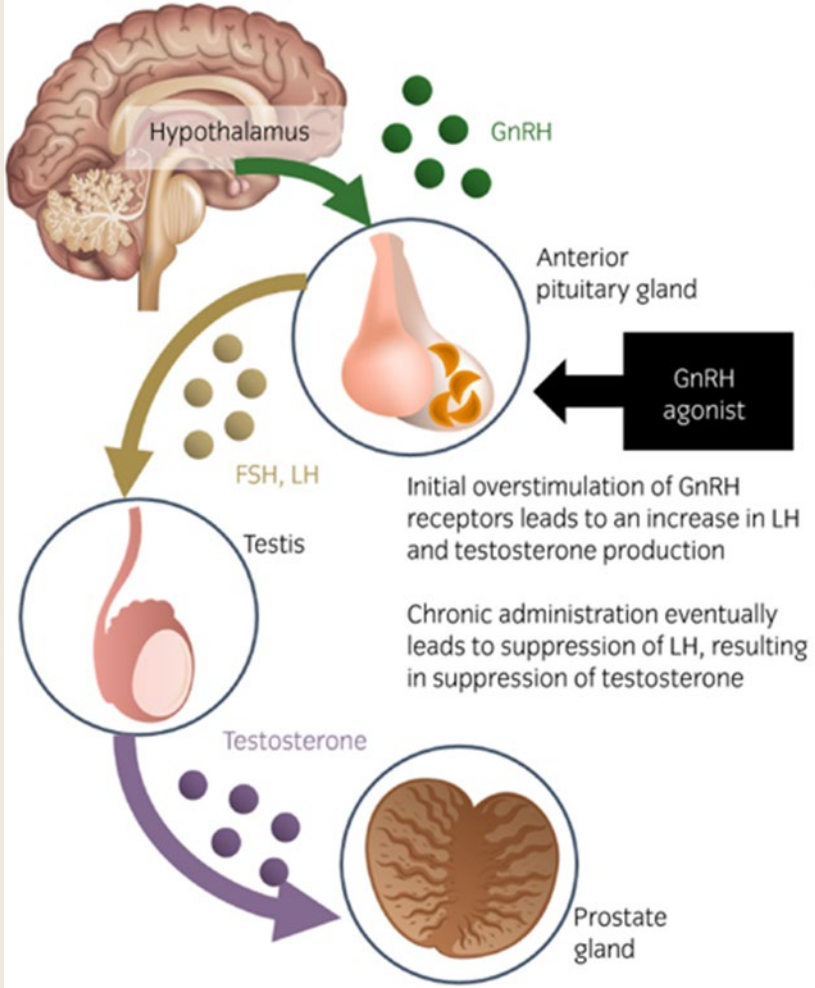
Fertility Desired

- Clomiphene citrate and enclomiphene
  - CC contains both enclomiphene (E antagonist) and zuclomiphene (E agonist)
- HCG (not available)
- Kisspeptin
- Gonadorelin
- Aromatase inhibitors (controversial)
- Testosterone + gonadorelin

Fertility not desired

- Testosterone ± gonadorelin

Gonadorelin



Van Poppel H, Abrahamsson PA. Int J Urol. 2020; 27(10): 730-837.

- What is it?
  - Gonadorelin is a GnRH agonist
  - GnRH receptors in anterior pituitary and testes
- What does it do?
  - Stimulates anterior pituitary LH and FSH release
    - LH >> FSH
  - Increases TT, maintains testicular size, and spermatogenesis

Crowley WF, et al. N Engl J Med. 1980; 302(19): 1052-1057.
Bhasin S, et al. J Clin Endocrinol Metab. 1985; 60(5): 998-1003.
Heber D, et al. J Clin Endocrinol Metab. 1984; 58(6): 1084-1088.
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Anderson RC, et al. Endocr Rev. 2018; 39(6): 911-937.
Van Poppel H, Abrahamsson PA. Int J Urol. 2020; 27(10): 730-837.
Marques P, et al. Endotext [Internet]. 2022.

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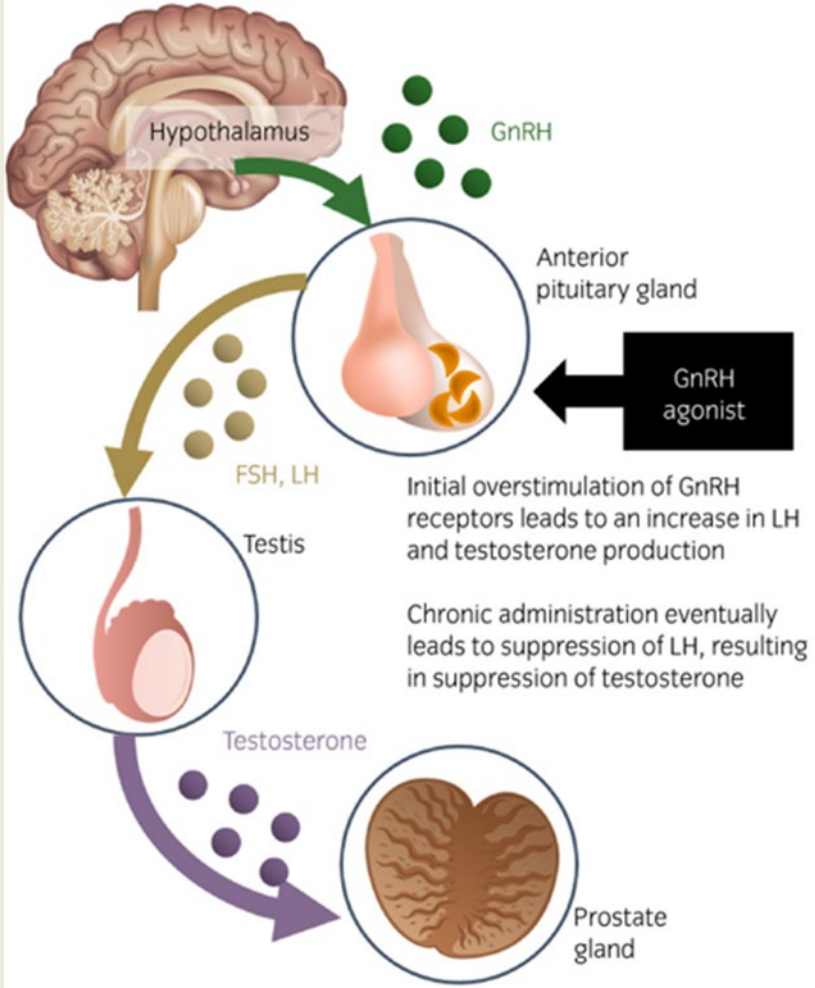
Gonadorelin



Van Poppel H, Abrahamsson PA. Int J Urol. 2020; 27(10): 730-837.

- Mechanism
  - GnRH receptors bind to anterior pituitary cells ➔ FSH and LH release
  - Stimulates and paradoxically inhibits GnRH secretion
    - Chronic/continuous exposure desensitizes the HPG axis
    - Chronic use and high doses leads to a suppressive effect
  - Down regulates pituitary GnRH receptors, decreasing LH and T
- Effectiveness
  - Probably less effective in males with LH levels at the higher end of the LH RR (LH RR: 1.5-9.3mIU/mL)

- Recommended dosing: 100mcg 1-2x week

Crowley WF, et al. N Engl J Med. 1980; 302(19): 1052-1057.
Bhasin S, et al. J Clin Endocrinol Metab. 1985; 60(5): 998-1003.
Heber D, et al. J Clin Endocrinol Metab. 1984; 58(6): 1084-1088.
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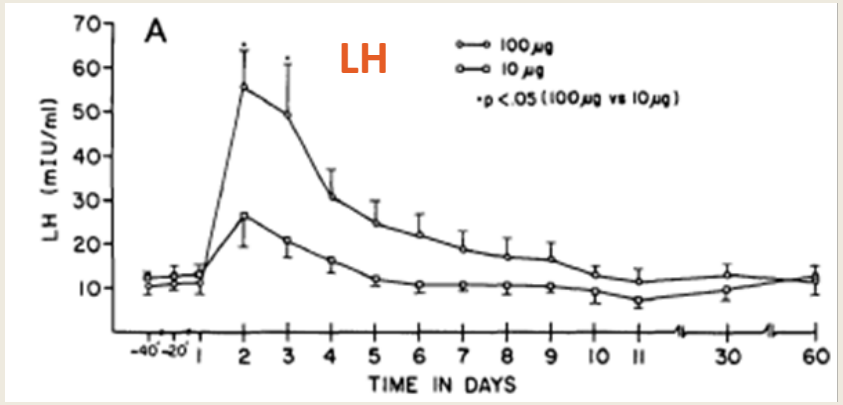
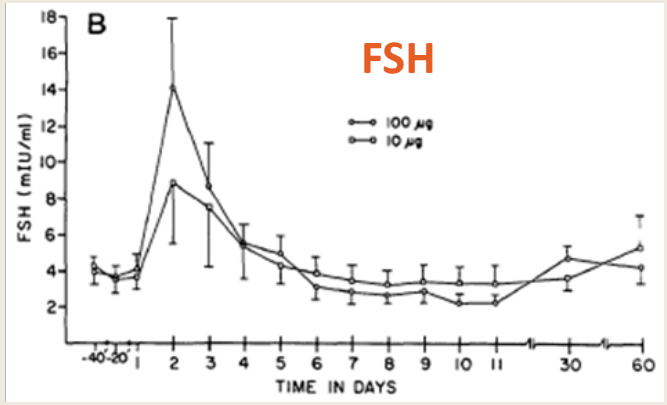
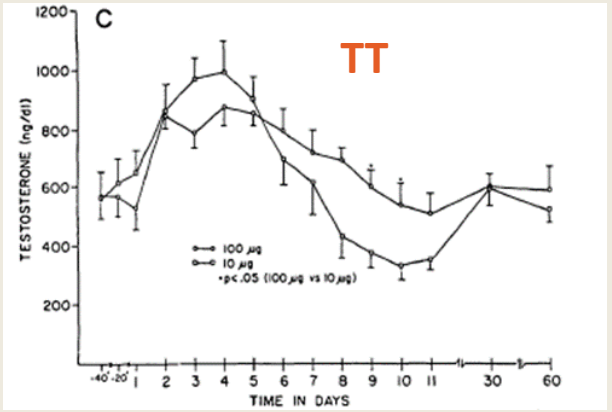
Gonadorelin







- Study: Determine GnRH's pituitary and testicular effects in 14 healthy males
- Methods: 7 males each were given either 10mcg or 100mcg GnRH daily for 10 days
  - All the male's had normal pretreatment semen parameters, FSH, LH, and TT levels
  - At least 2 weeks prior to GnRH agonist, all males were given IM hCG 3000IU and again at study end
  - Serum TT measured before, 24, 48, and 72 hours after hCG injection

Heber D, et al. J Clin Endocrinol Metab. 1984; 58(6): 1084-1088.

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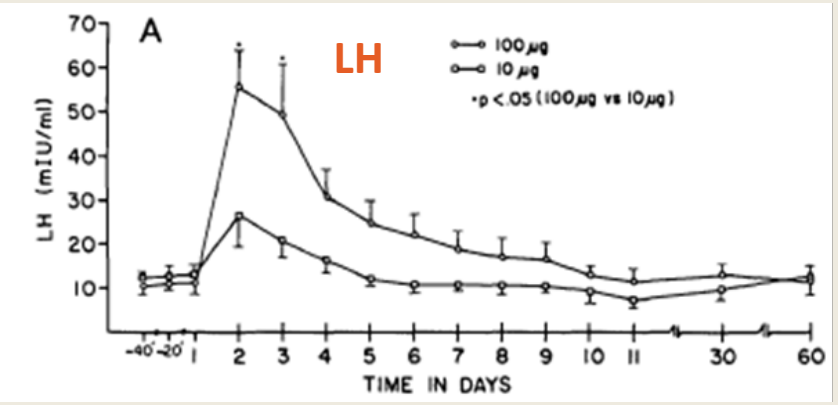
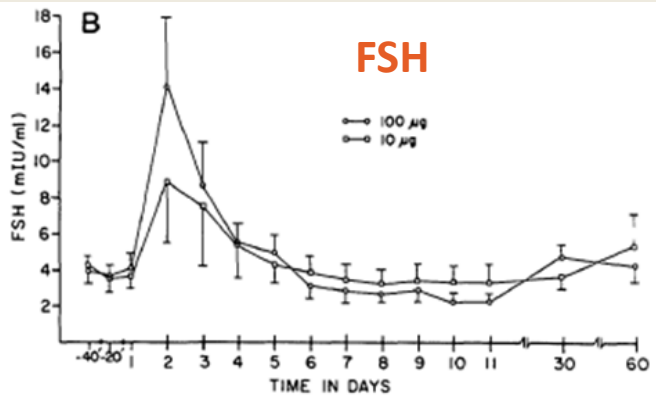
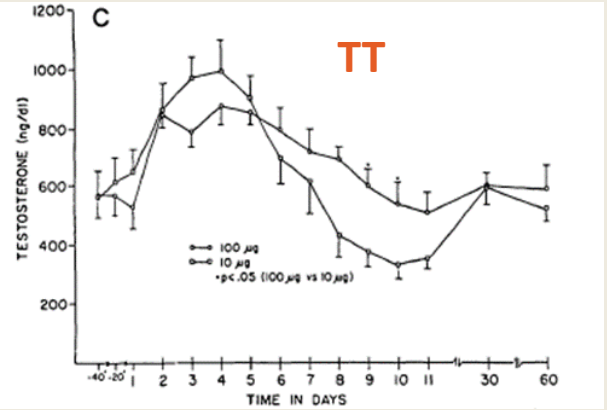
Gonadorelin







- Results: GnRH 100mcg vs 10mcg
  - LH: 100mcg higher serum LH days 2-3, slower return to pretreatment
  - FSH: 100mcg higher serum FSH day 2, similar return time duration to pretreatment
  - TT: 100mcg > TT at day 10 that 10mcg

- Daily GnRH's stimulatory effects are transient, followed by down-regulation after ~ 10 days

Heber D, et al. J Clin Endocrinol Metab. 1984; 58(6): 1084-1088.

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TTh + Gonadorelin: A Plausibility Argument

- Crowley WF, et al. documented that SQ gonadorelin 50mcg QOD in hypogonadotropic males, for 4-6 weeks, led to increased testicular size and increased TT levels
- Therefore, it is plausible that gonadorelin + testosterone therapy will maintain testicular size

- Recommend: TTh + gonadorelin 100mcg 1-2x per week

Crowley WF, et al. N Engl J Med. 1980; 302(19): 1052-1057.
Heber D, et al. J Clin Endocrinol Metab. 1984; 58(6): 1084-1088.

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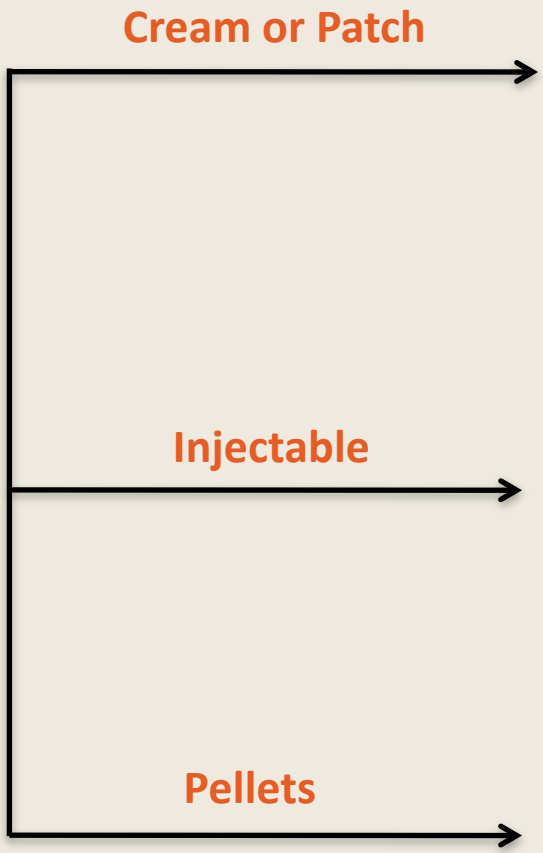
Testosterone Options



- Testosterone patch
  - 2.5 and 5mg patches, starting dose is 5mg/day
- Topical Testosterone
  - AndroGel: **50mg/d**; if using compounded cream, you may need higher dose
- Keep it above the belt and rotate sites: chest/abdomen/flank/shoulders
- Labs in 1, 3, 6, and 12 months, then 2x year

- IM or **Sub-Q** (more comfortable, use lower dose)
  - Propionate (shortest acting) **10-25mg 2-3x week**
  - Enanthate for older males (less fluid retention) **25-50mg biweekly**
  - Cypionate (most common) **25-50mg biweekly**

- Pellets are a viable option
  - Consider cost
  - Dosing: for every 75ng/dL want to increase TT (> 500 – 900ng/dL) give 75mg pellet; typical starting dose is 600-750mg

**Check PSA before and after initiation
**PSA increase > 0.75ng/mL worrisome PC

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TTh Benefits in Males with TD

- Regardless of delivery, a serum TT level > 500ng/dL improves sexual function, body composition, BMD, CV outcomes, and does not increase PC
  - AndroGel: 50-100mg/d; T pellets: average dose 750mg; T creams: 50-100mg/d
  - Testosterone Undecanoate: 750-1000mg initially, then at 6-weeks, then Q10-12 weeks
- Serum total E2 levels should be maintained between 20-40pg/mL (LC-MS/MS), goal 30-35pg/mL for optimum benefit
  - Sexual function, BMD, etc.
- Young men on clomid, gonadorelin, kisspeptin
  - After treatment for 6 months to 1 year + lifestyle changes, there will be a percentage of males who no longer require therapy
  - Stop treatment for 3 months and re-evaluate patient

Key Points and Clinical Pearls

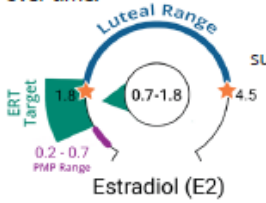
- Don’t use hCG
  - If willing to violate the law, what else are they willing to do?
- If fertility is desired and/or < 50 years old
  - Clomid is a reasonable option, watch for elevated estradiol and the need to add anastrozole
  - Kisspeptin and gonadorelin both excellent options depending on the circumstances, less is more
    - Gonadorelin is 1 step removed from kisspeptin activity: consider with HPA axis dysfunction, significant inflammation, etc.
- If fertility is not desired and > 50 years old
  - Testosterone therapy + gonadorelin for testicular size maintenance

MONITORING (B)HRT WITH LAB TESTING

Tutorials available at www.dutchtest.com/videos/hormone-tutorials

PRECISION ANALYTICAL INC.
CREATORS OF THE DUTCH TEST®

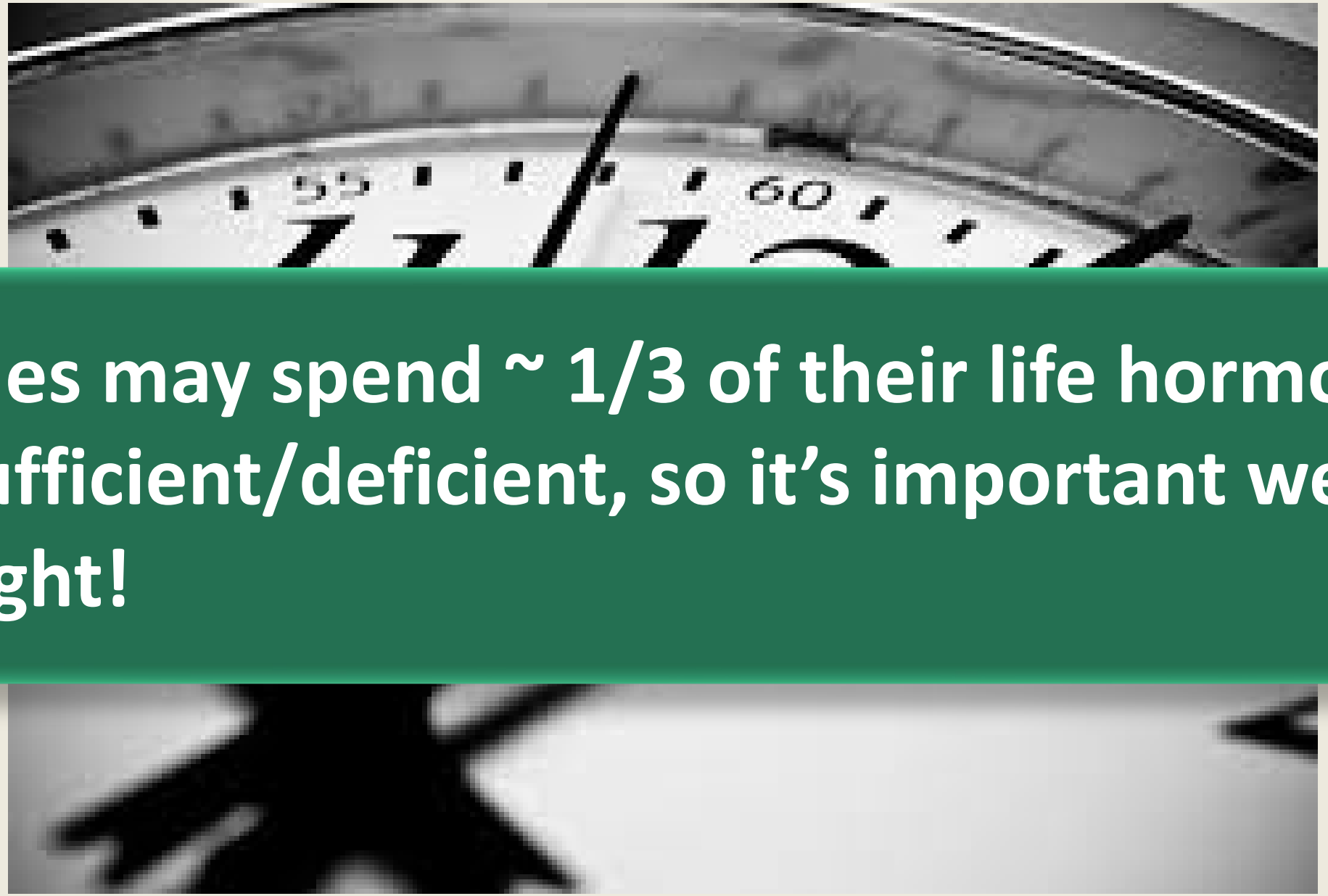
Can serum or DUTCH, as a standalone test, effectively monitor HRT? ✔ Yes ✘ No ? Maybe

Oral Progesterone (OMP)	Estradiol (E2) Patches	E2 Gels & Creams (Skin)	Vaginal E2 & Testosterone (T)	Vaginal Progesterone (Pg)	Transdermal (TD) Testosterone	Testosterone Injections & Pellets
✔ DUTCH	✔ DUTCH	✔ DUTCH	✔ DUTCH	✘ DUTCH	? DUTCH	? DUTCH
The DUTCH Test® provides useful feedback when using OMP in women with PMP sleep disturbances. 5a (more active) and 5b metabolites are measured to individualize OMP dosing. OMP's sleep effects are via its 5a metabolites, predominately allopregnanolone binding to the GABA receptor. No lab test reflects OMP's effect on the endometrium.	Values between the top of the postmenopausal range and the lower limit of the premenopausal range correlate with patient clinical improvement (bone density, hot flash relief, etc.). Doses that push levels to the middle of the premenopausal range and beyond may be excessive. DUTCH is preferred over serum because in addition to metabolites, dried urine averages out the daily up and down E2 patterns. This is particularly helpful with gels and creams that may have serum values that change rapidly over time.	 The aggregate clinical data suggests that a serum (LC-MS/MS) E2 level of ~20-40pg/mL improves clinical outcomes (VMS, VVA, BMD). This approximates a DUTCH value of ~ 0.7-1.8ng/mg.	The DUTCH Test® is unique in that it removes potential contamination, and monitoring is helpful with E2 and T. Very low doses may impact local tissue without increasing lab values. For local (not systemic) E2 therapy, keep urine E2 in PMP range.	Pg is measured indirectly in urine by measuring pregnanediols. These metabolites may be underrepresented when Pg is taken vaginally. Serum Pg seems to increase to a higher degree than urine metabolites with vaginal Pg application.	Levels generally parallel changes in serum and clinical outcomes (increased lean body mass, erythrocytosis, etc. in men). Epi-testosterone (Epi-T) values can be used to assess gonadal suppression due to TRT (Epi-T levels in men decrease as TRT increases and are <10ng/mg with complete suppression).	Injections and pellets increase levels, as expected, but the increase may exceed what is seen in serum testing. DUTCH allows for monitoring both the dosing of hormones as well as metabolic patterns.
			Vaginal E2, Pg, and T are systemically absorbed. If placed in the top 1/3 of the vagina, a higher dose will get to the uterus (uterine 1st pass effect), which may be helpful for Pg, but not E2.		Urine testosterone does not correlate as reliably to T serum values, compared to E2 and other tests. Urine testing is best suited as a complimentary test to serum for T and should not be used solely for TRT decisions.	
✘ SERUM	✔ SERUM	? SERUM	✔ SERUM	? SERUM	✔ SERUM	✔ SERUM
Results go up and down quickly. If taken at bedtime, levels return to baseline within a few hours. Results can also be inaccurate due to progesterone metabolites cross-reacting with immunoassay tests.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Most recommendations are to push serum E2 levels to 20-40pg/mL for clinical impact.	The only published data for E2 creams shows serum results move up and down within a few hours, so serum testing can easily underestimate clinical impact. DUTCH results average out the daily up and down pattern and may be a better option.	Serum results rise quite dramatically with what may seem like modest doses due to the high uptake of hormones across the mucosal membrane. However, values may rise and fall quickly, so be careful with the interpretation of both low and high results.	Serum values increase with dosing and likely represent systemic exposure to Pg. However, the uterine first-pass effect loads the uterus with high levels of Pg (which may be desirable) and serum does not reflect uterine hormone levels.	A great deal of published research shows that serum levels reflect clinical changes in both men and women taking TD T. Be aware of potential up and down patterns throughout the day, but serum is the best tool for monitoring doses of TD T in both men and women.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Test injections halfway between doses or right before a dose.

✘ SALIVA	The literature does not support salivary testing's use for monitoring TD hormone creams. The saliva data is limited and, in fact, there are no saliva testing outcome studies using TD creams, injections, estradiol patches, oral estradiol, or vaginal hormones. While salivary testing is the gold standard for free cortisol measurement, avoiding its use for monitoring HRT is advised. For situations where saliva testing may parallel the clinical impact, DUTCH or serum testing are better options (see above).
✘ Oral Estradiol, Estradiol Pellets, or Sublingual Hormones	Though not recommended, if you choose to use either oral estradiol or estradiol pellets, serum testing can monitor both, whereas urine should only be used with pellet therapy. Sublingual hormones may be used in some situations but lab monitoring is not helpful in optimizing doses.
✘ Transdermal Progesterone	In PMP women, the evidence does not support TD Pg's use to protect the endometrium. When prescribed, laboratory monitoring is not helpful for TD Pg dosing.

Final Thoughts

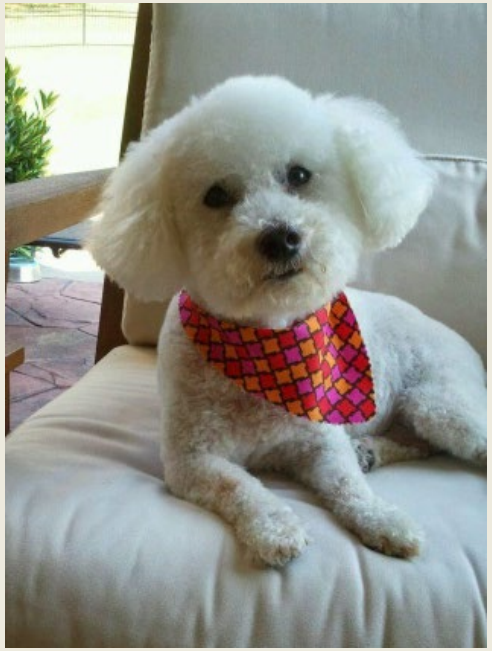
- In males who meet diagnostic criteria for TD, don't stop there
- Address the HPA axis, the gut, etc. ⇨ the whole person
- What ever therapy you choose, start low, go slow, and set expectations
- Laboratory monitoring is key, don't just treat
- Learn and understand hormone metabolomics, it is essential to a successful hormone practice
- Ask yourself: are your decisions evidence-based?
- Are you questioning the absolutes and asking: where is the evidence?

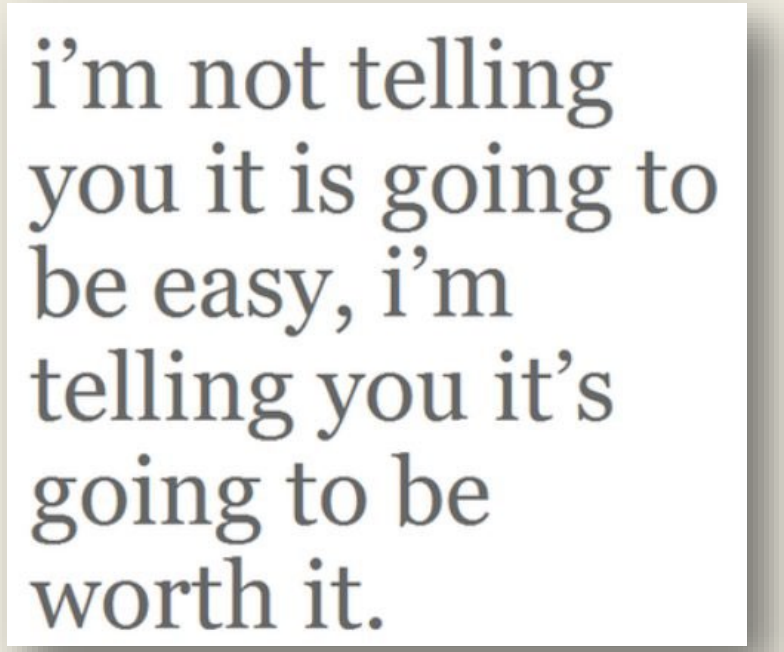


Males may spend ~ 1/3 of their life hormone insufficient/deficient, so it's important we get it right!

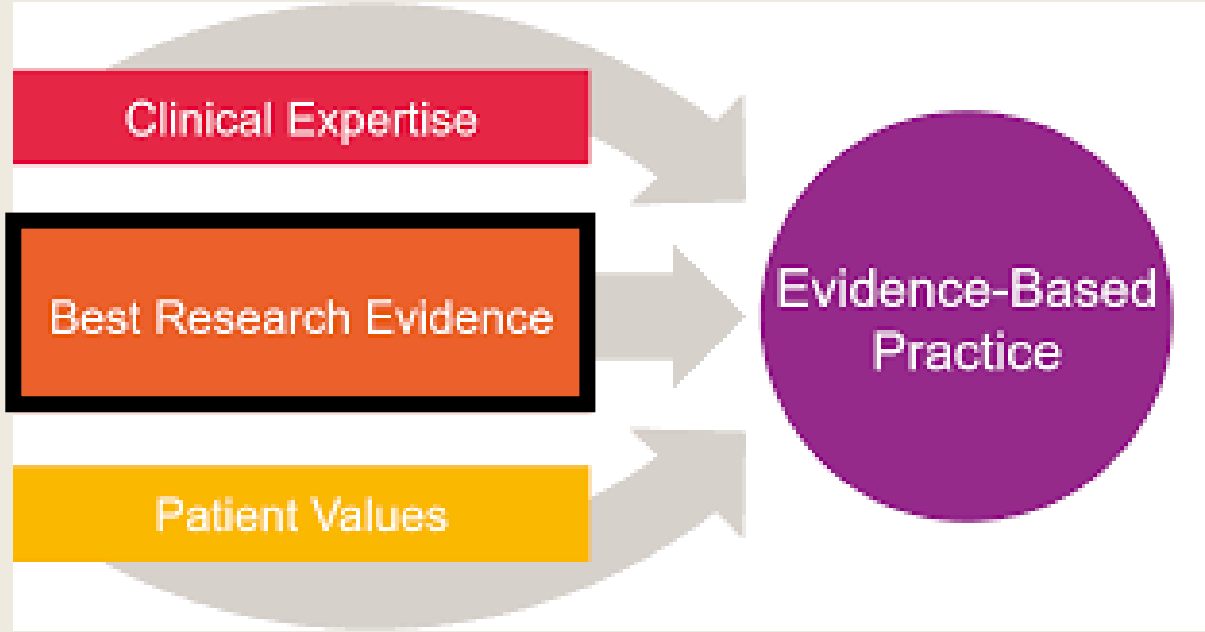
onhealth.com

Doreen Saltiel, MD JD FACC
Peak Health and Wellness, LLC
Asheville, NC 28748





Questions?



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For questions, contact:

info@dutchtest.com
(503)687-2050
www.dutchtest.com