TESTOSTERONE DEFICIENCY TREATMENT UPDATE

William J Terry Jr MD
Urology Associates of Mobile

UAM CENTER FOR MEN'S HEALTH

- Matthew McIntyre MD

William J Terry Jr MD

J. Kelley Gunn MHS PA-C

STRUCTURE OF THIS TALK

- Prevalence of Testosterone Deficiency
- Review and comparison of AUA and Endocrine Society Guidelines with discussion
- Review of primary and secondary hypogonadism
- Review of organic and functional hypogonadism
- Testosterone Lab Testing Considerations
- Review of SERMS, AIs, and HCG
- Review of Polycythemia / Erythrocytosis
- Review of Hereditary Hemochromatosis
- Review of the TRAVERSE trial

THE STATE OF TESTOSTERONE THERAPY

- Testosterone prescriptions have nearly tripled in recent years
- Many men are using testosterone without a clear indication
- 25% of men on Testosterone therapy have not had their levels tested
- 40% of men on treatment do not have follow up labs scheduled
- Approx 30% men on therapy do not meet treatment criteria
- Many men in need of testosterone are not receiving it
- Anti-aging and Low T centers are proliferating
- Simply put: we are in need of guidance

- Data referenced in AUA Guidelines, accessed 9/2024

TESTOSTERONE DEFICIENCY (TD)

- Serum T AND Symptoms
- AUA Core Curriculum

Table 3: Testosterone Deficiency – Signs and Symptoms

Sexual	Non-Sexual / Psychological	Physical/Metabolic
Diminished Libido	Diminished energy, sense of vitality, or well-being	Decreased bone mineral density
Decreased spontaneous erections	Fatigue	Decreased muscle mass and strength
Erectile Dysfunction	Depressed mood	Increased body fat
Diminished response to PDE5I	Irritability	Gynecomastia
	Impaired cognition	Reduced testicular size, firmness
	Reduced motivation	Anemia
		Insulin resistance

TESTOSTERONE DEFICIENCY PREVALENCE

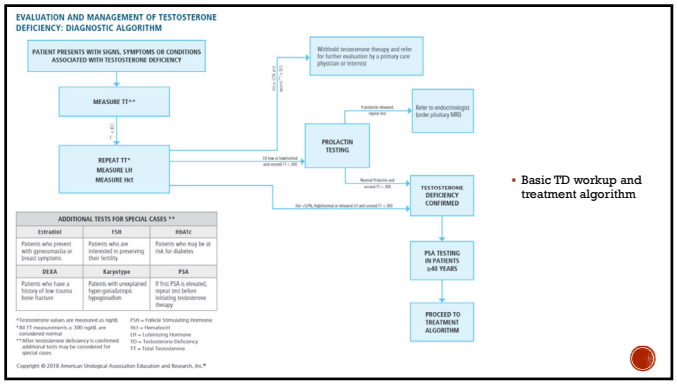
- Estimates of Testosterone Deficiency TD prevalence in adult men from 2-39%, due to differing definitions of TD in the literature.
- In the *Hypogonadism in Men* study, morning serum T levels <300ng/dl were seen in 39% of men 45 years or older recruited from physician waiting rooms.
- In contrast, the prevalence of TD (defined as T <320ng/dl plus three sexual symptoms) observed in the *European Male Aging Study* was only 2.1% in men 40-79 years of age.
- **Strict reliance on laboratory reference ranges alone to make the diagnosis of TD in clinical practice may lead to many false negative results** which may arbitrarily deprive some symptomatic men the potential benefits of T therapy.
- AUA Core Curriculum

OUR JOB: TO DIFFERENTIATE BETWEEN WHO NEEDS TESTOSTERONE AND WHO DOES NOT.

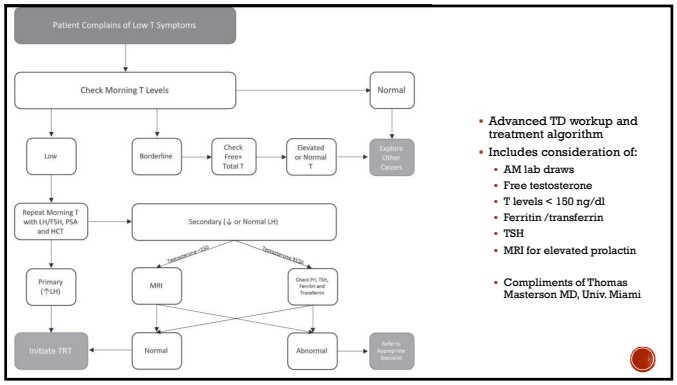
- This also involves an element of Uro-Psychiatry: convincing some men who WANT testosterone that they really don't need it.
- Or….convincing men who want MORE T that risks sometimes outweigh benefits.

TESTOSTERONE DEFICIENCY IN THE UROLOGY CLINIC

- WORKUP
  - HP
  - Labs
  - Follow up
  - More Labs
  - Possible Referral to Specialty
- SELECTION OF THERAPY
  - Topical
  - Injection
  - Oral***
- FOLLOW UP
  - Labs forever
  - Respond to inefficacy
  - Respond to side effects
  - Respond to other medical conditions which may develop



- Basic TD workup and treatment algorithm



- Advanced TD workup and treatment algorithm
- Includes consideration of:
  - AM lab draws
  - Free testosterone
  - T levels < 150 ng/dl
  - Ferritin /transferrin
  - TSH
  - MRI for elevated prolactin
  - Compliments of Thomas Masterson MD, Univ. Miami

TESTOSTERONE DEFICIENCY GUIDELINES

- Existing Guidelines:
  - **AUA Guideline** – updated 8/2018 with another updated lit review 2022
  - WORKUP:
    - Consider measuring total testosterone in asymptomatic patients with:
      - Unexplained anemia
      - bone density loss
      - Diabetes
      - exposure to chemotherapy or testicular radiation
      - HIV/AIDS
      - chronic narcotic use
      - male infertility
      - pituitary dysfunction
      - chronic corticosteroid use

TESTOSTERONE DEFICIENCY GUIDELINES

- Existing Guidelines:
  - **AUA Guideline** – updated 8/2018 with another updated lit review 2022
    - Inform / counsel patients re:
      - Low T is a risk factor for CV disease
      - Testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms.
      - Evidence is inconclusive whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and quality of life measures
      - No evidence linking testosterone therapy to the development of prostate cancer
      - No definitive evidence linking testosterone therapy to a higher incidence of venothrombolic events
      - No definitive evidence linking TRT to MACE
      - Risk of transference with some treatment forms
      - Lifestyle modification is a highly effective treatment strategy.

TESTOSTERONE DEFICIENCY GUIDELINES

- Existing Guidelines:
  - **AUA Guideline** – updated 8/2018 with another updated lit review 2022
    - Rigorous clinical eval including H&P plus:
    - Non fasted AM serum total T levels – cut point of 300 ng/dl
    - Confirmation of labs
    - Additional eval to ascertain cause of low T
      - **LH** for everyone
      - **Prolactin** if LH is low / normal – if abnormal pituitary MRI → specialty referral
      - **Estradiol** if breast symptoms exist
      - **Check PSA** and H/H baseline prior to initiating therapy
      - Caution TRT in men desiring fertility – refer for reproductive health eval prior to initiating tx
      - No recommendations regarding other labs such as TSH, Vit D, B12, folate, free T

TESTOSTERONE DEFICIENCY GUIDELINES

- Existing Guidelines:
  - **AUA Guideline** – updated 8/2018 with another updated lit review 2022
    - Treatment Recommendations
      - Correct T levels to the middle tertile of the ref range (350 – 550ng/dl)
      - No TRT for men trying to conceive
      - Use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination thereof in men with testosterone deficiency desiring to maintain fertility.
      - No TRT within 3-6 months of a MACE (thromboxane A2)
      - Commercial T products preferred over compounded products
    - Follow up every 6-12 months with repeat T levels
    - Discuss cessation of TRT in men not receiving clinical benefit

TESTOSTERONE DEFICIENCY GUIDELINES

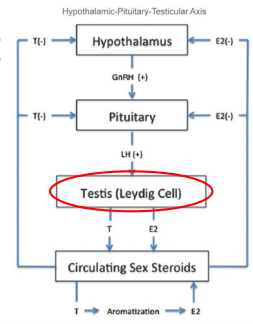
- **Endocrine Society Guideline** – updated 3/2018
  - Rigorous clinical eval
  - Fasted AM serum total and free T levels – 2.5% defined at total T of 264 ng/dl
  - Confirmation of am fasted labs
  - Define primary or secondary using LH / FSH
  - Additional eval to ascertain the cause of low T (H, P, T dysfunction?)
  - Caution TRT in men desiring fertility
  - No testosterone therapy in men:
    - planning fertility in the near term
    - with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level >4 ng/mL a prostate-specific antigen level >3 ng/mL combined with a high risk of prostate cancer
      (without further urological evaluation)
    - elevated hematocrit
    - untreated severe obstructive sleep apnea, severe lower urinary tract symptoms
    - uncontrolled heart failure
    - myocardial infarction or stroke within the last 6 months, or thrombophilia.

TESTOSTERONE DEFICIENCY GUIDELINES

- **Endocrine Society Guideline** – updated 3/2018
  - In hypogonadal men 65 to 69 years old, who are being considered for testosterone therapy and have a life expectancy >10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making
  - Against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations.
  - In men 65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits.
  - Consider short-term testosterone therapy in HIV-infected men with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain.

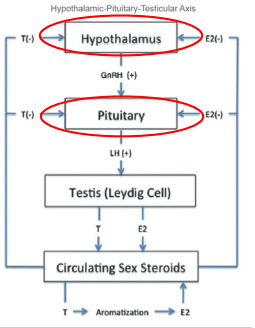
REVIEW: PRIMARY HYPOGONADISM

- Primary hypogonadism results in low T concentrations, impairment of spermatogenesis, and **elevated gonadotropin levels.**
- Causes of primary hypogonadism include:
  - Klinefelter syndrome (KS -47 XXY)
  - Cryptorchidism
  - some types of cancer chemotherapy
  - radiation to the testes
  - AZF deletions
  - Trauma
  - torsion
  - infectious orchitis
  - HIV infection
  - anorchia syndrome
  - myotonic dystrophy



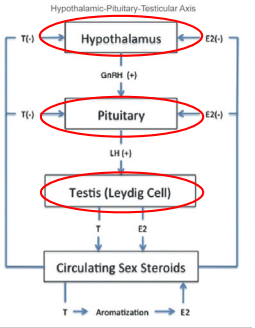
REVIEW: SECONDARY HYPOGONADISM

- Secondary hypogonadism results in low T concentrations, impairment of spermatogenesis, and **low or inappropriately normal gonadotropin levels**.
- Causes of secondary hypogonadism include:
  - Hyperprolactinemia
  - severe obesity
  - iron overload syndromes (hemochromatosis)
  - the use of opioids, glucocorticoids, or androgenic–anabolic steroid (AAS) withdrawal syndrome
  - androgen-deprivation therapy with gonadotropin-releasing hormone agonists
  - idiopathic hypogonadotropic hypogonadism
  - hypothalamic or pituitary tumors or infiltrative disease
  - head trauma
  - pituitary surgery or radiation.
- It is possible to have a combination of primary and secondary



MIXED PRIMARY /SECONDARY HYPOGONADISM

- Mixed occurs when there is a subnormal LH response in combination with reduced production of T.
- GnRh and LH production is inappropriately NORMAL due to a central issue AND testosterone level is low due to a Leydig cell issue
- Most common type in male aging



MIXED PRIMARY /SECONDARY HYPOGONADISM

- Any condition under primary can coexist with any condition under secondary

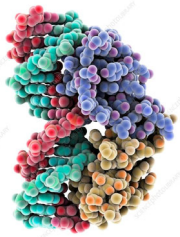
Primary Hypogonadism (Testicular Failure)	Secondary Hypogonadism (Hypothalamic/Pituitary Failure)	
Gonadotoxins	**Genetic Disorders**	**Drugs**
• Chemotherapy	• Kallman's Syndrome	• Opioid narcotics
• Heavy Metals	**Metabolic Disorders**	• Marijuana
• Pesticides	• Diabetes	• Anabolic Steroids
• Radiation	• Metabolic Syndrome	**Injury**
Neoplasia	• Hypertension	• Traumatic Brain Injury
• Testicular Cancer	• Renal Failure	• Pituitary Infarction
Injury	• Malnutrition	• Sub-arachnoid hemorrhage
• Testicular Torsion	• Liver Failure	**Autoimmune / Infiltrative**
• Testicular Trauma	**Neoplasia**	• Sarcoidosis
Infectious Disease	• Prolactinoma	• Wegener's Granulomatosis
• Mumps Orchitis	• Craniopharyngioma	• Lymphocytic hypophysitis
• HIV infection	• Other Pituitary Tumors	**Infectious Disease**
Congenital	**Iatrogenic**	• Tuberculosis
• Cryptorchidism	• Surgical Resection	• Tertiary Syphilis
• Anorchia	• Cranial Radiation	• Meningitis
• Klinefelter's Syndrome	• Corticosteroids	**Other**
• AZF Deletions	• Opioid	• Obstructive sleep apnea
Medications		• Disordered sleep
• Spironolactone		
• Ketoconazole		
• Anti-androgens		
Anatomic		
• Varicocele		

ORGANIC OR FUNCTIONAL HYPOGONADISM?

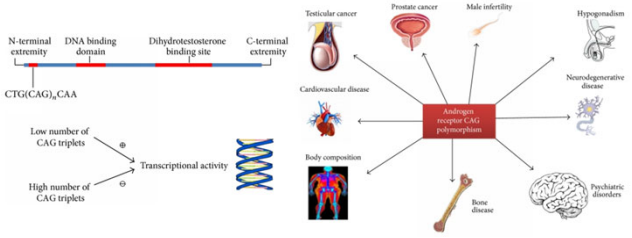
- T deficiency can also be categorized as organic or functional
- **Organic** hypogonadism is caused by a congenital, structural, or destructive disorder that results in **permanent hypothalamic, pituitary, or testicular dysfunction** (primary or secondary hypogonadism).
- **Functional** hypogonadism is caused by conditions that suppress gonadotropin and T concentrations but that are **potentially reversible** with treatment of the underlying etiology.
  - Obesity, opioids, systemic illness, steroid use / withdrawal, circadian disturbances, severe stress, other meds
- Important distinctions – can be used to counsel patients re: goals of therapy

ANDROGEN RECEPTOR

- The AR binds both T and DHT, but has greater affinity for DHT.
- The number of CAG repeats on Exon 1 of the AR gene can have a significant effect on T activity.
- The relationship between CAG repeats and physiological effects remains complex and incompletely understood; → contribute to the marked variability noted in T-related symptoms between men with similar serum T levels.
- Increased numbers of CAG repeats have been correlated with decreased symptomatic response to T therapy.
- No assay for CAG repeats is available for clinical use at present, assessment of CAG repeats may be used to individualize T supplementation in the future.
- [Info] from AUA Core Curriculum



ANDROGEN RECEPTOR



EVIDENCE SUPPORTED BENEFITS OF TRT

- Reduction of MACE risk
  - Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc. 2015 Feb;90(2):224-51.
    - Meta-analysis review of all TRT articles from 1940 – 2014
    - 200 articles identified, only 4 suggested increased CV risk with TRT
    - Dozens of studies suggested benefit
    - Low T levels ass'd with increased risk of mortality and CVD
    - Severity of CAD inversely correlated with low T levels
  - Tang L, Chen M, Li J, Xu X, Pu X. Association of testosterone with myocardial infarction and severity of coronary artery disease among male patients. Int J Cardiol Cardiovasc Risk Prev. 2024 May 7
  - Boden WE, Miller MG, McBride R, Harvey C, Snabes MC, Schmidt J, McGovern ME, Fleg JL, Desvigne-Nickens P, Anderson T, Kashyap M, Probstfield JL. Testosterone concentrations and risk of cardiovascular events in androgen-deficient men with atherosclerotic cardiovascular disease. Am Heart J. 2020 Jun;224:65-76.

EVIDENCE SUPPORTED BENEFITS OF TRT

- Reduction of MACE risk
  - How should TRT be resumed after a coronary intervention:
  - AUA guidelines state that a 3-6 month interval should be observed to allow for healing / endothelial regeneration
    - TRT can increase thromboxane A2 levels and increase TA2 receptor density on platelets.
    - Cardiologist approval also a good idea in this setting.
    - Could be a point of contention
    - Reference the 2015 Morgantaler / Miner meta-analysis AND the newer TRAVERSE study which both show no association with MACEs.

EVIDENCE SUPPORTED BENEFITS OF TRT

- AUA GUIDELINE STATEMENT # 14:
  - Increase in Bone Mineral Density
  - Improvement in some elements of ED
  - Improvement in Libido
  - Improvement in Lean Mass
  - Decreased symptoms of depression
  - Certain elements of DMt2
- Table from AUA Core Curriculum……. →

Table 1

Summary of purported beneficial effects of testosterone supplementation in hypogonadal males

Symptom	Level of evidence*
Body composition, physical activity, strength	
Increased lean body mass	1A
Decreased fat mass	1A
Improved bone mineral density	1A
Sexual function and libido	
Improved libido	1A
Improved morning erections	1A
Improved erectile function	1A
May improve response to PDE5s in those previously refractory to PDE5s	1B–
Medical comorbidities	
DM-improved fasting glucose, HbA1c, insulin sensitivity	1A
Lipids-improved TG, total cholesterol; variable results on HDL and LDL	1A–
Psychological/cognition	
Inconsistent and contradictory results with mood, cognition, behavior	1B–
Potential benefit in improving depression in hypogonadal or HIV positive males	1A–

NON EVIDENCE SUPPORTED "BENEFITS" OF TRT

- AUA GUIDELINE STATEMENT # 15:
  - evidence is **inconclusive** whether testosterone therapy improves:
    - Cognitive function
    - Energy / Fatigue
    - Lipid profiles
    - Other quality of life measures.

SIDE EFFECTS OF TRT

- AUA Core Curriculum

Table 5: Summary of Purported Adverse Effects of Testosterone Therapy in Testosterone deficient Men
Symptom
Cardiovascular Events and Mortality
No definitive evidence for worsened cardiovascular outcomes or increased mortality[26]
Beneficial effects on cardiac perfusion, ischemic threshold, exercise threshold, cardiac output
Dermatologic Changes
Increased sebum production
Increased acne
Increased hair loss
Hematologic Changes
Increased hematocrit
Increased deep venous thrombosis ?
Fertility
Exogenous T used alone results in reduced spermatogenesis

SIDE EFFECTS OF TRT

- AUA Core Curriculum

Gynecomastia
Hypothetical increased risk of gynecomastia and breast cancer
Prostate Events
Conflicting results on increasing PSA, PSA>4ng/ml, and rate of prostate biopsies
No increased risk of worsening urinary symptoms or flow
No increased risk of development of prostate cancer
Deleterious effects in locally advanced or metastatic prostate cancer
Unknown risks of prostate cancer progression in localized prostate cancer or in treated prostate cancer
Sleep Apnea
Early worsening of sleep apnea in patients with severe baseline symptoms (3-6 months)

?

TESTOSTERONE TESTING CONSIDERATIONS

- To fast or not to fast?:
  - Endocrine Society recs firmly recommend fasting state – "increased blood glucose and insulin response can reduce T concentration"
  - AUA guidelines do not reflect this (yet)
    - Mark Moyad MD and Marty Miner MD both agree that this is probably coming soon.
  - Yes or no for now, but be consistent
- The cut point
  - Controversy continues regarding 300, 350, 400 ng/dl
  - Patients who have a T over 300 ng/dL should be advised that their potential for benefit is less than men who have levels that are clearly low.
  - 6 month trial of T?
  - There is scant high-level evidence to suggest that men with total T greater than 400 ng/dL benefit from additional supplementation.
- Follicular Stimulating Hormone (FSH)
  - FSH does not play a significant role in stimulating production of T.
  - FSH IS a more sensitive indicator of testicular insufficiency than LH and thus may be measured together with LH to aid in the diagnosis. (if global testis function is in question)

TESTOSTERONE TESTING CONSIDERATIONS

- FREE TESTOSTERONE:
- Although free T only represents a small fraction of total T, some authorities consider it the most useful indicator of a man's T status due to its lack of significant interaction with SHBG.
- A 2017 study indicated that low free T was significantly associated with greater likelihood of sexual symptoms regardless of total T level, even after adjustment for age, comorbidities, and body mass index.
- The increased SHBG that occurs with aging tends to make total T appear normal, even though free T may be depressed.

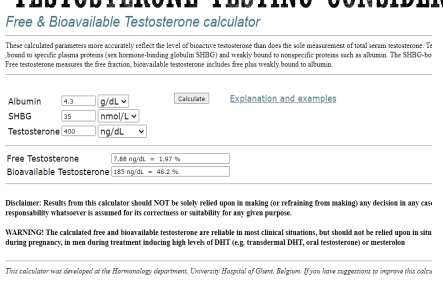
TESTOSTERONE TESTING CONSIDERATIONS

- FREE TESTOSTERONE:
- When SHBG is elevated and or total T concentration is at or near the low end of the ref range, Endo Soc recs checking total T levels along with SHBG and albumin and then manually calculating a free and % free T level.
  - Automated levels are not to be trusted
  - https://www.issam.ch/freetesto.htm
- AUA guidelines recommend against using free T values to guide the **initial** assessment of hypogonadism citing variability in testing assays but….
  - "Free testosterone also has a place in the diagnosis of testosterone deficiency in highly symptomatic patients with total testosterone levels in the low/normal or equivocal range."

TESTOSTERONE TESTING CONSIDERATIONS

- FREE TESTOSTERONE:
- No validated free / % free / bioavailable T level ranges exist.
- Free T is a useful adjunct that may be used by clinicians to aid in decision-making when required.
- Personally, in my clinic if a man has hypogonadism SS, I will calculate a % free T level if the total T level is > 300 but < 400 ng/dl. I target a %free T goal of 2%
  - CMP (for the albumin), SHBG, Total T all drawn on the same day

TESTOSTERONE TESTING CONSIDERATIONS



- https://www.issam.ch/freetesto.htm

LIFESTYLE AND BEHAVIORAL OPTIMIZATION

- Nutrition
  - No one food or diet to boost Testosterone in current literature
  - Nutrition is most relevant as it relates to weightloss
  - Some evidence exists for selenium, zinc, magnesium support
  - "Eat real food, mostly vegetables, and not too much" – Michael Pollan
  - Kuchakulla Meet al. The association between plant-based content in diet and testosterone levels in US adults. World J Urol. 2021 Apr;39(4):1307-1311.
    - Protein intake does not seem to influence T levels

- Exercise
  - Data exists to support benefits of BOTH aerobic and resistance training
    - Yeo JK, et al. Which Exercise Is Better for Increasing Serum Testosterone Levels in Patients with Erectile Dysfunction? World J Mens Health. 2018 May;36(2):147-152.
    - Kumagai H, et al. Increased physical activity has a greater effect than reduced energy intake on lifestyle modification-induced increases in testosterone. J Clin Biochem Nutr. 2016 Jan;58(1):84-9.

LIFESTYLE AND BEHAVIORAL OPTIMIZATION

- **Sleep / Circadian Rhythms / Shift Work**
- Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. JAMA. 2011 Jun 1;305(21):2173-4.
  - Daytime testosterone levels were decreased by 10% to 15% in this small convenience sample of young healthy men who underwent 1 week of sleep restriction to 5 hours per night, a condition experienced by at least 15% of the US working population.
  - Additional investigations of the links between sleep and testosterone are needed to determine whether sleep duration should be integrated in the evaluation of androgen deficiency.

- Wittert G. The relationship between sleep disorders and testosterone in men. Asian J Androl. 2014 Mar-Apr;16(2):262-5. doi:
  - Obstructive sleep apnea (OSA) appears to have no direct effect on testosterone, after adjusting for age and obesity.
  - A possible indirect causal process may exist mediated by the effect of OSA on obesity.
  - Treatment of moderate to severe OSA with continuous positive airway pressure (CPAP) does not reliably increase testosterone levels in most studies.
  - In contrast, a reduction in weight does so predictably and linearly in proportion to the amount of weight lost.
  - Apart from a very transient deleterious effect, testosterone treatment does not adversely affect OSA.

LIFESTYLE AND BEHAVIORAL OPTIMIZATION

- Stress
  - Not many studies exist on this
  - Theory of higher cortisol = lower Testosterone
    - COMPLEX relationship
  - Most likely relevant in the context of the effect of chronic stress on other behaviors such as food choices, alcohol intake, smoking, doom scrolling, sleep deprivation and other coping behaviors

TESTOSTERONE FORMS AND ADMINISTRATION

- Testosterone Cypionate
- Aveed (T undecanoate) q 10 week long acting injection
- Xyosted (Enanthate) weekly short acting injection
- Topical gels daily
- Compounded creams daily(versabase) daily
- Intranasal gel BID/TID(Natesto)
- Pellets q3-6 months
- Pills / Capsules BID (T undecanoate)… →

TESTOSTERONE FORMS AND ADMINISTRATION

- **Testosterone cypionate** injections are a mainstay of therapy
- Subcutaneous injections are feasible, effective and gaining popularity
  - Figueiredo MG, et al. Testosterone Therapy With Subcutaneous Injections: A Safe, Practical, and Reasonable Option. J Clin Endocrinol Metab. 2022 Feb 17;107(3):614-626.
  - Spratt DI, et al. Subcutaneous Injection of Testosterone Is an Effective and Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender Patients. J Clin Endocrinol Metab. 2017 Jul 1;102(7):2349-2355.
    - 25 ga needles to draw up and inject
    - Less painful
    - Improved pharmacokinetics – less of a serum T spike subcut
    - Ideally suited for more frequent injections
    - Twice weekly injections have been shown to decrease secondary polycythemia / erythrocytosis
    - Closer to physiologic patterns

TESTOSTERONE FORMS AND ADMINISTRATION

- Oral formulations:
  - Jatenzo
    - 87% men at T goal at steady state by day 7
  - Kyzatrex
    - 90% of patients who completed the study were at target range
    - SHBG decreases were observed
    - ~ 2x increase in mean T levels
  - Tlando
    - 80% men at T goal at one month
  - All are Testosterone undecanoate capsules
  - DO not cause liver toxicity
    - Are absorbed by intestinal lymphatics to avoid first pass metabolism
  - Can elevate BP, PSA, and Hg/HCT, HTN, nausea, and decrease HDL
  - Require PA almost always

Administration route	Preparation	Initial dosage	Usual dosage range
Oral	Capsule (Jatenzo)	237 mg twice daily	158 to 396 mg twice daily
	Capsule (Kyzatrex)	200 mg twice daily	100 mg **once** daily or 100 to 400 mg **twice** daily (maximum: 800 mg/day)
	Capsule (Tlando)	225 mg twice daily	
	Capsule (testosterone undecanoate)[b]	120 to 160 mg/day in 2 divided doses for 2 to 3 weeks	40 to 120 mg/day

TESTOSTERONE FORMS AND ADMINISTRATION

- Intranasal gel (Natesto):
  - BID / TID dosing
  - Peak and trough simulation (Ultradian rhythm)
  - 90% men therapeutic within 90 days, average Tmax to 800
  - Significant improvements in sexual function and mood and bone density
  - Fast absorption….rapidly occupies T receptors….remains bound while the serum levels then drop rapidly (low activity at the level of hypothalamus / pituitary)
  - Low incidence of secondary polycythemia / erythrocytosis
  - Preserves spermatogenesis in most men
  - Transference is rare
  - 10 seconds per dose
  - Avoids high spikes in T

TESTOSTERONE FORMS AND ADMINISTRATION

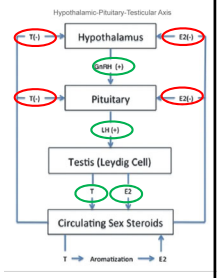
- Intranasal gel (Natesto)
- Intranasal gel is highly effective in treating symptoms of TD:
  - Gronski MA, Grober ED, Gottesman IS, Ormsby RW, Bryson N. Efficacy of Nasal Testosterone Gel (Natesto®) Stratified by Baseline Endogenous Testosterone Levels. J Endocr Soc. 2019 Jun 26;3(9):1652-1662.
    - Max TT was nearly identical across all cohorts at days 30 and 90.
    - LH levels remained normal but were decreased more in patients with higher starting baseline levels.
    - TNG works with an active hypothalamic-pituitary-gonadal axis that responds to each dose of TNG throughout the treatment period.
    - Patients with severe testosterone deficiency had similar efficacy improvements as the remainder of the study population

TESTOSTERONE FORMS AND ADMINISTRATION

- **Compounded topical formulations – are they safe and reliable?**
- AUA GL: 28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible. (Conditional Recommendation; Evidence Level: Grade C)
  - Opinion is based on one study by Grober et al where highly variable amounts of T were found in rx written to the same pharmacy one month apart
  - Also based on an analysis of creams ordered off the internet.
  - FDA studies conclude up to 33% of T compounds are inaccurate.
- Establish a relationship with your local compounding pharmacy and inquire into third party verification of contents and concentration
- Versa-Base cream is a uniquely stable hormone delivery cream well suited to deliver hormone compounds (125mg/ml; 4 clicks = 1ml of cream)

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS) : CLOMIPHENE

- Blocks estrogen binding to receptors in the hypothalamus and increases gonadotropin release, resulting in increased testicular stimulation and testosterone production.
- Huijben et al. Clomiphene citrate: A potential alternative for testosterone therapy in hypogonadal males. Endocrinol Diabetes Metab. 2023 May;6(3)
  - 153 hypogonadal men were treated with CC.
  - Mean TT, FT, LH and FSH increased during treatment. TT increased from 9 to 16 nmol/L, with a biochemical increase in 89% of the patients.
  - In patients who continued CC treatment, an increased level of TT persisted after 5 years of treatment.
  - With CC treatment, 74% of the patients experienced hypogonadal symptom improvement.
  - LH at the lower normal range before CC treatment was predictive for better TT response.
  - During CC therapy, few side effects were reported and no clinical important changes in PSA, HD and Hct were found.
- Safer than TRT? YES
- As effective? Usually



SERMS : CLOMIPHENE

- Keihani et al. Baseline Gonadotropin Levels and Testosterone Response in Hypogonadal Men Treated With Clomiphene Citrate. Urology. **2020**
  - 332 men
  - TT levels increased significantly on CC treatment (mean change: 329.2 ng/dL, 95% CI: 307.4-351.0)
  - 73% of men having at least 200 ng/dL increase over baseline TT levels.
  - In univariable linear regression models, only age was significantly associated with TT response.
  - Neither the baseline LH nor FSH significantly predicted TT response in linear regression models.
  - Adequate biochemical response with CC trial can be expected in most patients with normal or slightly elevated baseline gonadotropin levels.

SERMS : CLOMIPHENE

- Clomiphene potential side effects
  - Paradoxically lower libido
  - Mood swings
  - Blurred vision
  - Gynecomastia
  - Headache
  - Abdominal discomfort
  - Increased estrogen levels
- Clomiphene dosing
  - 25-50 mg po q 1-2 days
  - 25mg po Monday – Friday, off on the weekends

SERMS : CLOMIPHENE

- Clomiphene tips
  - A serum LH level can help guide clinical decision-making after initiation of clomiphene therapy.
  - If 8 weeks after starting the clomiphene the testosterone level remains low and the LH level remains low or normal, then dose escalation should be considered.
  - If after clomiphene the testosterone level is low but the LH level is high, then the patient likely has testicular dysfunction. SERM dose escalation in this case is not likely to increase testosterone levels.
- Did you know?....Clomiphene consists of two isomers:
  - (cis) Zuclomiphene – has been shown to be responsible for most of the adverse side effects of clomiphene administration
  - (trans) Enclomiphene – has been shown to be responsible for most of the estrogen receptor effects of clomiphene
    - Not commercially available….but…..

SERMS : ENCLOMIPHENE

- Big market for Enclomiphene Citrate

ENCLOMIPHENE CAPSULE 12.5MG - WARRIOR LABZ

★★★★★ (2)

$199.99

or 4 interest-free payments of **$50.00** with sezzle ⓘ

SERMS : ENCLOMIPHENE

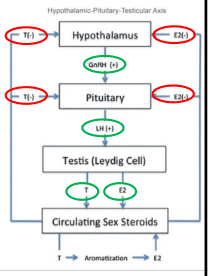
- Big market for Enclomiphene Citrate

DOUBLE YOUR TESTOSTERONE WITH SCIENCE

- 2x your testosterone levels [1]
- Improve energy, mood, & productivity [2]
- Does not harm your fertility [3]
- One daily pill, no need for weekly injections
- No lifelong dependence
- Starting at $99.99 per month

SERMS : TAMOXIFEN

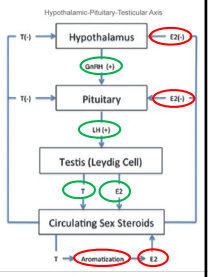
- Also occupies the hypothalamic E receptor preventing negative feedback but has significantly more SEs than clomiphene
  - Liver abnormalities
  - liver enzyme changes
  - ocular disturbances including cataracts
  - thromboembolic events including deep venous thrombosis and stroke
- Dosing: 20mg po daily



AROMATASE INHIBITORS

- AIs block the conversion of testosterone to E2
- Suppression of estradiol production increases circulating LH, FSH, and testosterone levels.
- AIs may be especially useful in treating **obesity-related hypogonadism** because of the high levels of aromatase in adipose tissue

- Anastrazole (Arimidex)
  - 1 mg every 1-3 days
- Letrozole (Femara)
  - 2.5mg daily



AROMATASE INHIBITORS

- Side Effects:
  - Hot flashes
  - Hypertension
  - Nausea
  - back pain
  - bone pain / bone loss
  - Dyspnea
  - peripheral edema
- AI tips:
  - AIs should in general not be used for extended periods of time due to concerns regarding loss of BMD. AIs can significantly suppress E2, which is essential in maintaining bone density.
  - With regular follow-up and careful titration of AI dosage, E2 can often be maintained in the therapeutic range, thus minimizing the risk of loss of bone density.
  - If AI therapy results in persistently elevated E2 levels, the AI should be discontinued due to lack of clinical efficacy.

HUMAN CHORIONIC GONADOTROPIN

- Is a direct LH analog
- Patients are taught to self-administer hCG.
- hCG given intramuscularly or subcutaneously in the thigh at an initial dose of 2000 units three times a week, always on the same three days (eg, Mondays, Wednesdays, and Fridays).
- The vial of hCG contains 5000 or 10,000 units of hCG powder; dissolving the powder with 2.5 mL or 5 mL yields 2000 units/mL.
- The serum testosterone concentration is measured every one to two months and, if it is not between 400 and 800 ng/dL within two to three months, the dose is increased.
- Some patients require as much as 10,000 units per dose. On rare occasions, the serum testosterone concentration fails to respond to hCG, even to 10,000 units three times a week. This problem is thought to be due to antibodies to hCG. Males with a history of cryptorchidism also often have a poor response.

POPULAR TESTOSTERONE BOOSTING SUPPLEMENTS

- **Ashwagandha**
  - Lopresti AL, Drummond PD, Smith SJ. A Randomized, Double-Blind, Placebo-Controlled, Crossover Study Examining the Hormonal and Vitality Effects of Ashwagandha (Withania somnifera) in Aging, Overweight Males. Am J Mens Health. 2019 Mar-Apr;13(2)
  - In this 16-week, randomized, double-blind, placebo-controlled, crossover study, its effects on fatigue, vigor, and steroid hormones in aging men were investigated.
  - A standardized ashwagandha extract (Shoden beads) for 8 weeks was associated with increased levels of DHEA-S and testosterone, although no significant between-group differences were found in cortisol, estradiol, fatigue, vigor, or sexual well-being.
  - Proposed mechanism: Dampening effect on the HPA axis – possible stimulating more DHEA and testosterone from the adrenal (NOT CONFIRMED)
  - Possible toxicity: Hepatotoxicity (rare but documented), increase in TSH / T4, GI upset

POPULAR TESTOSTERONE BOOSTING SUPPLEMENTS

- **Tongkat Ali; E, Longifolia; Longjack**
- Leisegang K, Finelli R, Sikka SC, Panner Selvam MK. *Eurycoma longifolia* (Jack) Improves Serum Total Testosterone in Men: A Systematic Review and Meta-Analysis of Clinical Trials. Medicina (Kaunas). 2022 Aug 4;58(8):1047.
- Nine studies published between 2012 and 2021 that investigated the effect of *E. longifolia* on serum testosterone levels in men.
- Proposed mechanisms:
  - Eurycomanone – Aromatase Inhibition, increased pregnenolone
  - Eurypeptides – may increase free T by aiding in the dissociation of T from SHBG
- Meta-analysis:
  - Significant increases in serum total T levels were found.
  - Significant study heterogeneity and bias was also found.
  - Unfortunately the studies were characterized by small numbers of subjects, short follow ups.
- In short, there may be some efficacy with Tongkat Ali but from an efficacy and safety standpoint this is not anywhere near ready for regular use in Urology clinic,

A BRIEF WORD ON FERTILITY IN THE SETTING OF TRT

- TD Patient who desires maintenance of fertility should avoid TRT*.
- Semen analysis, FSH should be obtained at baseline values
- Approx 2/3ds of men will regain spermatogenesis 6 - 24 months after stopping TRT but HCG stim may be needed
- * Intranasal T gel is currently the only form of exogenous TRT which preserves sperm count and quality.
- Think SERMs! – Clomid!

POLYCYTHEMIA / ERYTHROCYTOSIS

- TRT results in a dose-dependent increase in Hct, an effect which is more pronounced in elderly (>60 years) men.
- TRT can cause polycythemia / erythrocytosis by:
  - Stimulating erythropoietin transcription
  - Increasing Iron availability:
    - Testosterone increases iron availability for erythropoiesis by **suppressing hepcidin** transcription.
  - Multiplying Common myeloid progenitors: Red cell survival: Testosterone improves red cell survival.
- Different T formulations exhibit different effects, likely relating to maximum T levels achieved.
- In a retrospective analysis, the rate of erythrocytosis in men being treated with T injections, pellets, and gels was 66.7%, 35.1%, and 12.8%, respectively. A recent study of T nasal gel in 30 men reported no secondary polycythemia.

POLYCYTHEMIA / ERYTHROCYTOSIS

- **Erythrocytosis** – increase in the total RBC mass over 125% of weight based predictions
  - Secondary polycythemia is a subtype of polycythemia and is synonymous with erythrocytosis
  - Erythrocytosis is probably a better term to describe this phenomenon in TRT men.
- **Polycythemia** – absolute increase in RBC and sometimes other blood cellular mass
  - Subtypes:
    - True polycythemia:
      - **Low EPO state** 2/2 JAK2 mutation (**primary polycythemia**):
        - **Polycythemia Vera** - an increase in more than just the RBC cell type
          - Peaks b/t 40-60 and carries a 2:1 M:F incidence ratio
          - 22 cases per 100,000 people
        - Primary familial and congenital polycythemia

POLYCYTHEMIA / ERYTHROCYTOSIS

- Polycythemia – absolute increase in RBC and sometimes other blood cell mass
  - Subtypes:
    - True polycythemia:
      - **High EPO state (secondary polycythemia = erythrocytosis)**
      - Can be congenital (various mutations) or acquired:
        - **High altitude**
        - **Respiratory disorders**: Chronic obstructive pulmonary disease (COPD), Pickwickian syndrome, uncontrolled asthma
        - **Cyanotic heart diseases** with right-to-left shunts
        - **Renal disorders**: Renal cysts, kidney cancer, renal artery stenosis, Bartter syndrome, focal sclerosing glomerulonephritis
        - **Elevated carboxyhemoglobin:** Usually seen in smokers, people working on cars in closed spaces, or people working in boiler rooms
        - **Hemoglobinopathies**: High-affinity hemoglobins such as Hb Yakima, methemoglobinemia
        - **EPO-secreting tumors:** sources include hepatomas, uterine leiomyomas, and cerebellar hemangiomas
        - Iatrogenic causes: Including erythropoietin analog administration, anabolic steroids, and **testosterone replacement therapy**

POLYCYTHEMIA / ERYTHROCYTOSIS

- Are men on SERMs such as Clomid at risk for developing polycythemia?
- Wheeler KM, et al. A Comparison of Secondary Polycythemia in Hypogonadal Men Treated with Clomiphene Citrate versus Testosterone Replacement: A Multi-Institutional Study. J Urol. **2017**
  - Retrospective, multi-institutional study, included 188 men who received clomiphene citrate and 175 who received testosterone replacement therapy with symptomatic hypogonadism.
  - For testosterone replacement therapy and clomiphene citrate the mean change in hematocrit was 3.0% and 0.8%, and the mean change in serum testosterone was 333.1 and 367.6 ng/dl, respectively.
  - The prevalence of polycythemia in men on testosterone replacement was 11.2% vs 1.7% in men on clomiphene citrate ($p = 0.0003$). This significance remained on logistic regression after correcting for age, site, smoking history and pretreatment hematocrit.
  - **CLOMID admin has a much lower risk of polycythemia / erythrocytosis**
  - **The problem is that once a man is on T, it is difficult to get him to switch to C and also prob less likely that C will work.**

POLYCYTHEMIA / ERYTHROCYTOSIS

- **Treatment** of secondary polycythemia / erythrocytosis
  - Testosterone dose and dose interval reduction
  - Phlebotomy prn to Hg 16
  - Low dose Aspirin therapy (40-81mg po)
    - Daily for CV risk factors; BID for history of arterial thrombosis
    - Apixaban 2.5mg po BID plus ASA 81mg po daily in pts with history of DVT
    - Confers a decreased incidence of clots for the first three years of therapy
  - Treatment of other risk factors previously listed
    - Esp OSA, COPD, smoking status, obesity
  - Discontinuation / replacement of diuretic therapy if possible (volume contraction is bad)
  - Check ferritin and transferrin levels and replete iron if indicated
    - In iron deficiency, ferritin will be low and transferrin will be high leading to microcytosis
  - Consider Abdominal US to look for hepatomas, complex renal cysts, Renal artery stenosis
  - Consider referrals to hematology or GI as indicated

POLYCYTHEMIA / ERYTHROCYTOSIS

- Documented complications of secondary polycythemia / erythrocytosis include:
  - Strokes
  - VTE
  - Iron deficiency
  - Decreased mentation
  - Fatigue
  - MI

POLYCYTHEMIA / ERYTHROCYTOSIS

- MI due to **secondary** polycythemia data:
  - Ory J, Nackeeran S, et al. Secondary Polycythemia in Men Receiving Testosterone Therapy Increases Risk of Major Adverse Cardiovascular Events and Venous Thromboembolism in the First Year of Therapy. Journal of Urology [Internet]. **2022** Jun 1
  - A total of 5,842 men who received TT and developed polycythemia were matched and compared to 5,842 men who did not develop polycythemia.
  - **Men with polycythemia had a higher risk of MACE/VTE (number of outcomes: 301, 5.15%) than men who had normal hematocrit (226, 3.87%) while on TT (OR 1.35, 95% CI 1.13–1.61, p <0.001).**
  - **Consider adding ASA 81mg daily during first year of therapy**
  - ALSO…In hypogonadal men who received testosterone, no increased risk of MACE and VTE was identified as compared to hypogonadal men naive to TT.

HEMOCHROMATOSIS / HYPOGONADISM

- Hypogonadism can be a result of undiagnosed hemochromatosis
- Hemochromatosis is an iron overload disease characterized by normal erythropoiesis, an increase in the saturation coefficient of transferrin (≥ 45%), an increase in the concentration of serum ferritin (≥300 μg/L in a human) and a parenchymal iron deposition caused by low levels of hepcidin (master regulator of iron levels).
- In iron overload, hypogonadism is the second most common endocrine abnormality after diabetes.
- Iron deposition in the gonadotropic cells of the anterior pituitary gland leads to a defect of FSH and LH production that explains hypogonadism
- Relevant lab values: **Ferritin ≥300 μg/L, transferrin (TSAT)> 45%**
- What to look for?.....

HEMOCHROMATOSIS / HYPOGONADISM

- An individual may be suspected of having hereditary hemochromatosis (HH) based on signs or symptoms of iron overload and/or a positive family history of HH. Signs and symptoms of HH include the following:
  - Unexplained liver disease
  - Unexplained fatigue
  - Unexplained heart failure or arrhythmia
  - Unexplained arthropathy
  - High serum ferritin or TSAT
  - Porphyria cutanea tarda (PCT)
  - Unexplained hypogonadism or low libido
  - Type 2 diabetes mellitus with atypical presentation (eg, younger age than average or low BMI)
- **So, 2 potential reasons to test ferritin and transferrin: to eval potential iron deficiency in erythrocytosis and to screen for hereditary hemochromatosis in select individuals**

GLP-1 RECEPTOR AGONISTS

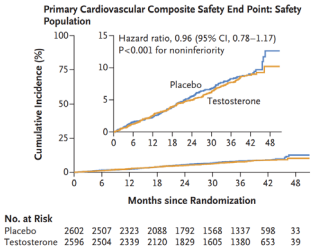
- **Semaglutide, Tirzepatide**
- Cannarella R, et al. Is there a role for glucagon-like peptide-1 receptor agonists in the treatment of male infertility? Andrology. 2021 Sep;9(5):1499-1503.
- Weightloss is a well established method of increasing T levels
- Leydig and Sertoli cells both express GLP-1 receptors
- In mouse studies Leydig cells actually secrete GLP-1 – possibly a paracrine function to support Sertoli cells.
- Hopefully with the massive number of people starting GLP-1 therapy, we might accrue some T data.
- Efficacy likely more significant in obese, diabetic men vs other etiologies
- Should we be rxing these agents for appropriately selected men in our clinics?

TRAVERSE TRIAL

- A. Michael Lincoff, M.D., et al. **Cardiovascular Safety of Testosterone-Replacement Therapy.** Published June 16, **2023**. N Engl J Med 2023;389:107-117
- Was designed and implemented in response to the FDA directive in 2015 which required manufacturers of approved TRT products to conduct a well designed clinical trial to assess the risks of MI and stroke.
- Multicenter, randomized, double-blind, placebo-controlled, noninferiority trial
- 5246 men 45 to 80 years of age who had preexisting or a high risk of cardiovascular disease and who reported symptoms of hypogonadism and had two fasting testosterone levels of less than 300 ng per deciliter.
- Patients were randomly assigned to receive daily transdermal 1.62% testosterone gel (dose adjusted to maintain testosterone levels between 350 and 750 ng per deciliter) or placebo gel.
- The primary cardiovascular safety end point was the first occurrence of any component of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

TRAVERSE TRIAL

- The mean (±SD) duration of treatment was 21.7±14.1 months, and the mean follow-up was 33.0±12.1 months.
- A primary cardiovascular end-point event occurred in 182 patients (7.0%) in the testosterone group and in 190 patients (7.3%) in the placebo group (hazard ratio, 0.96; 95% confidence interval, 0.78 to 1.17; P<0.001 for noninferiority).
- TRT was deemed noninferior to placebo at avoiding MACEs



TRAVERSE TRIAL

- Secondary endpoints: Card revasc procedures; occurrence of HG Pca (G4+3 or higher), sexual activity, remission of depression, bone fractures, diabetes dx, anemia dx.
- A higher incidence of atrial fibrillation (3.5% v 2.4%), of acute kidney injury (2.3% v 1.5%), and of pulmonary embolism (0.9% v 0.5%) was observed in the testosterone group.

TRAVERSE TRIAL

- CONCLUSION: In men with hypogonadism and preexisting or a high risk of cardiovascular disease, testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events.
- CV safety findings are limited to men who are actually hypogonadal at the initiation of TRT
- TRAVERSE findings should not be used to justify T admin to patients who simply wish to enhance their QOL.

TRAVERSE TRIAL

- CRITICISM:
- More than 60 per cent (1000 / 2596 subjects) of patients in **both groups** stopped taking the medication before the study ended.***
  - Unclear as to why
- Also, the trial was not a long term study
  - study mean treatment duration was only 21.7 ± 14.1 months
- The T levels achieved with T gel would not be considered therapeutic for most men.
  - median achieved testosterone hovered close to 350 ng/dL (or below) for much of the trial

TRAVERSE TRIAL

- **SEXUAL FUNCTION** sub-analysis:
- 1161 hypogonadal men with low libido enrolled in the sexual fxn arm
  - 587 received 1.62% T gel
  - 574 received placebo gel
- Primary Outcome: change from baseline in sexual activity
- Secondary Outcome: hypogonadal symptoms, EF, sexual desire
- RESULTS: TRT ass'd with sig improvement in frequency of sexual activity v placebo. TRT improved hypogonadal symptoms including sexual desire but did NOT improve erectile function.
  - Concurrent PDE5s were not used with these men during the trial

TRAVERSE TRIAL

- **PROSTATE CA SAFETY** sub-analysis:
- 5204 hypogonadal men total between 45 – 80 with hypogonadism, PSA < 3, and IPSS < 19 were enrolled
- Primary end point: development of HG PCA
- Secondary end points: incidence of any adjudicated prostate cancer, acute urinary retention, invasive prostate surgical procedure, prostate biopsy, and new pharmacologic treatment.
- RESULTS: During 14,304 person-years of follow-up, the incidence of high-grade prostate cancer (5 of 2596 [0.19%] in the TRT group vs 3 of 2602 [0.12%] in the placebo group did not differ significantly between groups
- The incidences of any prostate cancer, acute urinary retention, invasive surgical procedures, prostate biopsy, and new pharmacologic treatment also did not differ significantly.
- Change in IPSS did not differ between groups.
- The PSA concentrations increased more in testosterone-treated than placebo-treated men.

TRAVERSE TRIAL

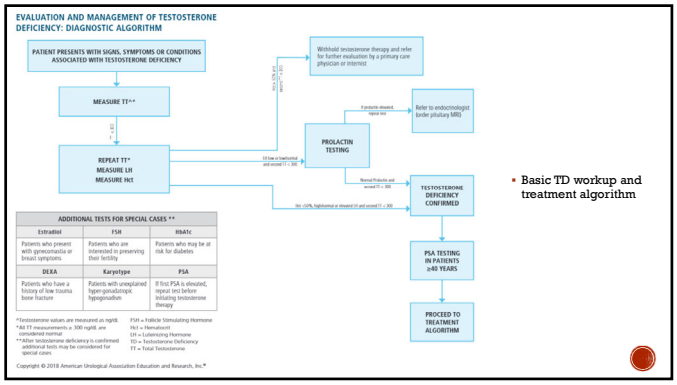
- Bone fracture sub analysis – revealed that TRT did not decrease incidence of fracture
  - 309 fractures were reported during the trial, with 186 in the testosterone group and 123 in the placebo group.
- Diabetes sub analysis – revealed no significant improvement although numbers looked encouraging
  - At the end of the two-year treatment phase, 12% of the testosterone group had type 2 diabetes compared to 21% of the placebo group.
- Anemia - improvement
  - A significantly greater proportion of testosterone-treated men had corrected anemia at 6, 12, 24, 36, and 48 months compared to placebo-treated men.

BRINGING IT ALL TOGETHER

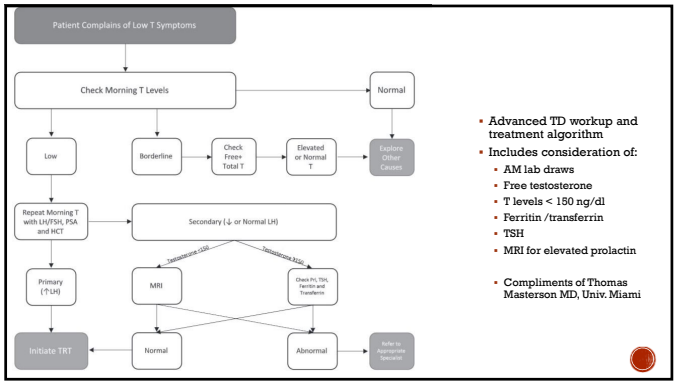
- AUA guidelines appear more robust vs Endocrine Society
- Anticipate AM fasting lab recommendation at next update
- Consider a more robust initial screening lab protocol possibly including
  - H/H, PSA, total T, LH, FSH, Prolactin, and HgA1c in select men
  - Followed by possibly adding SHBG, albumin, calculated free T, TSH, ferritin, transferrin, and pituitary MRI as indicated based on protocols
- Consider a more robust offering of lifestyle / behavior recommendations
  - Weightloss resources, nutritional advice, sleep resources, exercise resources, stress reduction resources
- Weightloss is probably more helpful than CPAP
- Lookout for secondary polycythemia / erythrocytosis and check iron studies if it develops
  - Ferritin / transferrin
  - Treat with T dose and interval reduction and phlebotomy initially

BRINGING IT ALL TOGETHER

- To minimize secondary polycythemia / erythrocytosis use: injections, pellets, and cutaneous gels in that order.
- T nasal gel carries lowest risk of secondary polycythemia / erythrocytosis.
- Consider low dose ASA for the first 6 months of TRT to counteract thromboxane A2 increase.
- Consider SERMS (clomiphene / tamoxifen) for any man desiring to avoid the major SEs of TRT and maintain testicular volume / fertility
- Consider Aromatase Inhibitors (anastrazole/ letrozole) for any obese man with TD or E2 increase on TRT
- Consider dosing TRT injections at lower doses more frequently and subcutaneously
- Consider underlying hemochromatosis in men with fatigue, early diabetes, unexplained low libido, arthropathy, arrythmia - check ferritin and transferrin then refer.
- Based on TRAVERSE trial: Confidently advise that safely administered TRT for men who need it should not increase MACE or prostate ca risk. DVT risk is very low. T should improve sexual desire but NOT erectile function as monotherapy.
- Encourage GLP-1 use but also warn patient of the potential loss of muscle mass!



- Basic TD workup and treatment algorithm



- Advanced TD workup and treatment algorithm
- Includes consideration of:
  - AM lab draws
  - Free testosterone
  - T levels < 150 ng/dl
  - Ferritin /transferrin
  - TSH
  - MRI for elevated prolactin
  - Compliments of Thomas Masterson MD, Univ. Miami

CLINICAL CASES

- ....
- If time allows