Complexities in the Diagnosis and Treatment of Hypogonadism: A Guideline-based, Patient-Centric Approach

Shalender Bhasin, MB, BS
Professor of Medicine, Harvard Medical School
Director, Research Program in Men's Health: Aging and Metabolism
Co-Director, The Center for Transgender Health
Director, Boston Claude D. Pepper Older Americans Independence Center
Brigham and Women's Hospital
Boston, MA, USA

13th Annual Endocrine Summit, Mumbai, India

BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL

VE RI TAS

Outline of the Presentation

- Complexities in the diagnosis of testosterone deficiency
- Emerging syndromes of androgen deficiency
- Age-related decline in testosterone
- Adverse Effects Associated with testosterone treatment
- Standardized monitoring of testosterone replacement therapy

Disclosures

- Research grants for investigator-initiated studies: NIA, NINR, NICHD-NCMRR, PCORI, Abbvie, Transition Therapeutics, MIB, and FPT
- Consultation: AbbVie, OPKO
- Equity interest/stock: FPT, LLC
- Not speaking to represent:
  - ABIM Endocrinology Board

Which of these men has/ have hypogonadism?

Normative ranges: Total T 263 – 914 ng/dL (9.2 to 33.0 nmol/L); free T 70 – 225 pg/mL; LH 2-9 U/L; FSH 1-7 U/L

1. 24 years old man is evaluated for failure to develop facial hair. PE reveals few facial hair, female pattern escutcheon, penis 4 cm, and testes 4 mL bilaterally. Total T 70 ng/dL, free T 10 pg/mL, LH 1 U/L, FSH 0.5 U/L.
2. An obese 35 years old man, with diabetes, hypertension, and heart disease complains of difficulty in achieving and maintaining erections. BMI 42 kg/m^2, normal hair growth, testes 25 ml b/l. Total T 265 ng/dL, LH 5 U/L, FSH 4 U/L.
3. 25 years old man complains of fatigue, low sex drive, and breast tenderness. At age 20, he underwent left orchiectomy for seminoma, and received bleomycin, etoposide, and cisplatin. Recent MRI revealed no residual tumor. Normal facial hair, bilateral tender breast tissue, and right testis 15 cm. Total T 310 ng/dL, free T 70 pg/ml.
4. 65 years old man complaints of ED, weight gain, low mood, and diminished energy. PE: BP 145/90, testes 25 ml B/L. T 260 ng/dL, free T 65 pg/ml, LH 6.0 U/L, FSH 9 U/L.

Definition

"Hypogonadism in men is a **clinical syndrome** that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa (sub or infertility) due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis"

— The Endocrine Society Clinical Practice Guidelines

Bhasin et al, J Clin Endocrinol Metab. 2018;103:1715.

Three-Step Workup of Men With Androgen Deficiency

STEP 1

Ascertain signs and symptoms; exclude systemic causes

STEP 2: Ascertain T Def.

Measure Fasting, Early AM Total T and if indicated Free T

Confirm Low Total T and/ or Free T

STEP 3: Ascertain Cause

Measure LH and FSH

Low T, low or inappropriately normal LH (hypogonadotropic)

- **Rule out systemic illness**
- **Measure prolactin and ferritin**
- **Evaluate other pituitary hormones**
- **MRI scan**
- **Identify by pattern recognition**

Low T, high LH (hypergonadotropic)

Primary testicular dysfunction

- **Obtain karyotype to exclude Klinefelter's syndrome**

Adapted from Bhasin et al, J Clin Endocrinol Metab. 2018;103:1715.

Sources of Diagnostic Imprecision and Inaccuracy

- Non-specificity of signs and symptoms
- Variation in circulating T levels
  - Biological factors
    - Genetic factors
    - Binding protein concentrations
    - Secretory rhythms of testosterone
  - Methodological factors
    - Assay imprecision and inaccuracy
    - Differences in calibrator
- Poorly-derived reference ranges

Symptoms and Signs with Higher Specificity

- Incomplete or delayed sexual development
- Loss of body hair (axillary and pubic) hair
- Very small testes (less than 6 mL)
- Sexual symptoms:
  - Reduced sexual desire (libido) and activity
  - Decreased spontaneous erections
  - Erectile dysfunction

Bhasin S et al. J Clin Endocrinol Metab. 2010;91:1995-2010;
Wu FCW et al. N Engl J Med 2010;363

Variability in T Levels During Repeated Testing

Sources of Variability

- Substantial variability in T levels over time within the same individual
  - BACH study: 1/3 of men with T<300 ng/dL had subsequent T > 300 ng/dL.
- Secretory Rhythms: Pulsatile secretion, circadian and circannual rhythm
- T levels decline after a meal or glucose.
- T Levels are lower during illness.

Steps to minimize influence of variability

- Avoid making a diagnosis based on a single T value.
- Measure early morning T level on 2 or more days.
- Obtain blood in a fasting state.
- Avoid evaluating during acute illness.

Bhasin S, Ozimek N. Endocr Pract. 2021;27:1252-1259.
Brambilla DJ, et al. Clin Endocrinol. 2007;67:853-62.

Reducing Measurement Error by Using Accurate Assays Certified by a Hormone Standardization Program

- Measure T using an accurate assay.
  - LC-MS/MS provides high precision and accuracy esp. in the low range.
  - Certification by an accuracy-based national or international benchmark (e.g., CAP, CDC's HoST Program)
- What to do if LC-MS/MS assays are not available:
  - Use an extraction immunoassay, if available, in a lab that participates in an accuracy-based certification program
  - Rely on multiple T measurements and ancillary clinical data to reduce the risk of misclassification

Bhasin et al. Steroids. 2008;73(13):1311-7;
Bhasin S et al. J Clin Endocrinol Metab. 2018;103:1715-1744.

Using Harmonized Testosterone Reference Range

- Reference ranges for T levels vary across labs and are not rigorously derived or representative of the general population.
- Generation of harmonized Reference ranges
  - T assays from 4 epidemiologic studies cross-calibrated by CDC, and T levels harmonized using Deming's regression.
  - 2.5th percentile ~263 ng/dL (9.2 nmol/L); 97.5th percentile 914 ng/dL (33 nmol/L).

Caveats

- Reference ranges may vary across racial and ethnic groups.
- The cut-points should not be viewed as absolute.
- In RCTs, testosterone treatment has generally improved sexual symptoms in men with baseline T levels 275 to 300 ng/dL.

Travison TG, et al. J Clin Endocrinol Metab. 2017;102:1161-1173

The Cutpoint Should not be Viewed as an Absolute Value: Impact of Assay Imprecision

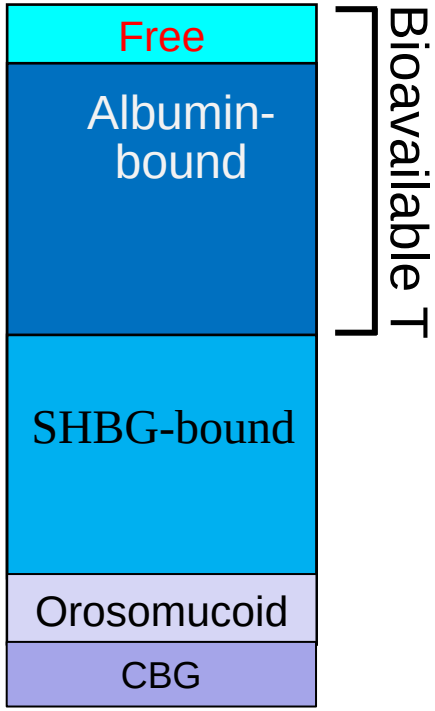
20-year-old man requests evaluation for sexual dysfunction. He is well virilized; testicular volume 20 mL. Serum T level 299 ng/dL (Lower limit of normal 300 ng/dL in an RIA with 15% CV).

Which is the true T concentration in the patient?

A. 299 ng/dL
B. 240 ng/dL
C. 360 ng/dL
D. Cannot tell from the information provided

Assay imprecision and physiologic variation in T levels over time increase the risk of misclassification when T levels are within 2 SDs of the cutpoint.

Partitioning of Circulating Sex Hormones Among Binding Proteins



- Most hormones, micronutrients and many drugs are hydrophobic with limited solubility in aqueous plasma and are carried bound to binding proteins.
  - Binding proteins regulate the transport, bioavailability, and metabolism of ligands
- Free Hormone: The fraction that is not bound to any plasma protein
- Bioavailable Hormone: The fraction that is not bound to SHBG (unbound plus albumin-bound)

Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. Endocr Rev. 2017;38:302-324.

Conditions in which Measuring Free T is Particularly Important

- Patients in which a binding protein abnormality is suspected, or
- When the total testosterone levels are within in the borderline zone (225 to 400 ng/dL)

Bhasin S, Ozimek N. Endocr Pract. 2021;27:1252-1259.

Methods for Assessing Free Testosterone (FT) Levels

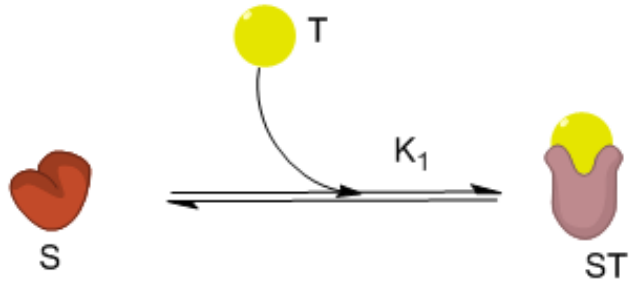
Two ways of assessing FT levels

Direct Measurement
- Equilibrium dialysis (reference method)
- Ultrafiltration
- Ammonium sulfate precipitation
- Tracer analog methods

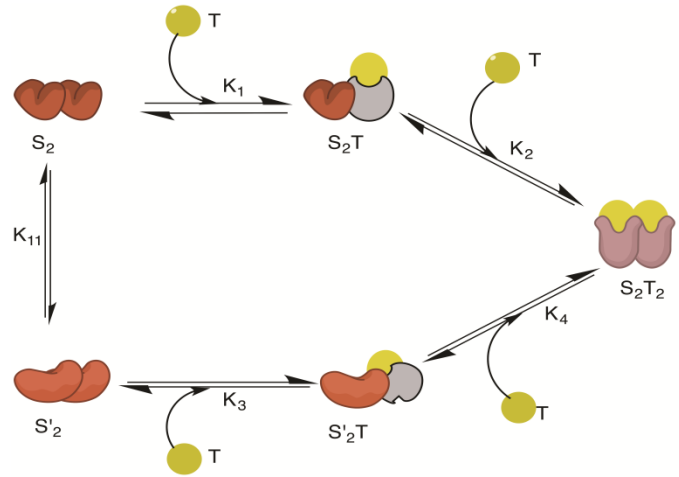
Calculated FT (cFT)
- Calculation based on Total T, SHBG and albumin
- Empirically-derived equations

Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. Endocr Rev. 2017;38:302-324.
Bhasin S, Ozimek N. Endocr Pract. 2021;27:1252-1259.

A Dynamic Multi-Step Ensemble with Allostery Model of Testosterone's Binding to SHBG

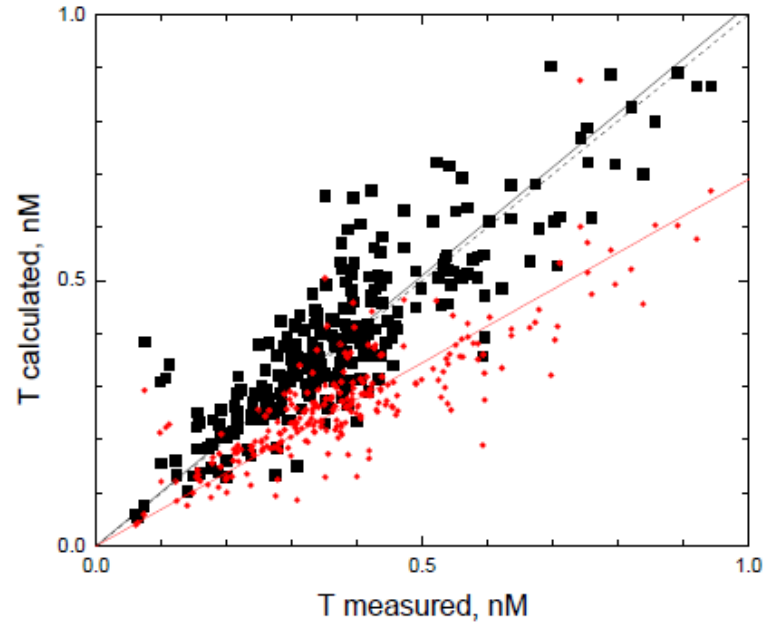


Extant Linear Model



Multi-Step Ensemble Allostery Model

A

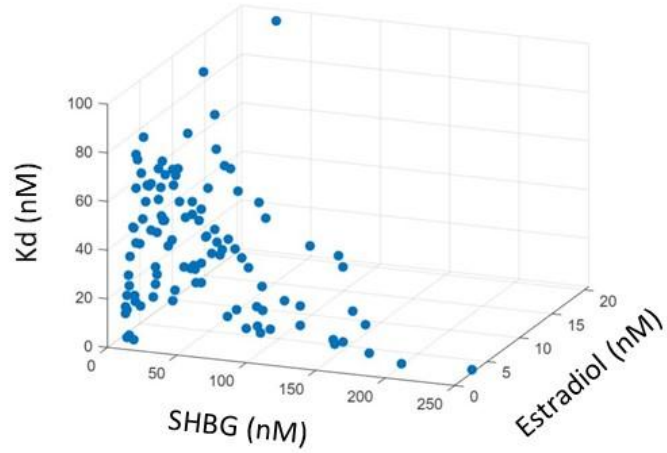


https://tru-t.org

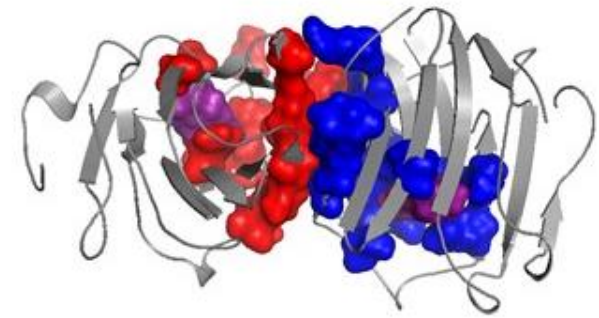
Zakharov MN, Bhasin S, Travison TG, Ulloor J, Vasan RS, Wu F, Jasuja R. Mol Cell Endocrinol. 2015;399:190-200

Estradiol Binding to SHBG Involves Inter-Monomeric Allostery and Partitioning of Monomers in Distinct Conformational and Energetic States

Apparent affinity of estradiol for SHBG varies with altered SHBG/E2 ratios



Upon E2 binding, the two monomers are conformationally and energetically distinct.



Jasuja R, Spencer D, Jayaraj A, Peng L, Krishna M, Lawney B, Patel P, Jayaram B, Thayer KM, Beveridge DL, Bhasin S. iScience. 2021;24(6):102414.

Using ancillary data to reduce risk of mis-classification when T level is close to the cutpoint

29-year-old man is being evaluated for sexual dysfunction and infertility. He started shaving at age 15 and became sexually active at age 18. He appears well virilized but has bilateral breast enlargement. His total T is 325 ng/dL, free T 68 pg/ml.

Is he hypogonadal?

A. Yes
B. No
C. Cannot tell, need more information

Emerging Androgen Deficiency Syndromes in Men

- Androgen deficiency associated with opioid use
- Androgenic-Anabolic Steroid Withdrawal Hypogonadism
- Oligogenic mutations associated with IHH
- Age-Associated decline in testosterone level

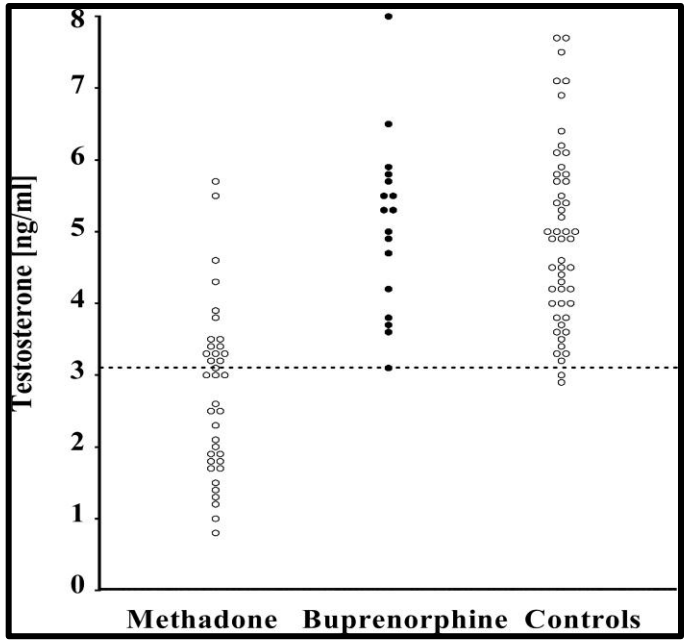
Chronic prescription opioid use and AAS withdrawal hypogonadism have emerged as the most common antecedents of a testosterone prescription within the VA Healthcare System.

Jasuja GK, et al. J Gen Intern Med. 2017;32:304-311.

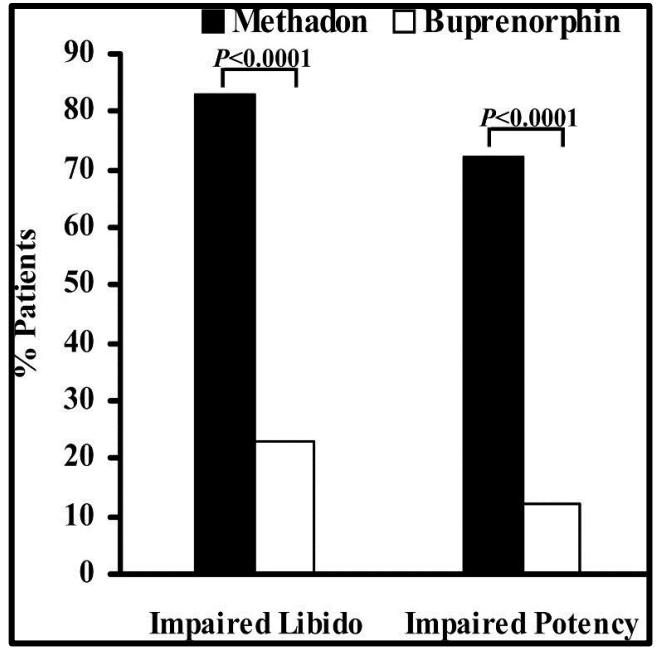
Jasuja GK, et al. JAMA Netw Open. 2019;2:e1917141.

High Prevalence of Low Testosterone, Sexual Dysfunction, and Osteoporosis in Patients Receiving Opioid Analgesics

Lower T in Methadone-Treated Men



Sexual Dysfunction in Methadone-Treated Men



Osteoporosis in Methadone-Treated Men

- *T*-scores <−2.5 (osteoporosis range) in 35%
- BMD <-1.0 and >−2.5 (osteopenia range) in 48%

Bliesener N et al. JCEM 2005;90:203-206

Kim et al, Drug and Alcohol Depend 2006;85: 258-262

AAS Use and Muscle Dysmorphia in Men – a Form of Body Image Disorder

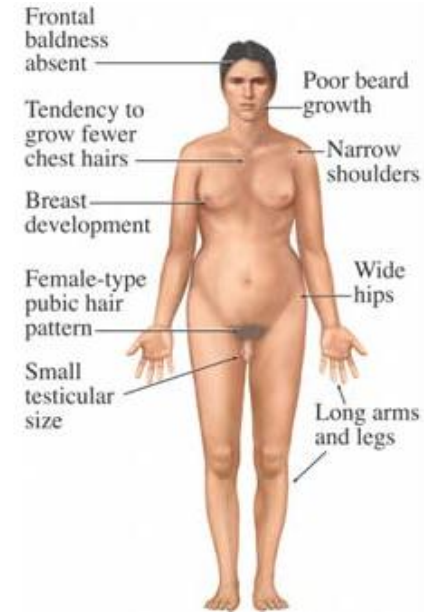
- After prolonged use of anabolic steroids, the HPT axis may not recover, recover slowly or incompletely leading to AAS withdrawal hypogonadism.
- Muscle dysmorphia – a form of body image disorder - exhibits preoccupation with muscularity and leanness; dissatisfaction with body size and shape; poor functioning in social life
- Highly engaged in weightlifting and body building
- Highly likely to use performance enhancing drugs, especially anabolic-androgenic steroids.

Because AAS use has elements of body image disorder and addiction, evaluation and treatment should address the body image disorder as well as addiction behavior.

Bhasin S. In: Harrison Textbook of Medicine 19th ed. 2020

Klinefelter's Syndrome

- 47, XXY karyotype: nondysjunction during meiosis
- Presentation:
  - Behavioral and learning problems, normal puberty
  - Adulthood: Infertility, gynecomastia, or T deficiency
  - Small testes, eunuchoidal proportions, gynecomastia
  - Normal performance IQ, but low verbal IQ
- KS patients are at
  - increased risk for mortality, breast cancer, certain non-Hodgkin's lymphomas, autoimmune diseases
  - Lower risk for prostate cancer
- TESE plus ICSI:
  - Successful sperm retrieval in 40% of men with KS;
  - ~40% with successful sperm retrieval achieve a live childbirth.
  - Thus ~16% of men with KS can achieve a childbirth with TESE + ICSI.



Men with KS should receive appropriate fertility counseling and undergo periodic screening for breast cancer.

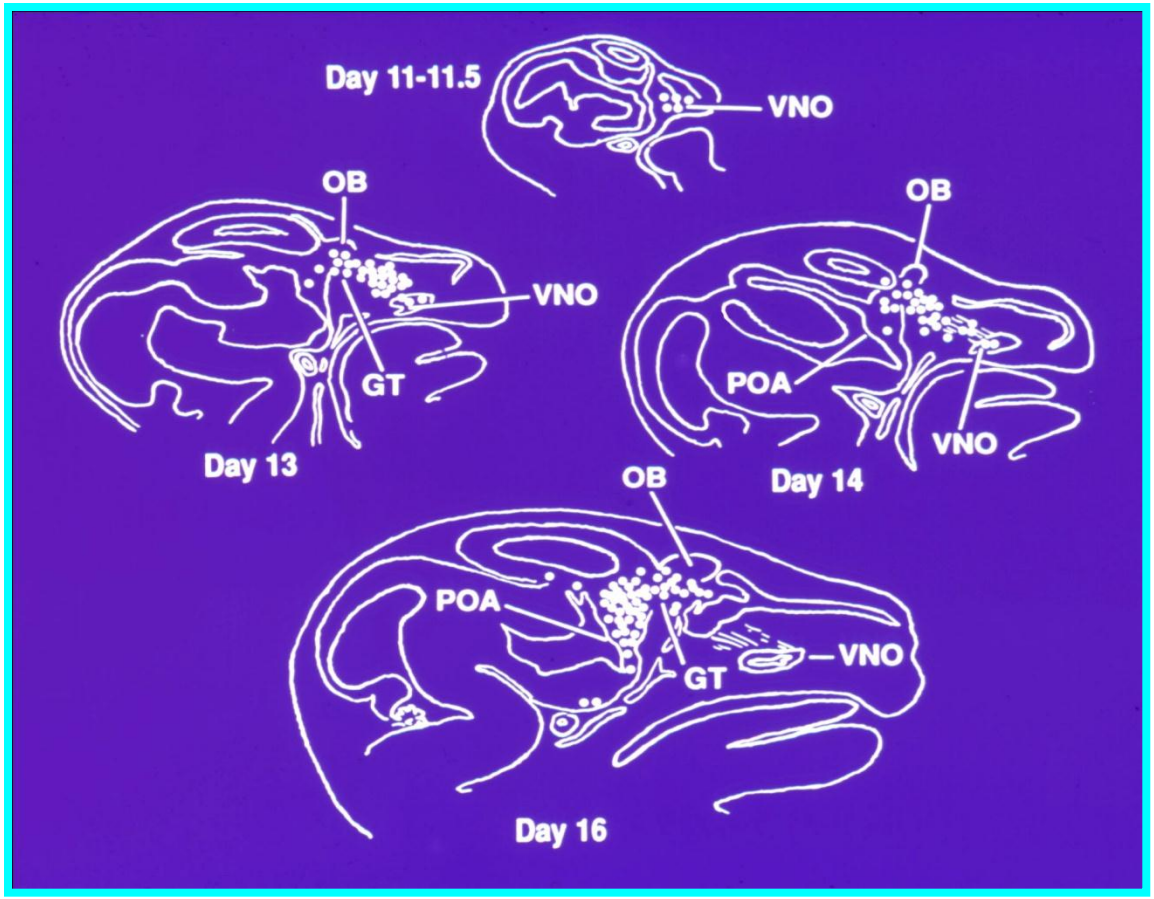
Bhasin S, Oates RD. J Clin Endocrinol Metab. 2020;105:e1918–20; Swerdlow et al. J Natl Cancer Inst. 2005;97:1204.

Wide Genotypic and Phenotypic Spectrum of Patients with Mutant IHH Alleles

- Genetics:
  - A substantial proportion of IHH patients have oligogenic inheritance rather than monogenic Mendelian inheritance
  - Disease expression influenced by gene : environment interaction
- Wide Phenotypic spectrum
  - Classical lifelong IHH
  - Adult onset IHH in men
  - IHH with reversal
  - Hypothalamic amenorrhea in women
  - Normal HPG axis

Mitchell et al. Trends Endocrinol Metab 2011;22:249

A Network of Genes Involved in GnRH Neuronal Migration, and GnRH and Gonadotropin Secretion



- GnRH Neuronal Development and Migration

  Kal-1, NELF, FGFR1, FGF8, PROKR2, PROK2, WDR11, CHD7
- GnRH Secretion

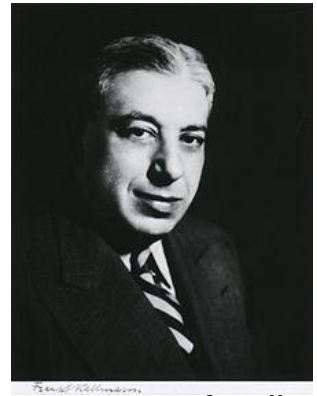
  GnRH1, KISSR1, LEPR, LEP, DAX1, TAC3, TACR3
- Gonadotropin Secretion

  DAX1, GnRHR

Pfaff 1985; Mitchell 2011; Seminara 2010; Bianco 2009

Two Forms of IHH

- Kallmann syndrome, the anosmic form
  - Mutations in genes associated with olfactory bulb morphogenesis or the migration of GnRH neurons
  - *KAL1;* NMDA Receptor Synaptonuclear Signaling and Neuronal Migration Factor (NSMF); genes involved in FGF signaling*;* genes involved in *PROK* signaling
- Normosmic form
  - GnRH, GnRHR, KISS-R, NK3b, N3KR, and others



Franz Josef Kallmann

Stamou MI, Georgopoulos NA. Metabolism. 2018;86:124-134.
Bhasin S, Jasuja R, Jayasena C. In: DeGroot's Textbook of Endocrinology. 12th ed. 2022

Golden Rules for Accurate Diagnosis of Androgen Deficiency Syndrome

- Weigh the specificity of symptoms and exam findings.
- Use an accurate assay (preferably an LC-MS/MS assay), and appropriate reference range.
- Do not make a diagnosis of AD based on a single T measurement or only on T level.
- Measure free T using an accurate method when binding protein abnormality is suspected.
- Use ancillary data (testicular volume, LH, FSH levels) to aid in the diagnosis.

Bhasin S, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:1715-1744.

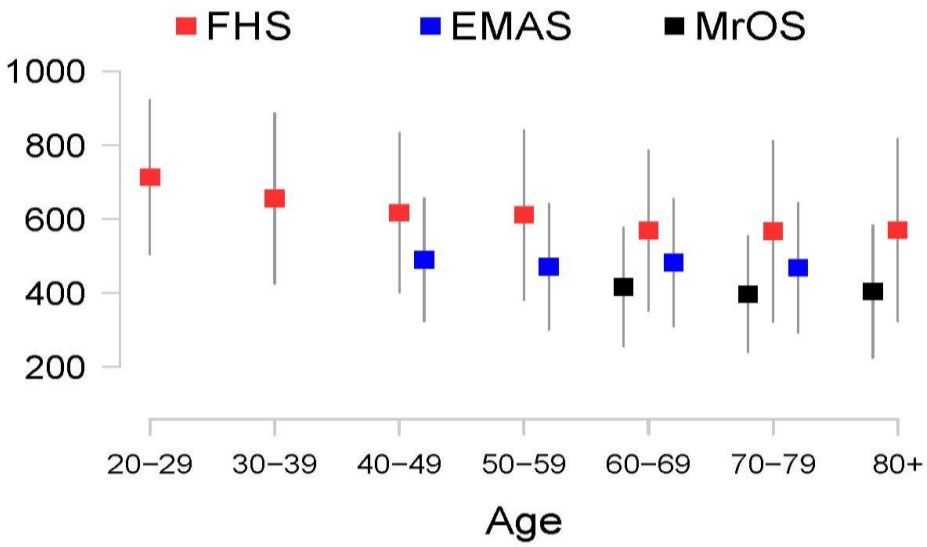
Case Discussion

Answer: Cases 1 and 3

Case	Rationale
1. 24 years old man with delayed pubertal development	Yes, delayed pubertal development, diminished facial hair, small testes, very low total and free T along with low LH and FSH; needs further evaluation to find cause of gonadotropin def.
2. 35 years old man with obesity, T2DM, ED	No, low T likely due to low SHBG; normal testicular volume, normal hair,
3. 25 years old man S/P chemotherapy for seminoma	Yes, has mild T deficiency Has low libido, painful breast enlargement, hx of chemotherapy, and elevated FSH
4. 65 years old man with fatigue and ED	Has age-related decline in T

- Age-Associated Decline in Serum Testosterone Levels

Total Testosterone by Decades of Age in Framingham Heart Study, EMAS, and MrOS



Percent of Community-Dwelling Older Men with Unequivocally Low Testosterone Level

Study	PI	# Men > 65	% Men with T <250 ng/dL
FHS	Bhasin	1870	**12.1%**
MrOs	Orwoll	2623	**10%**
EMAS	Wu	1080	**7.3%**
CHS	Hirsch	639	**14.3%**

Bhasin S, et al. J Clin Endocrinol Metab. 2011;96:2430-9
Wu F, et al. N Engl J Med. 2010;363:123-35.

Epidemiological Data: Weak Association of Low T and Outcomes

- Positively associated with:
  - Sexual desire and sexual activity
  - Muscle mass, strength, and physical function
  - aBMD, vBMD, and bone strength
- Negatively associated with:
  - All cause mortality
  - Whole body and visceral adiposity
  - Metabolic syndrome
  - T2DM
  - CAD
  - Frailty, mobility limitation, falls and fractures
  - Late life low grade persistent depressive disorder
  - Dementia, fibrillar amyloid beta deposits

Santos M, Bhasin S. Annu Rev Med. 2021;72:75-91.

Major RCTs of Testosterone's Effects in Older Adults

Trial	Eligibility	Baseline T	Symptom Requirement	Primary Outcomes
The TTrials – n=780, 1 year	≥65 years	Average of two T levels < 275 ng/dL	Low sexual desire, fatigue, or mobility limitation	Sexual function, mobility, vitality, vBMD, anemia of aging, cognition, and noncalcified coronary plaque
T4DM Trial N=1,007; 2 years	50 to 74 years	< 403 ng/dL	Impaired OGTT or newly diagnosed T2DM	Progression to or reversal of T2DM
Trials that focused primarily on muscle performance and physical function				
TEAAM Trial (n=308); 3 years	≥60 years	TT <400 ng/dL or free T <50 pg/mL	No symptom requirement	Progression of atherogenesis by CCA-IMT and coronary calcium using MDCT
TOM Trial (n=209); 6 months	65 years or older	TT <350 ng/dL or free T <50 pg/mL	mobility difficulty, SPPB 4 to 9	Physical function measures, LBM, muscle strength and power,
Wu et al (n= 274); 6 months	Men, >65	TT <340 ng/L, or free T <83 pg/mL	Frail and intermediate frail	LBM, strength, muscle strength, physical function, and self-reported quality of life
Emmelot-Wonk Trial (n=237); 6 months	60 to 80 years	TT <400 ng/dL	No symptom requirement	LBM, strength, TUG, self-reported functional mobility
Nair et al (n=58); 2 years	60 or older	Bio-T < 103 ng/dL	No symptom requirement	LBM, strength, VO2max, BMD

Snyder et al, NEJM 2016;374:611; Wittert et al Lancet Diabetes Endocrinol 2021;9:32; Basaria et al, JAMA 2015;314:570; Basaria et al, NEJM 2010;363:109.; Srinivas Shankar et al, JCEM 2010;95:639; Emmelot-Wonk et al, JAMA 2008;299:39; Nair et al, NEJM 2006;355:1647.

What Have We Learned from recent large RCTs about Testosterone's Efficacy: Sexual Function

- No beneficial effects in men with normal T and no symptoms
- In older men with unequivocally low T and decreased libido, TRT improves:
  - ❖overall sexual activity,
  - ❖sexual desire,
  - ❖erectile function, and satisfaction with erectile function.
- TRT does not improve ejaculatory function.

Snyder et al, NEJM 2016;374:611-24; Basaria et al, JAMA 2015;314:570-81; Brock et al, J Urol 2016;195:699-705; Basaria et al, NEJM 2010;363:109-22.

Testosterone's Effects on Muscle Mass, Muscle Performance and Physical Function

- Testosterone administration increases:
  - Skeletal muscle mass,
  - Maximal voluntary strength and muscle power
  - VO_{2peak}
  - Self-reported physical function
  - Stair climbing speed and power; and
  - Modestly improves walking ability
- Anabolic effects are augmented by resistance exercise training and rhGH.
- These anabolic effects have been demonstrated in healthy older men, older men with mobility limitation, and in men with HIV-associated weight loss, COPD, and ESRD.

Snyder et al, NEJM 2016;374:611-24; Basaria et al, JAMA 2015;314:570-81; Basaria et al, NEJM 2010;363:109-22; Srinivas Shankar et al, JCEM 2010;95:639-50; Emmelot-Wonk et al, JAMA 2008;299:39-52; Nair et al, NEJM 2006;355:1647.

Effects on Other Efficacy Endpoints

Endpoint	Findings of RCTs
Diabetes risk	In T4DM Trial, T treatment with lifestyle intervention for 2 years was associated with lower proportion of men having diabetes and greater reduction in 2 hour OGTT glucose
Bone	Improvements in vBMD, aBMD, and estimated bone strength of hip and spine
Anemia	Corrects unexplained anemia of aging and anemia of other causes
Depressive symptoms	Small but consistent improvements in depressive symptoms; some efficacy in late-onset PDD
Cognition	No improvement in men without cognitive deficit or AD; Efficacy in men with preclinical AD?

Snyder et al, JAMA IM 2017; Bhasin et al, JAMA Psych 2018; Basaria et al, NEJM 2010; Basaria et al, JAMA 2015; Huang et al, Lancet Diabetes Endocrinol 2016; Resnick et al, JAMA 2017; Travison et al, J Gerontol 2011; Wittert Lance Diab Endocrinol 2021

Adverse Events Associated with TRT

- Overall low frequency of AEs and SAEs in RCTs.
- Erythrocytosis the most frequent AE.
- Increased risk of detection of subclinical prostate disease.
- No significant change in LUTS in men with IPSS < 21.
- Suppression of spermatogenesis and infertility
- Very low rates of gynecomastia, VTE events, and sleep apnea
- The trials not large enough or long enough to evaluate effects on MACE and prostate cancer risk.

Bhasin et al, J Androl 2003; Basaria et al, NEJM 2010;363:109-22**.** Basaria et al, JAMA 2015;314:570-81; Huang et al, Lancet Endocrinol Diab 2016; Travison et al, J Gerontol 2011; Spitzer et al, Nature Endocrinol Metab 2013

Managing Erythrocytosis During Testosterone Therapy

- Significantly higher frequency of erythrocytosis (hematocrit >54%) compared to placebo (RR: 8.14, CI 95% [1.87, 35.4])
- Increases in Hb/Hct related to dose and circulating T level
- If hematocrit rises above >54%
  - Hold T dose until hematocrit drops to a safe level, evaluate for other causes of erythrocytosis, and then restart at a lower dose

Bhasin S, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:1715-1744.

Prostate Effects: Inherent Bias Towards Detection of Greater Number of Prostate Events in T-treated Men

- TRT does NOT worsen lower urinary tract symptoms
- AR signaling plays an important role in prostate cancer biology, but no clear evidence that testosterone causes prostate cancer
- MR Study using UK Biobank data: genetically determined bioavailable T associated with increased risk of prostate cancer
- T increases PSA and prostate biopsies usually triggered by PSA increments in clinical trials leading to increased risk of detection of subclinical prostate cancers.

Calof et al J Gerontol 2006; Spitzer et al, Nature Rev Endocrol 2013; Ponce OJ, J Clin Endocrinol Metab. 2018 Mar 17. doi: 10.1210/jc.2018-00404; Ruth KS, et al. Nat Med. 2020;26(2):252-258.

Prostate Monitoring Guidelines

- Obtain urological consultation if there is:
  - A confirmed increase in serum PSA concentration >1.4 ng/mL within 12 months of initiating T treatment
  - A confirmed PSA >4 ng/mL at any time
  - Detection of a prostatic abnormality on DRE
  - Substantial worsening of LUTS

Bhasin et al, J Clin Endocrinol Metab. 2018;103:1715; Bhasin et al, J Androl 2001;22:718

Testosterone and Cardiovascular Risk

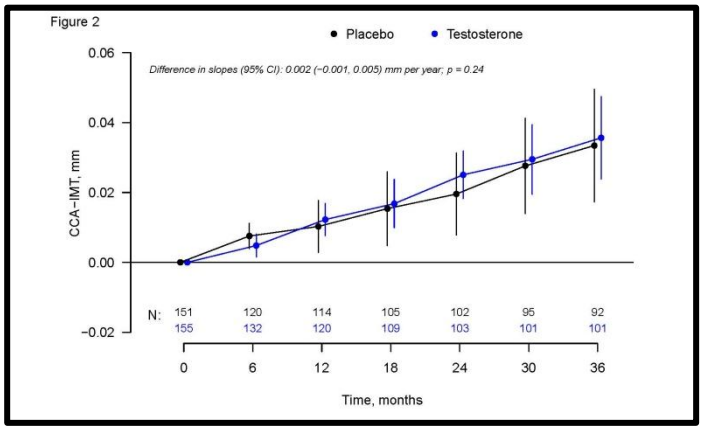
- No RCT has been large enough or long enough to determine testosterone's effects on major adverse cardiovascular events.
- Results of epidemiological and pharmacovigilance studies based on retrospective EMR data and meta-analyses of RCTs are inconclusive.
- There is insufficient RCT data to determine whether TRT increases the risk of VTE: most case reports of VTE have occurred in men with pre-existing hypercoagulable state.

Vigen et al. JAMA. 2013;310:1829-36. Shores et al. J Clin Endocrinol Metab. 2012;97:2050-8. Luo et al. BMJ. 2019;364:l476. Sharma et al, Eur Heart J. 2015 Oct 21;36(40):2706-15; Cheetham et al, AMA Intern Med. 2017;177:491-499.

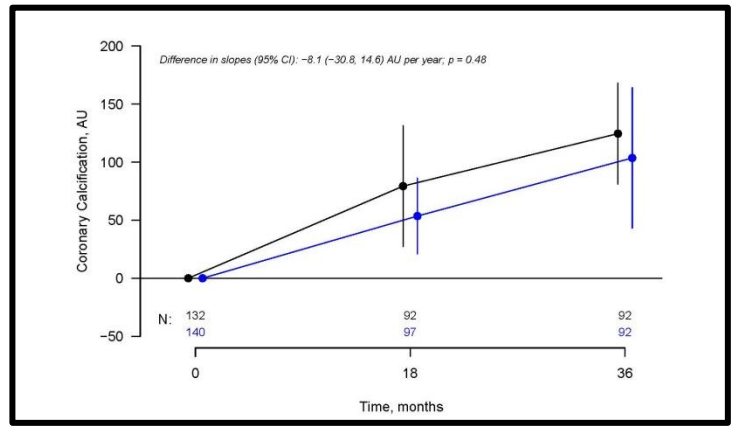
Effects of Testosterone on Atherosclerosis Progression and Coronary Plaque Volume in Older Men

The TEAAM Trial

CCA- Intima Media Thickness

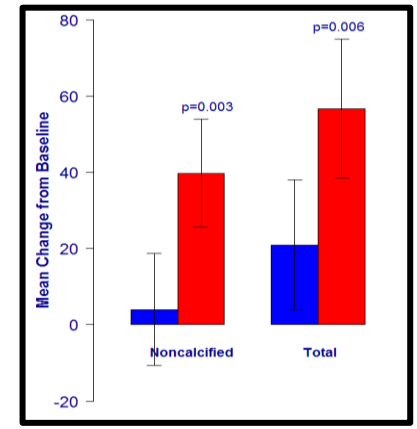


Coronary Artery Calcium, AUs



The TTrials

Plaque Volume



Basaria S, et al. JAMA. 2015;314:570-81.
Budoff MJ, et al. JAMA. 2017;317:708-716.

The TRAVERSE Cardiovascular Safety Trial

- The TRAVERSE trial is the largest RCT of testosterone replacement therapy in middle-aged and older hypogonadal men, 45 to 80 years, who are at increased risk of CV events.
- Sample size: 6,000
- Duration: up to 5 years
- Primary outcome: MACE
- Other outcomes: incidence of prostate cancer, invasive prostate procedures for BPH, clinical fractures, remission of dysthymia, progression from pre-diabetes to diabetes, and remission of anemia

Co-PIs: S Bhasin and M Lincoff; Study Chair: S Nissen

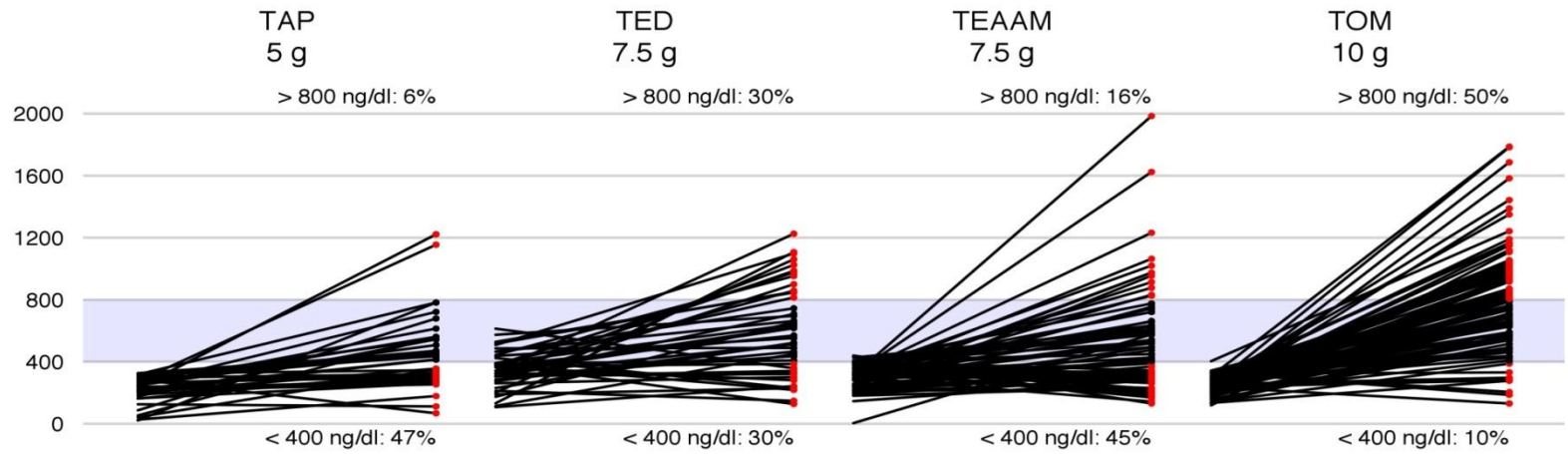
Funding: AbbVie and Pharma Consortium

Bhasin S, et al. Am Heart J. 2022;245:41-50.

Standardized Monitoring Plan is Necessary for Ensuring Safety, Efficacy and Adherence

- Endocrine Society: Monitor improvement in symptoms, adverse effects, testosterone levels, hematocrit, and PSA at 3 to 6 months, 12 months and annually thereafter.

50% of Men have Out-of-Range T Levels on Initial T Gel Dose

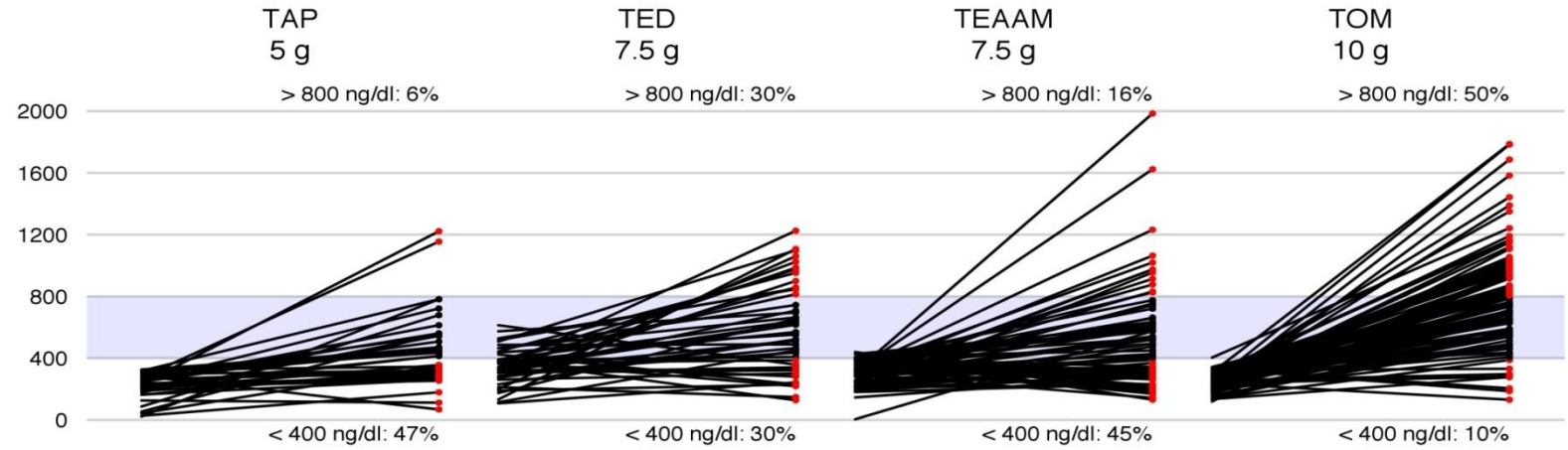


50% of Men Discontinue T Therapy within 3 Months

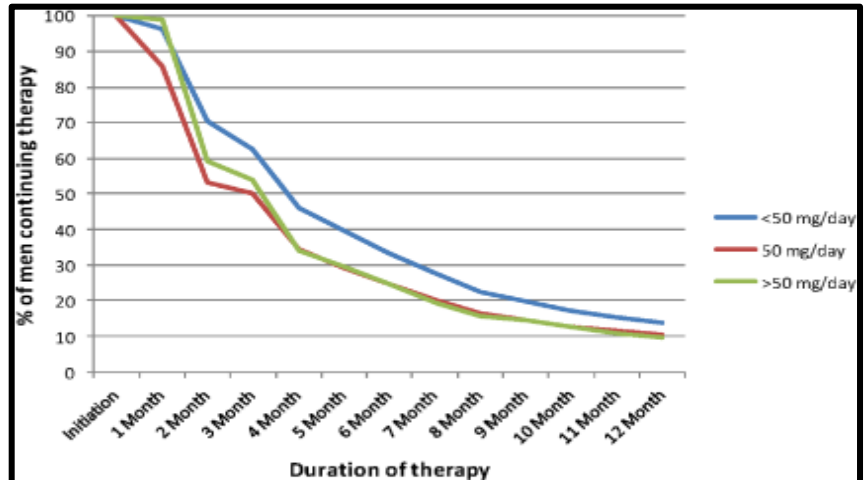
Bhasin S, et al. Andrology. 2018;6:151-157.

Enormous Variation in On-Treatment T Levels Contributing to Poor Adherence

50% of Men have Out-of-Range T Levels on Initial T Gel Dose



50% of Men Discontinue T Therapy within 3 Months



Shoenfeld et al,
J Sex Med 2013;10:1401

Synthesis and Conclusions

- Important to distinguish between classical hypogonadism and age-related decline.
  - In young men with classical hypogonadism, TRT improves symptoms with low AE frequency.
  - In older men with age-related decline, TRT improves sexual function, anemia, bone density and quality, muscle mass, strength and some measures of physical function, but long-term benefits and safety remain incompletely understood.

US Endocrine Society:
We recommend against routinely prescribing T therapy to all men 65 years or older with low T concentrations (1 | ⊕⊕OO).
In men >65 years who have symptoms or conditions suggestive of T deficiency and consistently low T concentrations, clinicians should offer TRT on an individualized basis. (2 | ⊕⊕OO).

Bhasin S, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:1715-1744.

A Shared Approach to Treatment Decision

1. Establish that the patient has testosterone deficiency – consider the high level of diagnostic imprecision.
2. Weigh the burden of symptoms/ conditions against the known benefits and uncertainty of long-term harm.
3. Ascertain conditions that might increase the risk of harm.
4. Establish a standardized monitoring plan.
5. Share the burden of decision making with the patient.

Shared Decision Making	
Clinical Context and Clinician's Values	**Patient's Goals and Values**
Benefits and risks of TRT	Burden of symptoms
Strength of evidence	Preferences
Risks of tests and monitoring	Risk tolerance, cost

Bhasin S. J Clin Invest 2021;131:e146607.

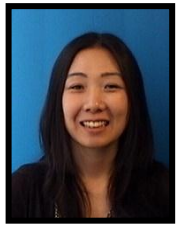
The Men's Health Team at BWH and Collaborators

Clinical Trials
- **Shehzad Basaria**
- **R Valderranbano**
- Grace Huang
- Anna Ross
- Matt Spitzer
- Rich Eder
- Eric Bachman




Biostatistician
- **Tom Travison**
- **Karol Pencina**


Mechanisms
- **Ravi Jasuja**
- **Wen Guo**
- Carlo Serra
- Rajan Singh

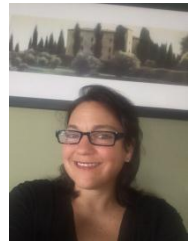


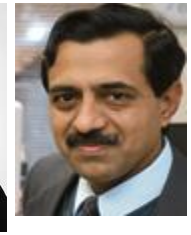

Exercise Physiology
- **Kieran Reid**
- **Tom Storer**
- Linda Woodhouse
- Erin Woodbury
- Jennifer McKinnon

Behavioral Studies
- Peter Gray
- Ray Tricker

Epidemiologic Studies
- Guneet Kaur
- Tom Travison
- Andrea Coviello
- Joanne Murabito

Hormone Assays
- Liming Peng
- Helene Stroh






Collaborators
- Richard Casaburi
- Harrison Pope
- Hubert Vesper
- Vasan Ramachandran
- Joanne Murabito
- Kevin Yarasheski
- Fred Sattler
- Stefan Arver
- Fred Wu
- Eric Orwoll




Grant Support: NIA, NINR, NICHD, PCORI, FNIH, Pepper Center P30; AbbVie, FPT

- Thank you!

T4DM: An RCT to Determine Testosterone's Effects on Progression to and Reversal of T2DM

Participants: 50–74 years at increased risk for T2DM or newly diagnosed T2DM

Intervention: Lifestyle intervention WW plus T vs. Lifestyle intervention X 2 years

Primary outcomes: Proportion of men with T2DM (2-h OGTT glucose ≥11·1 mmol/L) and mean change in 2-h OGTT glucose

Outcome variable	Placebo group (n=413)	Testosterone group (n=443)	Treatment effect (unadjusted)
2-h glucose on OGTT ≥11·1 mmol/L	87 (21%)	55 (12%)	0·59 (0·43 to 0·80; p=0·0007)
Mean change in 2-h glucose in OGTT (mmol/L)	–0·95 (2·78)	–1·70 (2·47)	–0·75 (–1·10 to –0·40; p<0·0001)

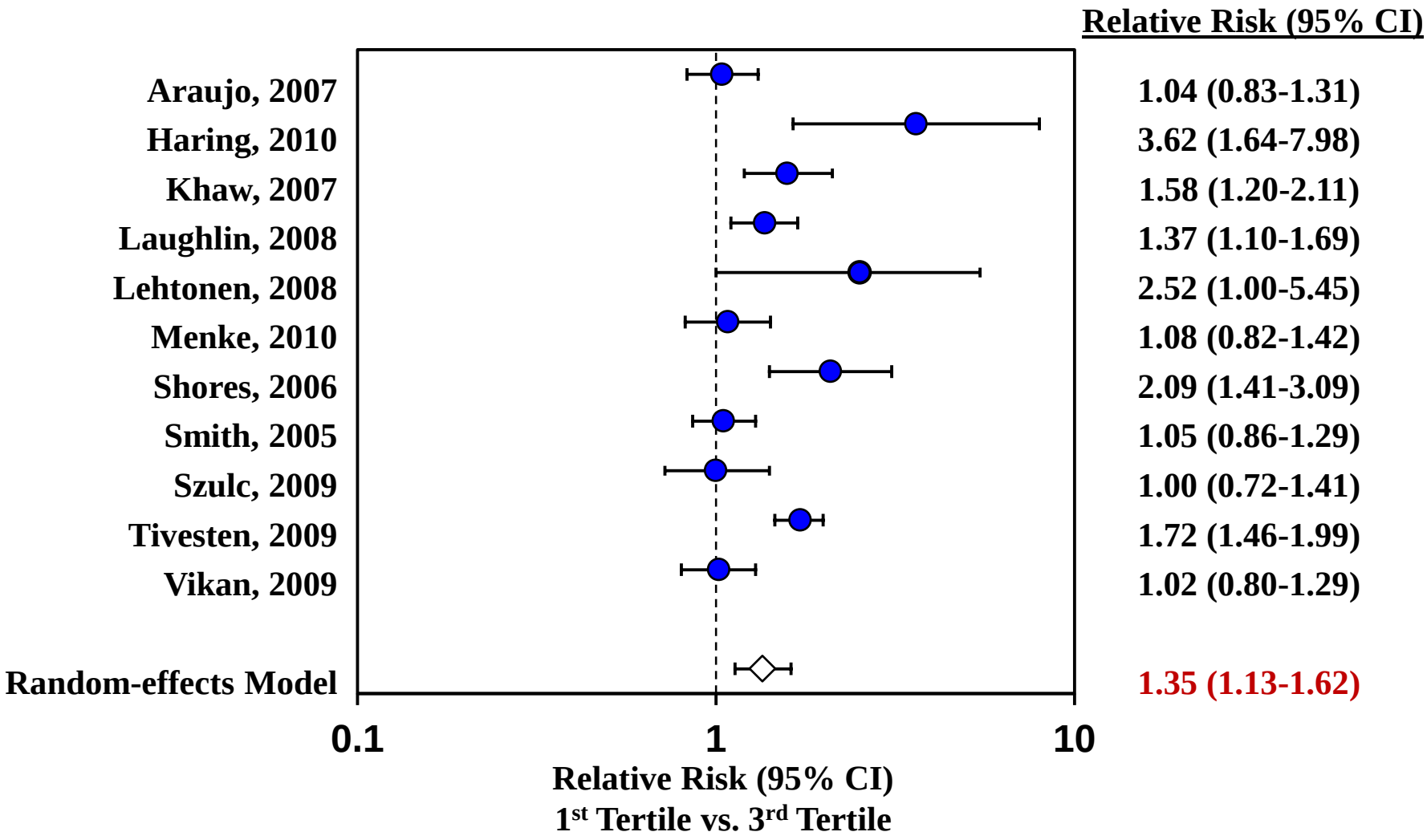
Wittert G, et al. Lancet Diabetes Endocrinol. 2021;9:32-45.

The Testosterone Trials (The TTrials)

- 7 Placebo-controlled, double blind, coordinated trials: Sexual Function, Physical Function, and Vitality
- Aim: To determine the efficacy of TRT in improving sexual function, physical function, and vitality in older men with unequivocally low testosterone levels and low libido, mobility limitation, and/or low vitality
- Eligibility: An average of 2 fasting, early AM TT <275 ng/dL by LC-MS/MS plus sexual symptoms
- Intervention duration: 1 year
- Intervention: Placebo or T gel, target T 400-700 ng/dL

Snyder PJ, Bhasin S, Cunningham GR, et al, N Engl J Med. 2016;374:611-24

Lower Testosterone Levels Associated with Higher All-Cause Mortality And Telomerase Length



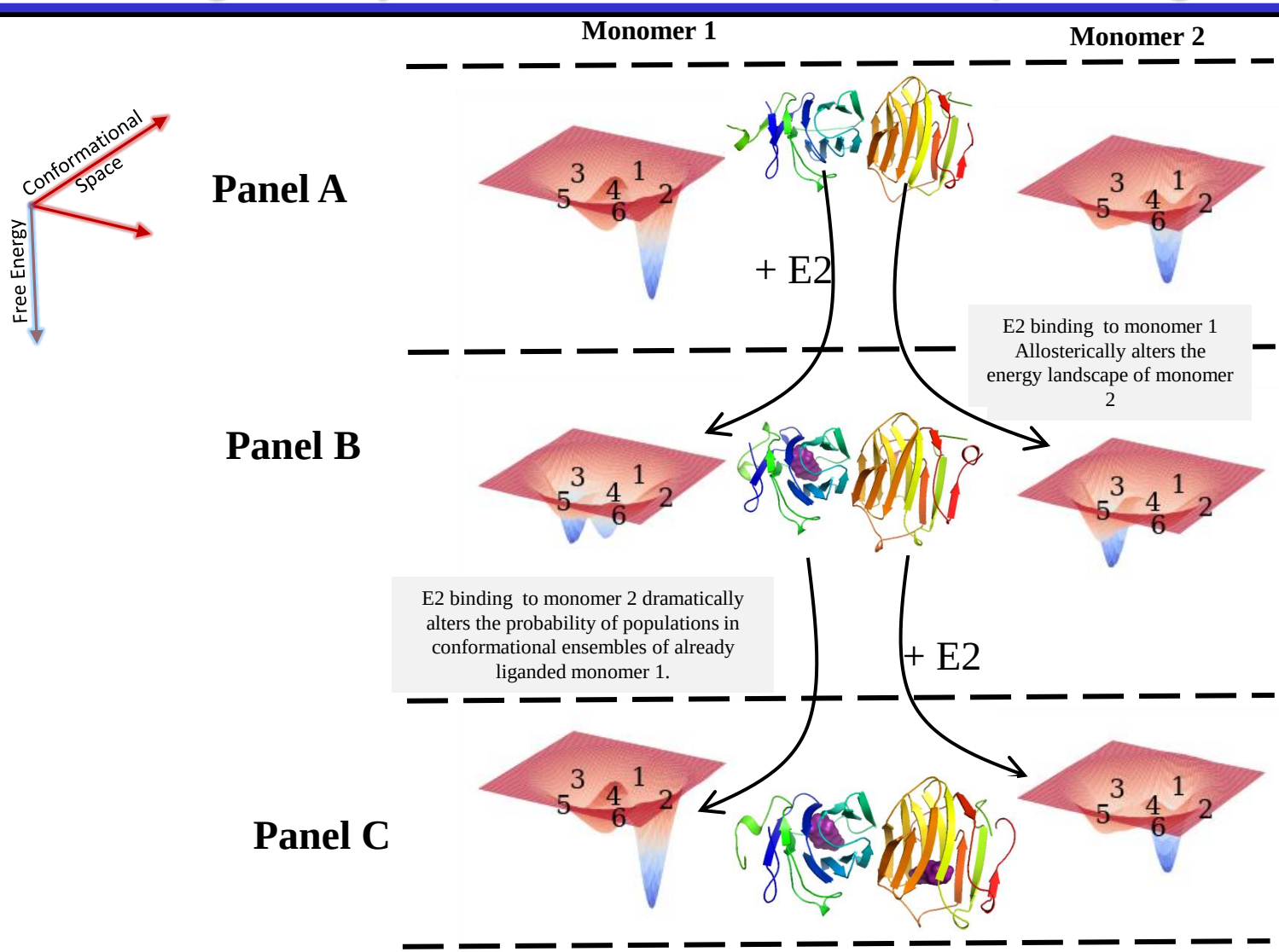
Araujo AB, et al. J Clin Endocrinol Metab. 2011;96:3007-19.

Fertility Induction in KS

- Majority of germ cells in pre-pubertal boys with KS have a 47, XXY karyotype and suffer a meiotic block and undergo apoptosis shortly after puberty. Only spermatogonia with a normal 46, XY complete spermatogenesis and form haploid sperm in rare islands of spermatogenesis.
- TESE plus ICSI:
  - Successful sperm retrieval in 40% of men with KS;
  - ~40% of those with successful sperm retrieval achieved a live childbirth.
  - Thus, ~16% of men with KS can achieve a live childbirth with TESE plus ICSI.
- Sperm retrieval rates in early adolescent are not as high as in the older adolescent which are equivalent to those in the adult (~50%).

Bhasin S, Oates RD. Fertility Considerations in Adolescent Klinefelter Syndrome. J Clin Endocrinol Metab. 2020;105:e1918–20.

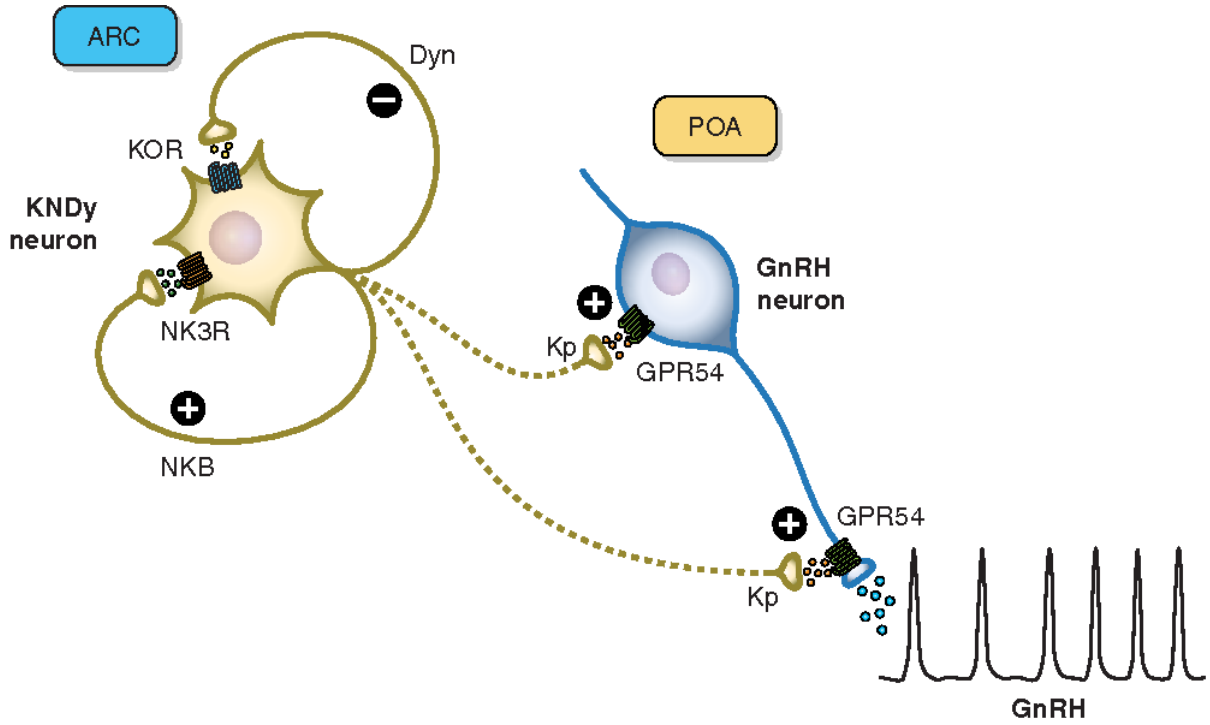
Inter-Monomeric Allostery and Conformational Heterogeneity of Two Monomers upon Ligand Binding



https://tru-t.org

Jasuja R, Spencer D, Jayaraj A, Lawney B, Patel P, Jayaram B, Thayer KM, Beveridge DL, Bhasin S. iScience. 2021;24(6):102414.

Important Role of the KNDy Neurons in the Control of Pulsatile GnRH Secretion



- KNDy neurons are major driving signal for GnRH pulsatile release.
- Kisspeptin signals via the kisspeptin receptor (GPR54) to activate GnRH neuronal activity.
- NKB signals via NK3R to drive GnRH pulse initiation, possibly autoactivating KNDy neurons.
- DYNorphin signals via the kappa opioid receptor (KOR), which mediates GnRH pulse termination.

Bhasin S, Jasuja R, Jayasena C. In: DeGroot's Textbook of Endocrinology. 12th ed. 2022

Inter-Laboratory and Inter-Assay Variability in Testosterone RIAs

Instrument/Assay	Laboratories (n)	Mean	SD	CV	Median	Range	
						Low	High
Abbot Architect	11	243.5	13.8	5.7	243	219	262
Bayer ACS:180	83	317.6	39	12.3	314	227	410
Bayer Centaur	231	324.0	41.5	12.8	319	234	454
Bayer Immuno-1	43	300.6	16.7	5.6	300	254	335
Beckman Access/2	98	297.8	15.3	5.1	298	239	330
Diagnostic Systems	10	352.7	80.1	22.7	375	177	440
DPC Coat-a-Count	76	277.8	34.2	12.3	281	196	363
DPC Immulite	86	232.0	32.9	14.2	228	160	330
DPC Immulite 2000	83	210.8	33.5	15.9	215	130	299
Roche Elecsys/E170	87	349.9	23.0	6.6	348	299	408
Ortho Vitros ECi	54	282.3	15.8	5.6	280	254	324
All Instruments	891	293.6	56.2	19.1	297	**130**	**508**

Wang C et al. *J Clin Endocrinol Metab.* 2004;89:534-543.

Excess Morbidity and Mortality in Klinefelter Syndrome

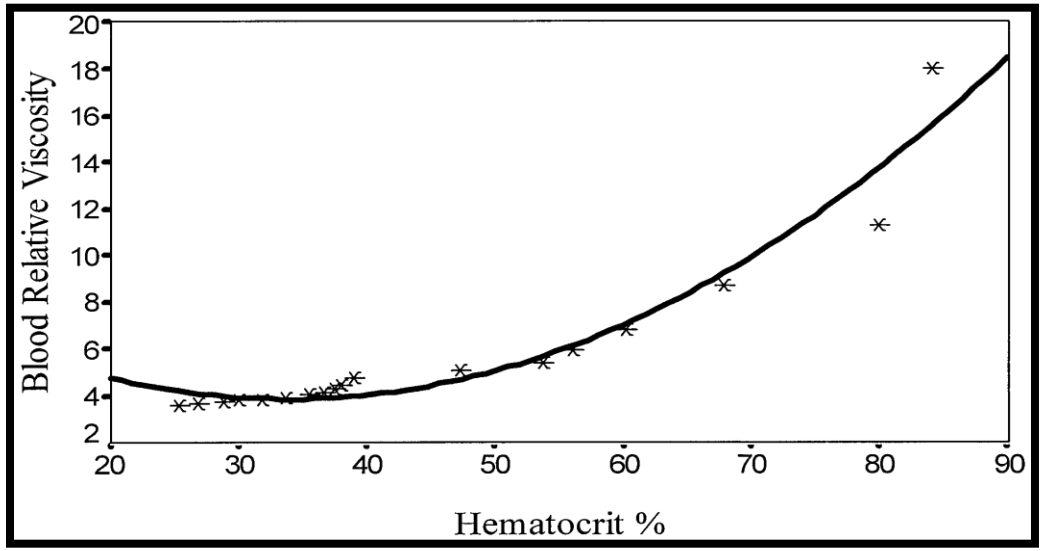
- KS patients are at increased risk for:
  - Overall mortality
  - Breast cancer
  - Certain types of non-Hodgkin's lymphomas
  - Autoimmune diseases, esp SLE and Sjogren Syndrome
- Lower risk for prostate cancer

Men with KS should undergo periodic screening for breast cancer.

Swerdlow et al. J Natl Cancer Inst. 2005;97(16):1204-10.

Hematocrit Relationship with Plasma Viscosity and O_2 Delivery

Increase in viscosity with increasing hematocrit



Hematocrit relationship with O_2 carrying capacity and transport

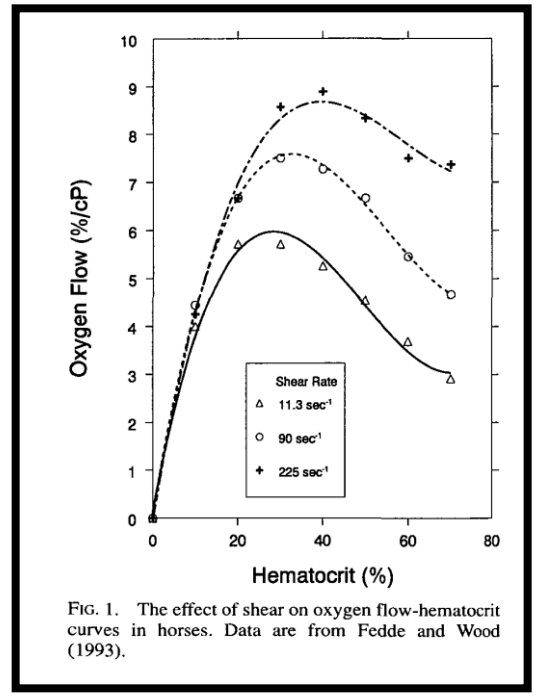


FIG. 1. The effect of shear on oxygen flow-hematocrit curves in horses. Data are from Fedde and Wood (1993).

Cinar Y, Demir G, Pac M, Cinar AB. Am J Hypertension 1999;**12**(7):739-43.

AAS Withdrawal Hypogonadism as an Increasingly Prevalent Cause of Hypogonadism

- After prolonged use of large doses of AAS, the recovery of HPT axis may be incomplete or may not occur at all leading to AAS Withdrawal Hypogonadism
- In a retrospective review of 6,033 patients in a Men's Health clinic, 43% of those with profound hypogonadism (total T <50 ng/dL) reported prior AAS exposure.
- High rates of dependence and relapse

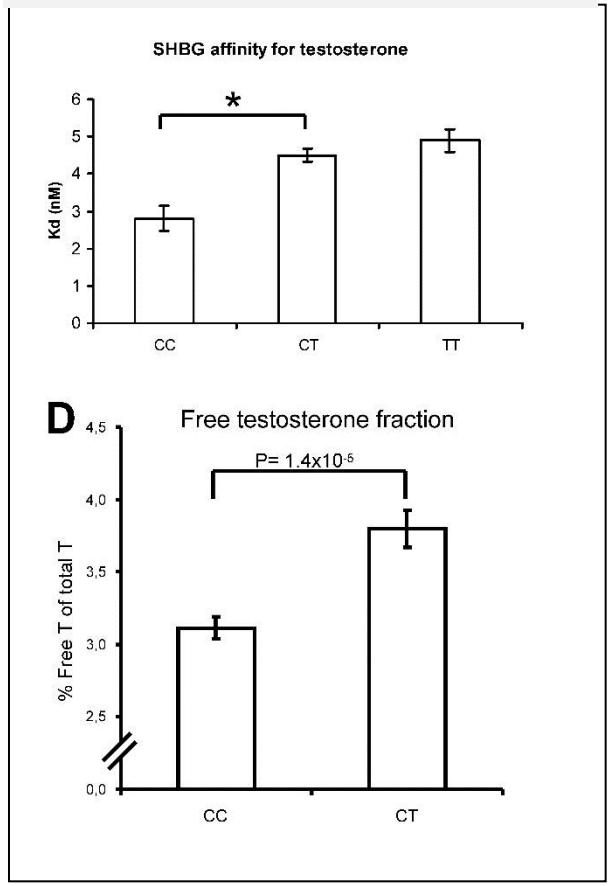
Because AAS use has elements of body image disorder and addiction, evaluation and treatment should address the body image disorder as well as addiction behavior.

Coward RM, et al. J Urol 2013;190:2200-5;
Rahnema C, et al, Fertil Steril 2014;101:1271

Heritability and Genetic Determinants of Testosterone Levels in Men

- Strong heritability: genetic factors account for 65% of variation in serum T levels
- Over 75 genetic variants, including some on SHBG locus and X chromosome are associated with variation in serum T levels and increased risk of low testosterone.
- rs6258 polymorphism affects SHBG binding affinity for T and the measured free T fraction.

Rs6258 affects SHBG binding to T



Ohlsson et al, PLoS Genet. 2011;7:e1002313