To T or not T?
5-3-19
Alaska ACP

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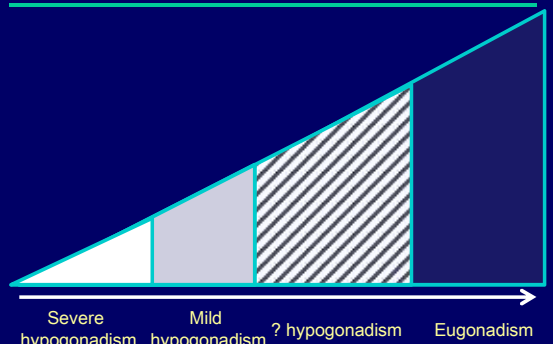
Disclosures

Author of chapters in UpToDate

Testosterone continuum



Epidemiology of ♂ hypogonadism

How common is hypogonadism in men > 60 yrs?

A. 0.5%
B. 1.0%
C. 2%
D. 10%
E. 20%

BDA

Epidemiology of ♂ hypogonadism

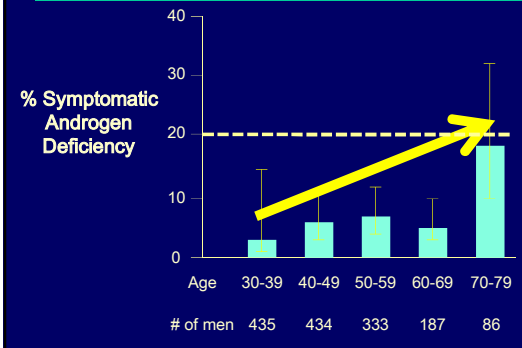
Based on "low" serum T levels alone

- < 5% in 20s & 30s
- 12% in 50s
- 19% in 60s
- 28% in 70s
- 49% in 80s

Harman SM, et al. JCEM. 2001;86:724-731.

BDA

Prevalence of Symptomatic ♂ Hypogonadism



Araujo AB, et al. JCEM 2007;92:4241-4247

BDA

Prevalence of Symptomatic ♂ Hypogonadism

Large population study in UK (2010)

Hypogonadism = threshold [T] when symptoms (sexual dysfunction) become increasingly common

Prevalence of hypogonadism is ~ 2% in middle-aged and older men

- ↑ prevalence with ↑ age, obesity & illnesses

Wu FW, et al. N Engl J Med 2010;363:123-135.

BDA

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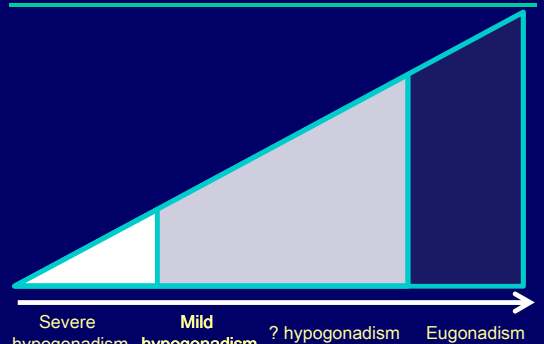

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Symptoms of ♂ hypogonadism

Which symptom is most suggestive of male hypogonadism?

A. Low libido
B. Erectile dysfunction
C. Low energy
D. Fatigue
E. Depression

BDA

Symptoms of hypogonadism

Study of ~ 3400 European men
Questionnaires and AM blood samples
Predictive value of sexual, physical & psychological symptoms

- ↓ libido, ↓ fantasies, or ↓ AM erections had the highest probability of being associated with low [T]
- Triad of ↓ libido, ↓ fantasies, ↓ AM erections
  Odds ratio > 2 for low [T] compared to normal sexual fx
- Limited vigor had modest predictive value
- Sadness, fatigue & ↓ energy low or no predictive value

Wu, et al. N Engl J Med. 2010;363:123
BDA

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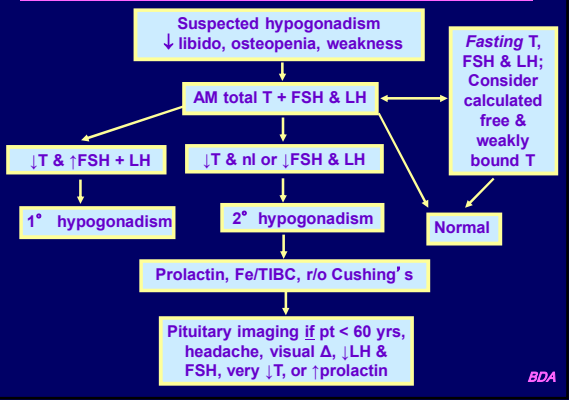
Evaluation of ♂ hypogonadism

Which is the best initial blood test for the evaluation of male hypogonadism?

A. Random total testosterone
B. Non-fasting early AM total testosterone
C. Fasting early AM total testosterone
D. Non-fasting early morning free testosterone by analog (platform) assay

BDA

Hypogonadism algorithm



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When should we measure [T]?

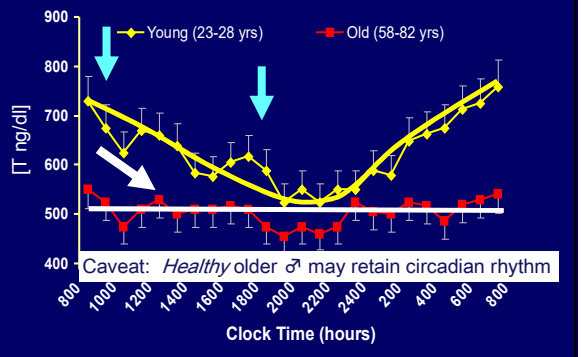
- Initial test may be any time of day (early AM preferable)
- Avoid testing during acute illness

- Confirm a low value on another day
  - Large day to day variation for [T]:
    - ~ 10% day-to-day CV within individuals
- Confirm a low value with an early AM blood sample
  ~ 20-25% Δ between early AM & late afternoon [T]
  J Clin Endocrinol Metab. 2009;94:907

- Confirm a low value with a *fasting* sample
  - Fasting [T] higher than non-fasting
  - Fasting [T] lower variation

BDA

Older men lose circadian T rhythm



Bremner WJ et al. *JCEM*.1983;56:1278.

Effects of fasting on [T]

The Healthy Man Study

325 Australian men reporting "very good" or "excellent" health

9 blood samples during 5 visits over 3 months

Results:

Fasting [T] significantly > non-fasting (10-15%; ~ 40-50 ng/dl)

[T] variation within individuals was high *but less with fasting*.

- Non-fasting CV = ~ 10% between and within day
- Fasting CV = ~ 5% between and within days

BDA

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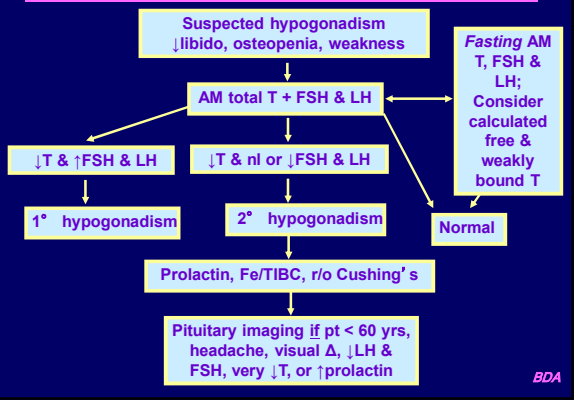

BDA

Free Testosterone Hypothesis

- Free T is the hormonally active form
- T bound to SHBG is inactive
- T bound to albumin is bioactive ("weakly bound")
  - Tissue-mediated dissociation of T from albumin

BDA

Free Testosterone Hypothesis: Assumptions

- All tissues equally responsive to T-albumin
  - Tissue-specific dissociation (liver, brain)
  - Dependent on capillary flow
- SHBG-bound T is inactive
  - megalin (endocytotic receptor) takes up SHBG-T complex
- SHBG is a passive player
  - Highly specific SHBG receptors in some tissues (prostate)
  - Linked to cAMP intracellular signaling

Pardridge WM. JCEM 1986;15,259-78
Caldwell JD, et al. Horm Metab Res. 2006;38:206-218.
Adams JS. Cell. 2005;122:647-649.

BDA

SHBG deficiency case

SHBG deficiency due to a missense mutation in a ♂

- Undetectable SHBG
- Low total T and E_2, but normal LH and dialyzable free T
- Normal gonadal development & spermatogenesis
- However, subtle phenotype of muscle weakness, ↓ AM erections, ↓ libido, ↓ shaving compared to peers

J Clin Endocrinol Metab. 2014;E1798-1982

BDA

EMAS data

♂ with low free T, but normal total T *vs.* normal free T

- More likely to report sexual and physical symptoms
- Had lower serum hemoglobin
- Had lower bone mineral density

J Clin Endocrinol Metab. 2016;101:2640-2 and 2647-57
Endo Rev. 2017;38-304-322.

BDA

Free Testosterone and Dx of Hypogonadism: Summary and Conclusions

1. The free testosterone hypothesis is controversial, but it remains the best that we have.
2. A clearly normal serum total T (> 350 ng/dl) remains useful in excluding hypogonadism.
3. Calculated free T measurement remains useful in ♂ with factors known to alter [SHBG].
4. Measurement of free [T] by equilibrium dialysis may be useful when cFT is discordant with clinical presentation.

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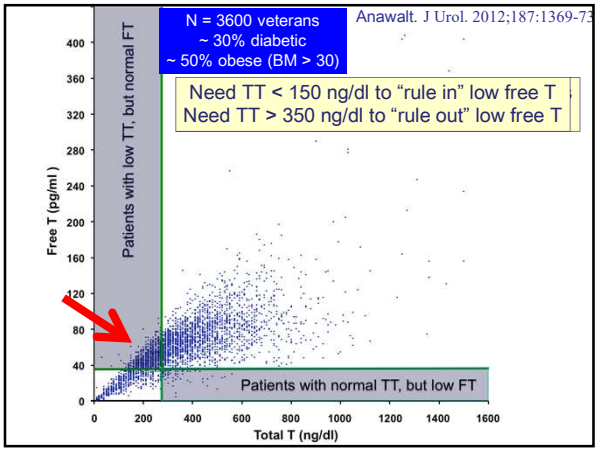
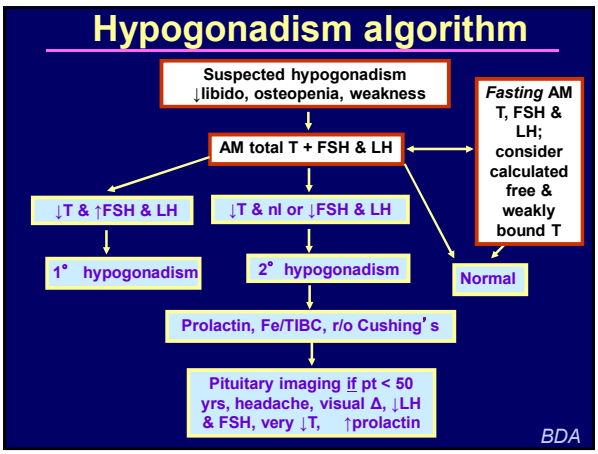
Common causes of altered SHBG

Low SHBG	High SHBG
• Obesity	• Aging
• Diabetes mellitus	• Medications – (anti-epileptics)
• Metabolic syndrome	• Cirrhosis, hepatitis
• Corticosteroids	• Estrogens
• Anabolic steroids	• Hyperthyroidism
• Hypothyroidism	

BDA



Hypogonadism algorithm



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Common causes of hypogonadism

- Primary hypogonadism
  - Klinefelter's syndrome (1:500)
- Secondary hypogonadism
  - Kallmann's syndrome
  - Pituitary disease
    - Macroadenomas
    - Hemochromatosis
    - Excessive corticosteroids & opioids
    - Hyperprolactinemia
  - Systemic disease (severe)
    - Sleep apnea

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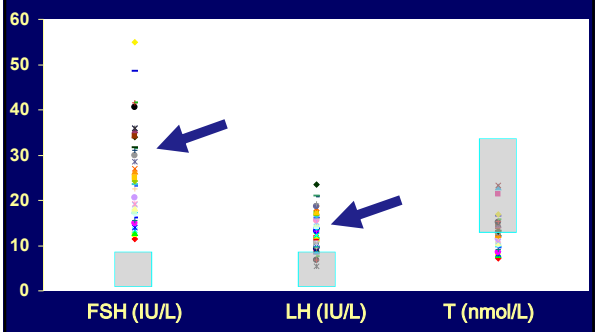
↑ ↑ FSH & LH in Klinefelter's



Recent Prog Horm Res. 1968;29:321-363

AMM/BDA

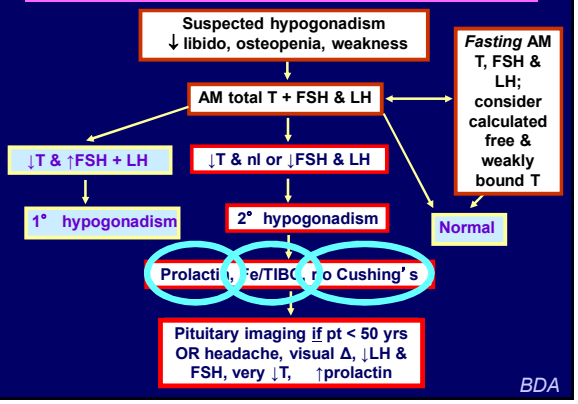
Evaluation of secondary ♂ hypogonadism

Which is the following is the most <u>important</u> test to order in a 65-year old man with a normal physical examination and secondary hypogonadism (by laboratory)? (He has no headaches or visual complaints.)

A. Iron saturation and ferritin
B. 24-hour urinary free cortisol
C. Serum prolactin
D. Sella CT
E. Sella MRI

BDA

Hypogonadism algorithm



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BDA

Evaluation before T Rx initiation

- 24% of clinicians (members of international endocrinology and andrology societies) would initiate T rx based on a single low [T].
- 12% of these clinicians would initiate T rx without measuring serum gonadotropins.

Clin Endocrinol 2015;82:234-241

Summary of diagnosis of ♂ hypogonadism

- Screen with total T assay
  - Assay with validated normal range of ~ 300-1000 ng/dl
- Confirm with repeat *fasting* morning total T
  - Measure calculated free T
    - Age > 65, BMI > 30, DM, hepatitis
    - Medications: anti-epileptics, corticosteroids
- Measure gonadotropins (FSH > LH in 1° hypogonadism)
  - FSH & LH tend to be slightly ↑ in older men
- In ♂ > 60, sella imaging only if very ↓ T, ↓ LH & FSH, ↑ prolactin, or clinical suspicion

BDA

"n of 1" trial?

In some patients with symptoms of hypogonadism and borderline [T] values, "n of 1" trial is indicated

Tips for "n of 1" trial

1. Be clear with patient about the goals
2. Have some clearly defined endpoint(s)
   - Length of time of "n of 1" trial dictated by endpoints
     6-12 months for bone effects *vs.*
     2-6 months for sexual effects
2. Use IM testosterone cypionate or enanthate
   - Assures adequate levels of T
   - Helps sort out "true" responders

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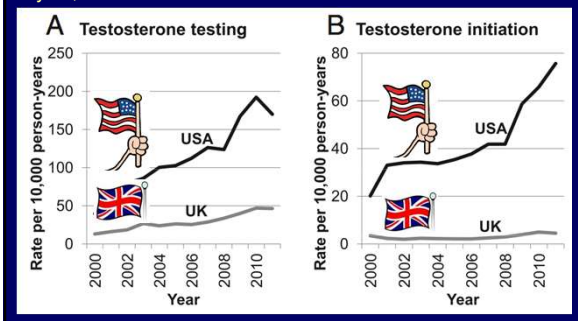
The US "n of 1,000,000" trial

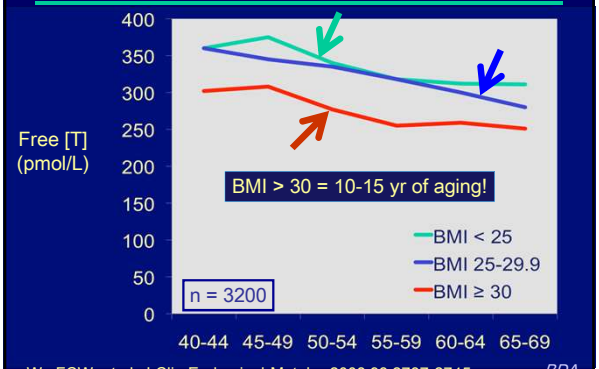
T prescriptions ↑ in US

Layton, et al.



J Clin Endocrinol Metab. 2014;99:835-842

Obesity & aging synergistically ↑[T]



Wu FCW, et al. J Clin Endocrinol Metab. 2008;93:2737-2745 *BDA*

Obesity, weight loss and T

Several case series of effects of bariatric surgery on serum T

Nascent story:
Significant weight loss (>10%) appears to ↑ [T]

2 RCT of diet and exercise:

Weight loss of < 10% in overweight -obese men weighing ~ 100 kg resulted in minimal change in serum [T]

J Diabetes Obesity. 2014;1:1-7
J Sex Med 2013;10:1823-1832

Safety monitoring of T during Rx: Older ♂

1. Hematocrit after initiation or increase in dosage
   a. Annual check
2. Offer prostate cancer screening
   a. If previous PSA done, then re✓
   b. If previous PSA not done, offer prostate cancer screening. Advise that benefit controversial, risk of false ⊕ test results and need for biopsy is significant.
   c. PSA generally increases ≤ 0.5 ng/ml. Increase significantly greater than 1.0 ng/ml (e.g., > 1.4)

Unnecessary

Monitoring of lipids, liver function tests, BMD

Screening for sleep apnea

Safety monitoring of T during Rx: Younger ♂

1. Hematocrit after initiation or increase in dosage
   a. Annual check
   *Low likelihood of erythrocytosis due T Rx in ♂ ≤ 50 yrs

Unnecessary

Screening for prostate cancer

Monitoring of lipids, liver function tests, BMD

Screening for sleep apnea

Selection of T Rx

Key elements

1. Patient preference
   a. Cost (US: IM TU >> gel and SC > IM T cypionate)
   b. Convenience (Depends on patient)
2. Safety (Relative)
   a. Severe bladder outlet obstruction symptoms: gel
   b. Higher risk of erythrocytosis: gel
   c. Higher risk of transference to children: IM
3. Adherence
   a. Some patients might do better with IM (e.g., teens)
4. Availability
   a. Oral testosterone undecanoate available outside the US

T Treatment & CV Disease

March 3, 2015
FDA requires manufacturers to include warning about possible increased risk of MI and stroke and advises practitioners to make patients aware of these potential risks when deciding whether to initiate **or continue** T.

Finkle: T Rx ↑ nonfatal MI

Finkle, et al.

- Cohort study (1223 ♂) starting T after coronary angiography (mean initial 1.5 yrs later)
- Controls: Phosphodiesterase inhibitor users
  - Followed for 90-180 days after initial prescription of T
- ♂ prescribed oral phosphodiesterase inhibitor
- Outcome: ICD-9 diagnosis of acute MI
- Results: ↑ risk of non-fatal MI by 3-4 per 10,000 pt-years compared to PDE inhibitor users

PLOS. 2014;9:85805

T ↓ MI in older, high risk ♂

Baillargeon, et al

- 6355 ♂ Medicare beneficiaries with T Rx
  - Developed a prognostic index for MI
- 19,065 prescription T non-users
- Mean follow-up = 4 years
- Outcome: ICD-9 diagnosis of acute MI
- Results:
  No increased risk of MI with T Rx (HR = 0.84)
  ↓ risk of MI in the men with the highest risk

Ann Pharmacother. 2014;48:1138-114

T Rx & CV risk: Summary and Conclusions

1. No clear pattern between T Rx & CV risk
2. Based on epidemiologic studies, T Rx confers no or little risk on CV events.
3. Testosterone trial: more CV events in placebo group *vs.* testosterone gel in older men in f/u year
1. Uncertainty about CV risk should be factored into decision-making about T Rx when the diagnosis of hypogonadism or benefit of T Rx is uncertain
2. For truly hypogonadal ♂, T Rx is safe

Conclusions

- Hypogonadism is common, but low [T] is more common
- Sexual symptoms are most predictive of hypogonadism
- Dx of hypogonadism requires confirmation of low [T]
  - Check in AM
  - Check during fasting state
- Check calculated free [T] in ♂ with obesity, DM
- Determining who will benefit …is an art not a science
  - "n of 1" trial
  - Controversy about T and CV risk may be useful

BDA

T Treatment & Venous Thrombotic Disease

June 19, 2014
U.S. Food and Drug Administration (FDA) is requiring manufacturers to include a general warning in the drug labeling of all approved testosterone products about the risk of blood clots in the veins.

T Rx and thromboembolism

Glueck, et al.

- 2011 report of 6 ♂ with thromboses after T Rx
- All 6 with thrombophilia
- 2014 report of 13 ♂ & 1 ♀ with thromboses short time after T Rx initiated (mean = 11 mos)
  (deep venous or osteonecrosis of hips or knees)
  12 of 13 had a clotting disorder
  'Thrombophilia should be excluded before administration of exogenous testosterone."
- More accurate: Consider evaluation for clotting disorder if unexplained thrombosis while on T Rx

Clin Appl Thromb Hemost. 2014;20:244-9. (+ 4 more case reports since)

T Rx and thromboembolism

Li, et al. J Urol. 2016;195: 1065-1072

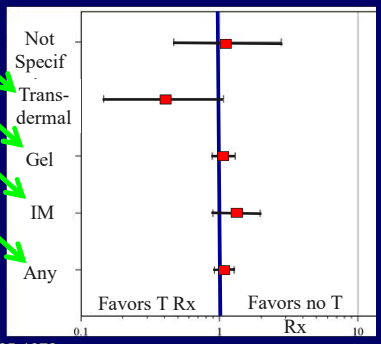
Large insurance database (> 1 million ♂ with diagnosis of hypogonadism; treated *vs.* not)

- Nested case-control
- Retrospective cohort study with propensity and sensitivity analyses
- Outcome "Idiopathic venothromboembolism"
- Results: No Δ in risk of DVT with T therapy

Database study: TRx does not increase idiopathic DVT or PE

> 100,000 T users *vs.* equal # of untreated ♂ with dx of hypogonadism Cohort analysis

Confirms smaller study of Ballairgeon, et al. Mayo Clin Proc.2015;90:1038-45



J Urol. 2016;195: 1065-1072

T & DVT: Summary

1. Little evidence that T ↑ thrombophilia in ♂
   Thromb Res. 2018 ;172:94-10
2. T Rx might provoke venous thrombosis in ♂ with an underlying thrombophilic disorder

T Rx and venous thrombotic disease: Conclusions

1. Based on large epidemiologic studies, T Rx does not increase the risk of idiopathic venous thrombotic disease
2. It is unknown whether DVT increases the risk of DVT in with known thrombophilia
3. It is likely safe to treat hypogonadal ♂ with a history of a DVT, but patients with known thrombophilia (e.g., recurrent DVT/PE) should be cautioned about the uncertainty.

T treatment & Prostate disease

T Rx and prostate disease

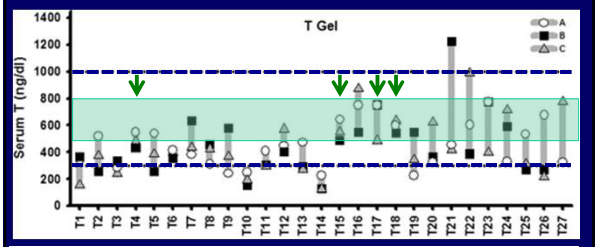
Summary:

1. Prostate cancer (past or present) has been considered a contraindication to T Rx.
2. Advanced prostate cancer is treated with androgen deprivation therapy (ADT)

   Gleason 6/7 prostate cancer, confined to the prostate, is treated with prostatectomy or XRT, but not ADT.
3. It is controversial, but reasonable to treat hypogonadal ♂, to use T Rx in ♂ with a history of localized CaP with low PSA after prostatectomy or XRT.

   Level of evidence for any approach to such men = opinion!*

Large variation in serum [T] during T gel therapy



1. Despite 3 dosage adjustments over previous 3 months, only 30% had C_{avg} concentrations 500-800 during 24-hr sampling
2. Poor correlation between ambulatory and inpatient (CRU) concentrations
3. >80% achieved normal total T concentrations (300-1000)

JCEM. 2015;100:3280-3287