

# Recognizing and Managing Testosterone Deficiency

**J. Bruce Redmon, M.D.**

**Professor**

**Division of Endocrinology**

**Departments of Medicine and**

**Urologic Surgery**

# Disclosure Information

I have no financial relationships to disclose. I will discuss off label use and/or investigational use in my presentation.

# Outline

- ◆ Evaluate men for testosterone deficiency
- ◆ Summarize current data on risks/benefits of testosterone treatment
- ◆ Identify options for management of testosterone deficiency in various clinical situations

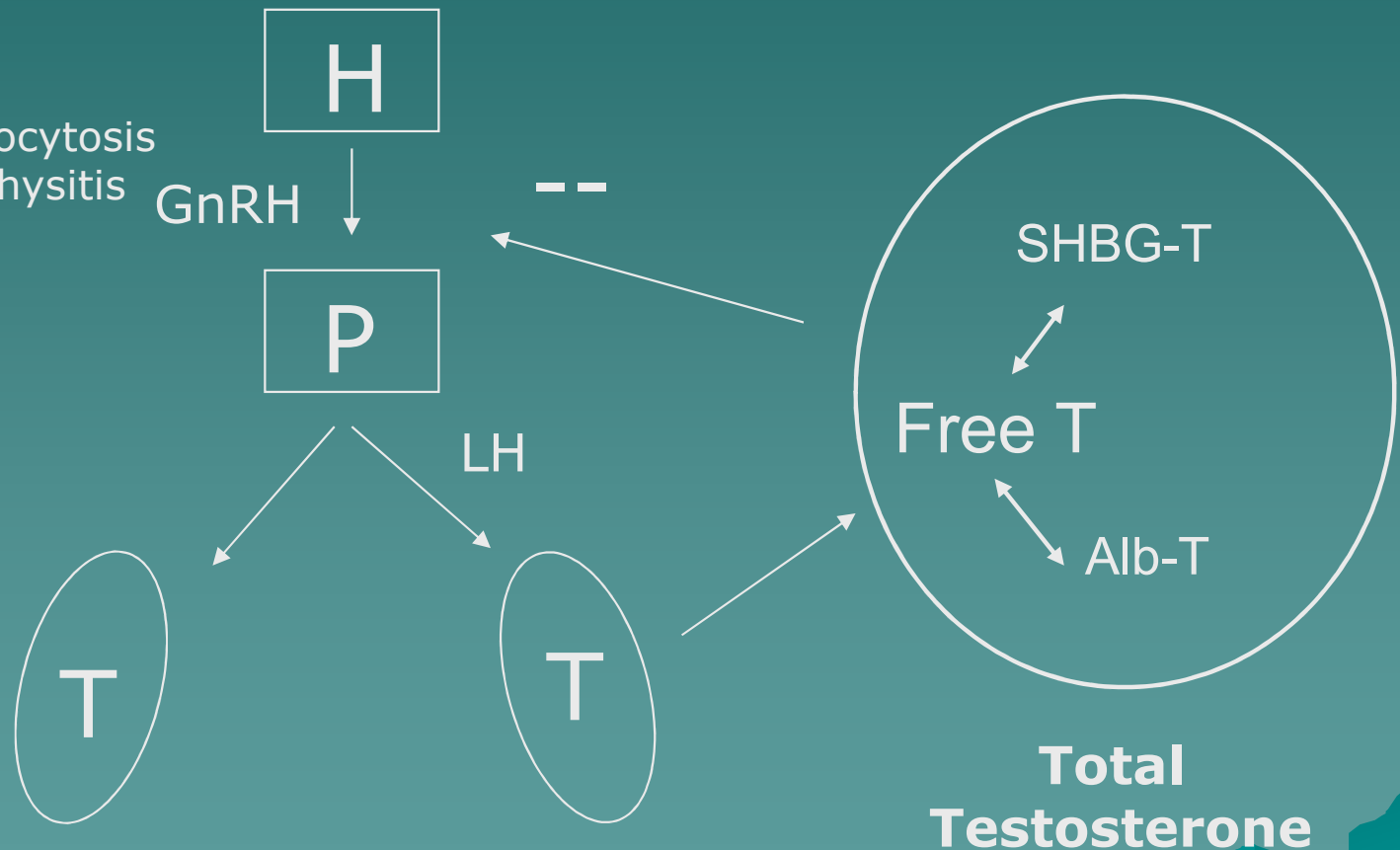
# Testosterone Deficiency

## Secondary

Hyperprolactinemia-tumor, drugs  
 Sellar/suprasellar tumor  
 Infarction  
 Medication-opiates, MJ  
 Infiltrative-sarcoidosis, histiocytosis  
 hemochromatosis, hypophysitis  
 Chronic illness, malnutrition  
 Congenital-Kallmans  
 Iatrogenic – Surgery, XRT  
 Idiopathic

## Primary

Congenital – Klinefelter  
 Trauma  
 Infection  
 Iatrogenic-XRT, chemo  
 Idiopathic  
 Autoimmune - ?



SHBG  
 ↑ - aging, hyperthyroidism, hepatitis, estrogens,  
 anticonvulsants  
 ↓ - obesity, hypothyroidism, nephrotic syndrome  
 androgens

# Testosterone and Aging



# Testosterone and Aging



# “Normal” Testosterone

- ◆ Framingham Heart Study
  - Young healthy men
  - Mean/Median  $\approx 700$  ng/dL (FT  $\approx 14$  ng/dL)
  - 2.5<sup>th</sup>  $\approx 350$  (FT  $\approx 7$ )
  - 1<sup>st</sup>  $\approx 280$  (FT  $\approx 5-6$ )
- ◆ Univ Washington – very healthy older men
  - Mean  $\approx 420$  ng/dL; 20%  $< 300$  ng/dL
- ◆ EMAS – Late onset hypogonadism
  - 3 sexual symptoms-libido, AM erections, ED
  - T  $< 320$  ng/dL and FT  $< 6.4$  ng/dL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men

Joel S. Finkelstein, M.D., Hang Lee, Ph.D., Sherri-Ann M. Burnett-Bowie, M.D., M.P.H., J. Carl Pallais, M.D., M.P.H., Elaine W. Yu, M.D., Lawrence F. Borges, M.D., Brent F. Jones, M.D., Christopher V. Barry, M.P.H., Kendra E. Wulczyn, B.A., Bijoy J. Thomas, M.D., and Benjamin Z. Leder, M.D.

NEJM 9/12/13



# T Levels and Effects

- ◆ Baseline T  $\approx$  500 – 550 ng/dL
- ◆ Incr body fat < 350
- ◆ Decr lean mass < 200
- ◆ Decr leg strength < 45 (female levels)
- ◆ Decr sexual desire < 200
- ◆ Decr erectile function < 200

# Clinical Trials



# Randomized Trials of Testosterone Therapy in Older Men

Study	Snyder (1999)	Sih (1997)	Amory (2004)	Nair (2006)	T Trials (2016)
N	108	32	48	58	790
Age (yrs)	73	66	71	66	72
Duration	3 yr	1 yr	3 yr	2 yr	1 yr
T (ng/dL) Pre/Post	367/625	294/370	295/744	358/483	230/450 (FT 6/11)
Outcomes	LBM/FM Strength Physical perf Subjective physical fxn Sex fx, E BMD	Body fat Grip strength Memory	LBM/FM Grip strength Physical perf BMD Cognitive fxn Anxiety/depression	LBM/FM Strength Physical perf QOL BMD Glu tol/IS	Sexual fxn Physical fxn Vitality

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

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## Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators\*

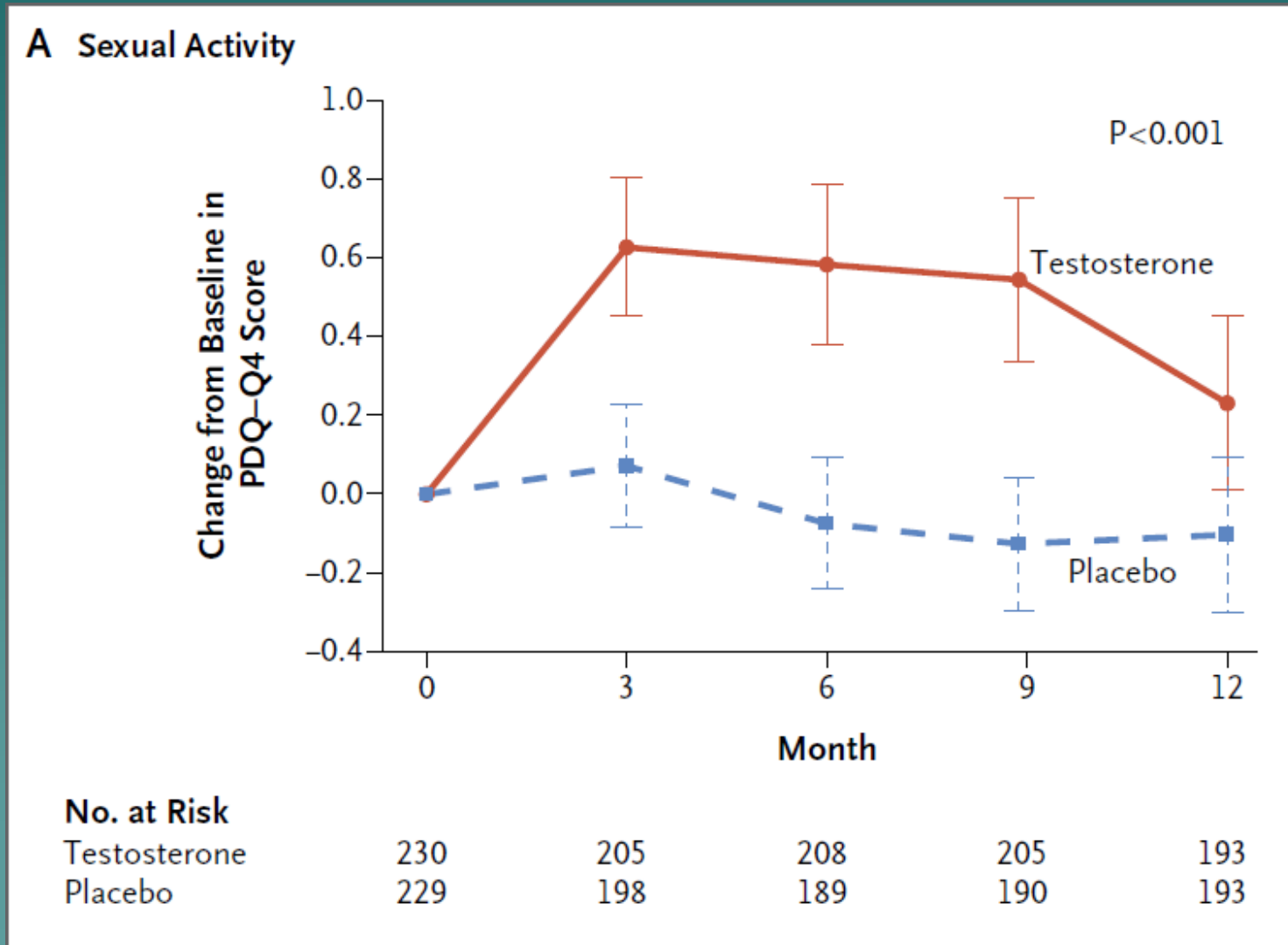
# The Testosterone Trials

- ◆ Response to 2003 IOM recommendation for short term clinical trials in older men with low T and clinical conditions possibly related to low T.
- ◆ Coordinated set of 7 DB/PC trials.
  - Three main trials – Sexual Function, Physical Function, Vitality
  - Four additional – Cognitive Function, Anemia, Bone, Cardiovascular
- ◆ Men  $\geq 65$ , av T  $< 275$  ng/dL on 2 samples (neither  $> 300$ ).
- ◆ One year active treatment – daily T gel or placebo.
- ◆ Treatment target – 500 – 800 ng/dL.

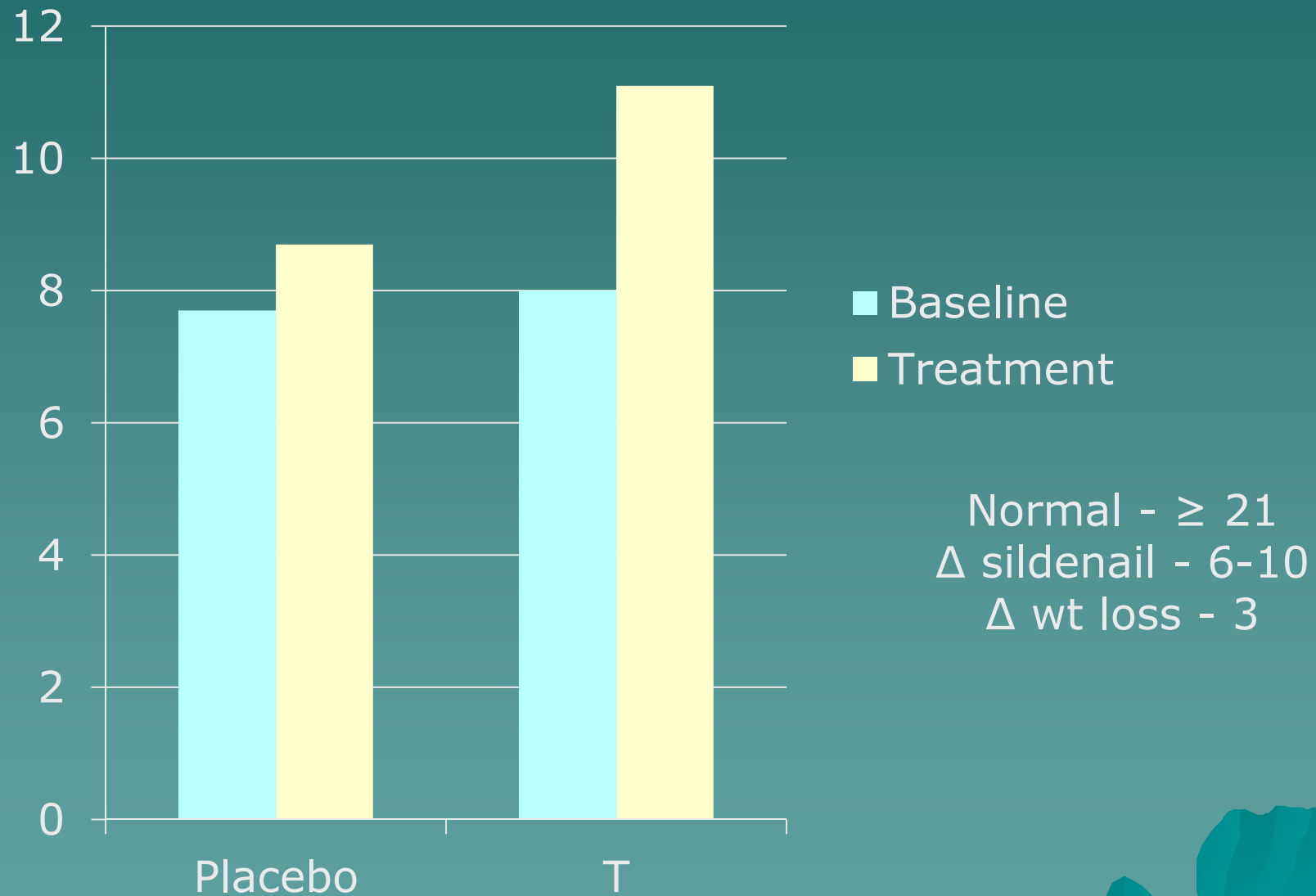
# The Testosterone Trials

- ◆ Screened 51,000 men to enroll 790 (1.5%) – main reason insufficiently low T.
- ◆ Baseline –
  - Age 72, BMI 31
  - Av T/FT 230/6 ng/dL; SHBG 30 nM, E2 20 pg/ml.
- ◆ Treatment
  - Av T/FT 450/15 ng/dL; SHBG 30 nM, E2 30 pg/ml.

# SFT - 1<sup>o</sup> Outcome



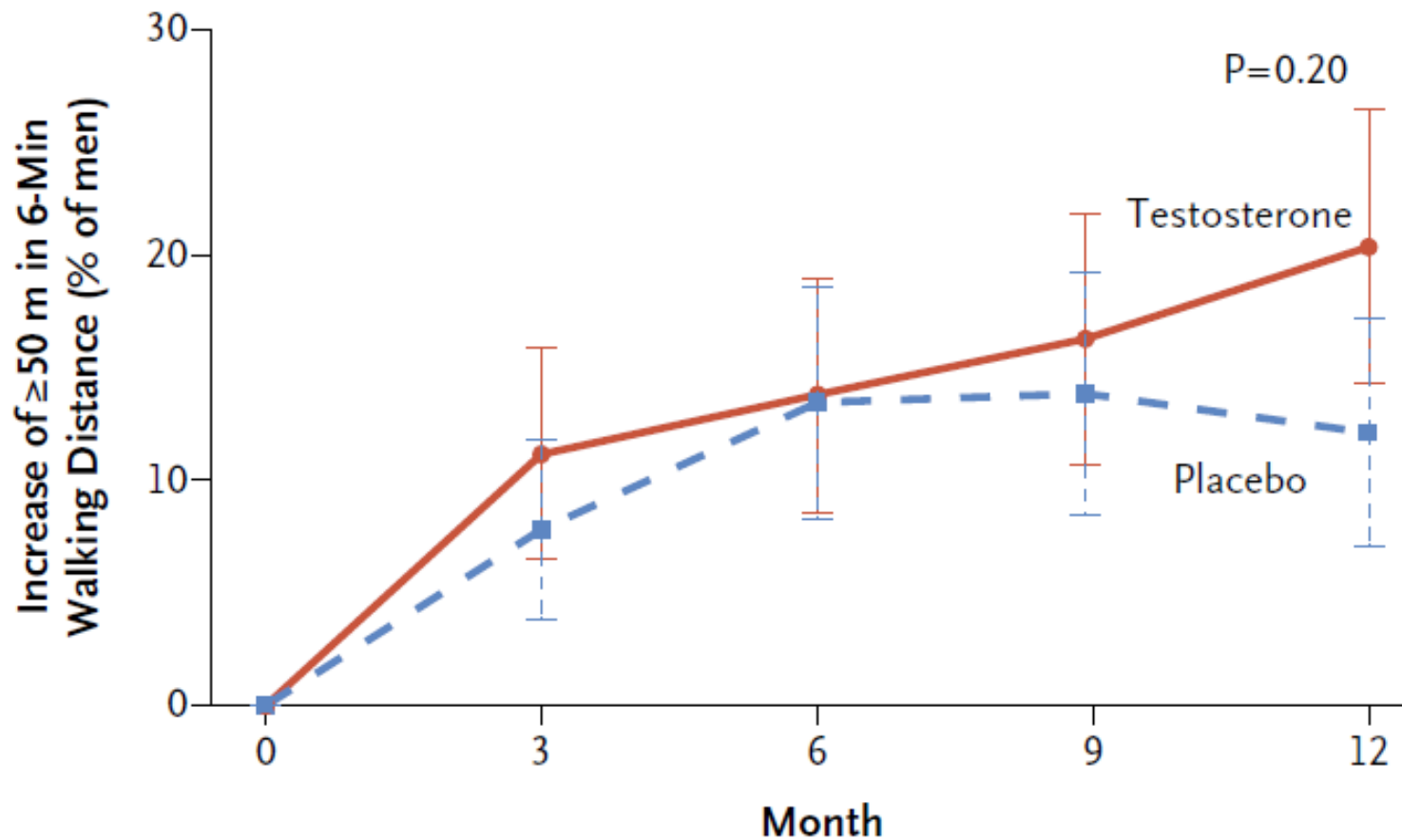
# IIEF EF Score





# PFT - 1<sup>o</sup> Outcome

## B Walking Ability

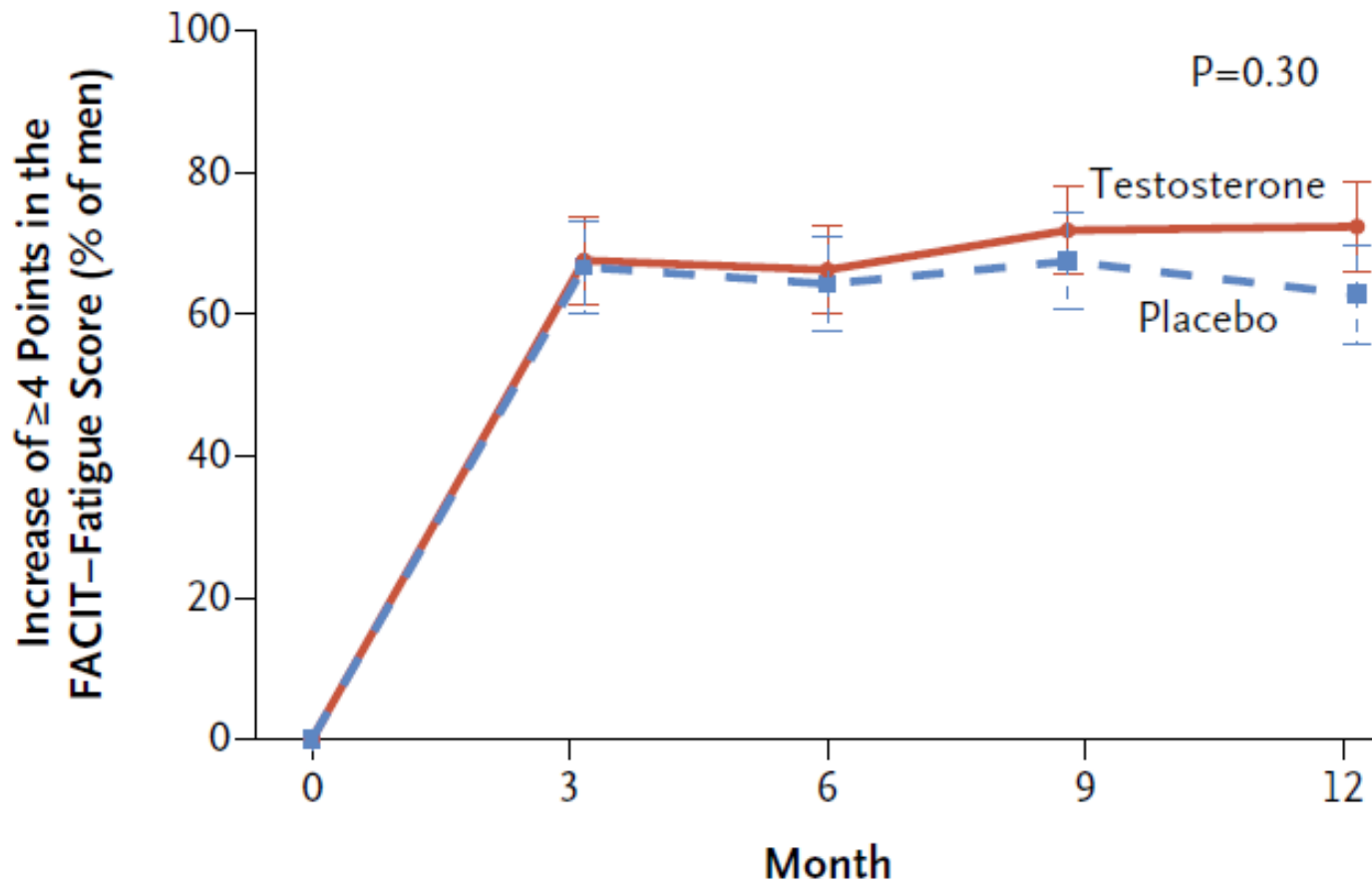


### No. at Risk

Testosterone	193	179	174	172	172
Placebo	197	179	171	159	165

# VT - 1° Outcome

## C Vitality

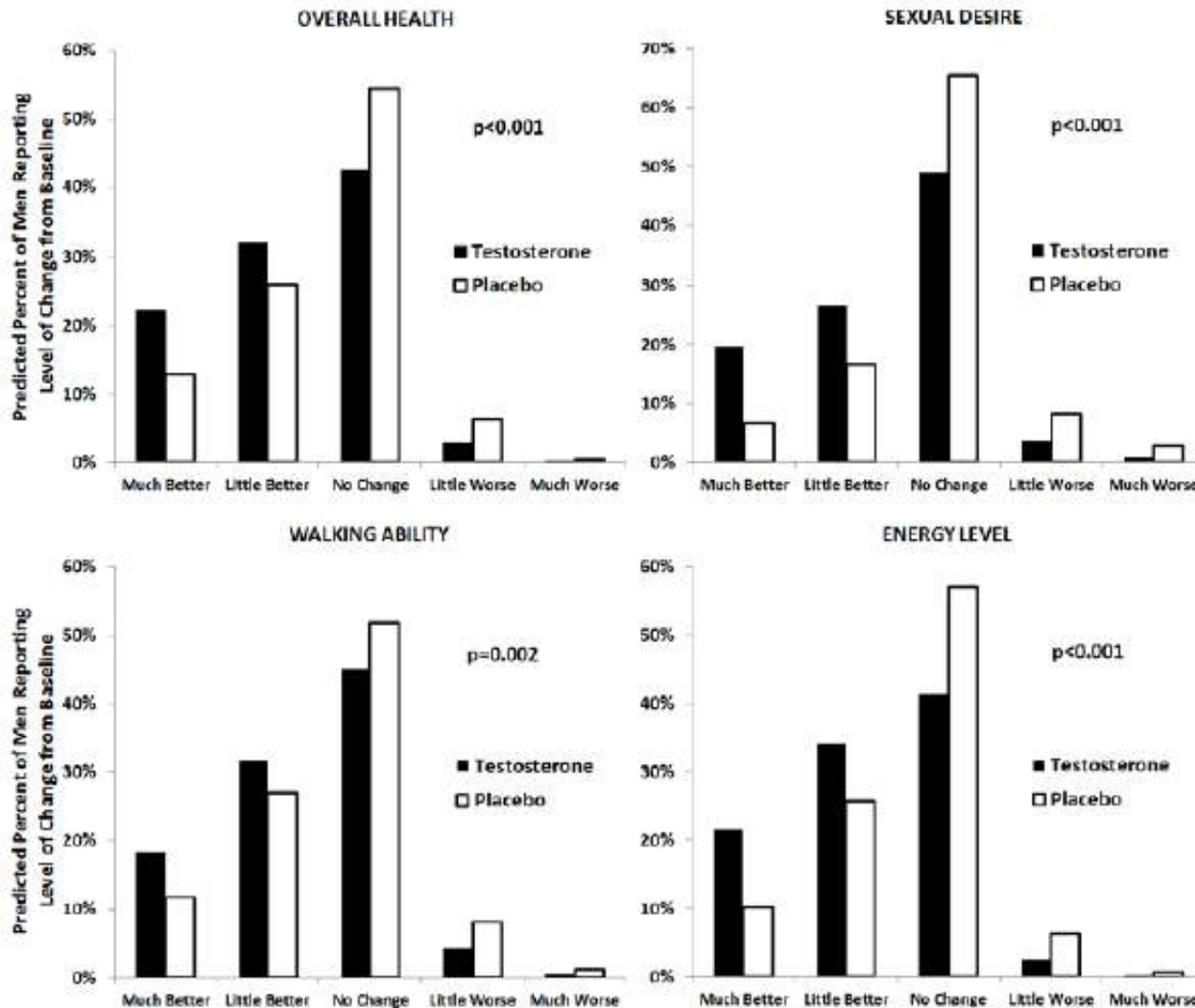


### No. at Risk

Testosterone	236	219	217	206	203
Placebo	238	207	196	188	191

# Global Responses

Figure S4. Patient Global Impression of Change



# Adverse Events

	Deaths		Prostate Cancer		Incr Hgb		MI, Stroke, CV Death	
	P	T	P	T	P	T	P	T
Year 1	7	3	0	1	0	7	7	7
Year 2	4	4	1	2	-	-	9	2
Total	11	7	1	3	0	7	16	9

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## Adverse Events Associated with Testosterone Administration

Shehzad Basaria, M.D., Andrea D. Coviello, M.D., Thomas G. Travison, Ph.D., Thomas W. Storer, Ph.D., Wildon R. Farwell, M.D., M.P.H., Alan M. Jette, Ph.D., Richard Eder, B.A., Sharon Tennstedt, Ph.D., Jagadish Ulloor, Ph.D., Anqi Zhang, Ph.D., Karen Choong, M.D., Kishore M. Lakshman, M.D., Norman A. Mazer, M.D., Ph.D., Renee Miciek, M.S., Joanne Krasnoff, Ph.D., Ayan Elmi, B.A., Philip E. Knapp, M.D., Brad Brooks, B.S., Erica Appleman, M.A., Sheetal Aggarwal, B.S., C.C.R.P., Geeta Bhasin, B.A., Leif Hede-Brierley, Ashmeet Bhatia, M.B., B.S., Lauren Collins, R.N.P., Nathan LeBrasseur, Ph.D., Louis D. Fiore, M.D., and Shalender Bhasin, M.D.


### TOM Trial

- 65 and older (av age 74)
- Some degree of limited mobility
- T 100 – 350 ng/dL or FT < 5 ng/dL (av 240/4.5 ng'dL)
- Aggressive Rx goal – 500 – 1000 ng/dL (av 574 ng/dL)

# Conclusion ?

- ◆ If testosterone is low enough and you raise it high enough there may be some (statistical ?) benefit?
- ◆ Sexual symptoms may be those most likely to benefit?
- ◆ Short term (1 yr) seems safe (if not too aggressive)?

# Management Issues

- ◆ Men on T treatment who may not need it.
  - ◆ Men on T who want to have children.
  - ◆ Monitoring therapy.
- 
- A decorative graphic at the bottom of the slide showing a silhouette of a mountain range in shades of teal against a darker teal background.

- ◆ Dec 2013 – 28 yo man with dx of hypogonadism recently on T Rx with severe oligospermia and desire to conceive.



- ◆ Oct 2011– Eval of ED
  - Easy fatigue, decr strength/endurance
  - Father with hx of hypogonadism.
  - Pertinent (-)
    - ◆ Libido not low
    - ◆ Not sad, grumpy
    - ◆ No decrease in ability to play sports
    - ◆ Doesn't fall asleep after dinner
    - ◆ No deterioration in work performance
  - BMI 32, “atrophic L testis”

## ◆ Lab tests

- T 274 ng/dL (175 – 781)
- FT 7.5 (9-30)
- SHBG 12 nM (13-89)
- LH 3.2 mIU/ml (1.24 – 8.62)
- FSH 1.8 (1 – 10)

## ◆ Testicular US – nl size testes

## ◆ Dx of hypogonadism

- ◆ Started on daily transdermal T Rx.
- ◆ T levels over next year 560 – 1074 on Rx, NI Hgb (15 – 16 range), LH suppressed

- ◆ Summer 2013 - married
- ◆ Aug 2013 – wished to conceive
  - T 928, LH < 0.2
  - Semen analysis – volume 2 ml, no sperm
- ◆ Stopped T.
  - Sept 2013 – SA – 2.5 ml, no sperm
  - Oct 2013 – SA – 1 ml, 1 mil/ml

- ◆ Dec 2013 – came to see us.
  - Continued off T
  - More problems maintaining erections
  - No HA, change in vision, breast sx
  - No medications, drug use
  - BMI 27, nl BP, nl virilized, VF full, no gynecomastia, testes L 12 ml, R 15-20, nl consistency.
- ◆ Assessment – Suppression of HPG axis by exogenous T; question dx of hypogonadism.

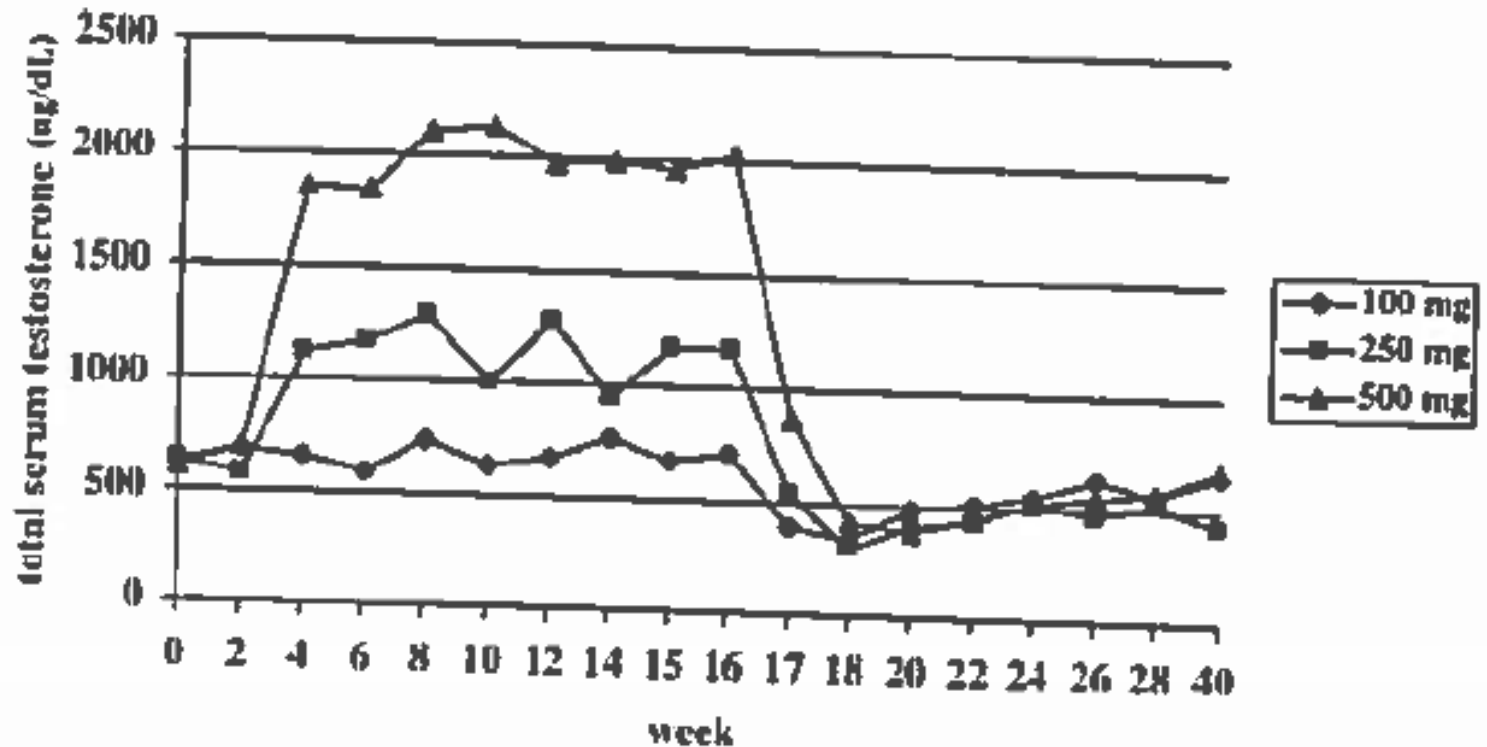
## ◆ Recc:

- Recheck labs now – assuming low:
- Wait – let HPG axis recover on its own, might take a few more months.
- Clomiphene citrate to stimulate axis, speed recovery.
- ED - ? Relationship to T status, use PDI.

## ◆ Labs

- T 456, SHBG 28, LH 2.5
- SA - 3.5 ml, 52 mil/ml

# HPG Axis Recovery



*Figure 1A. Mean total serum (A) testosterone concentrations and mean free serum testosterone concentrations (B) for the testosterone cypionate 100 mg/wk, 250 mg/wk, and 500 mg/wk administered from weeks 2 through 15.*



# Recovery of Spermatogenesis

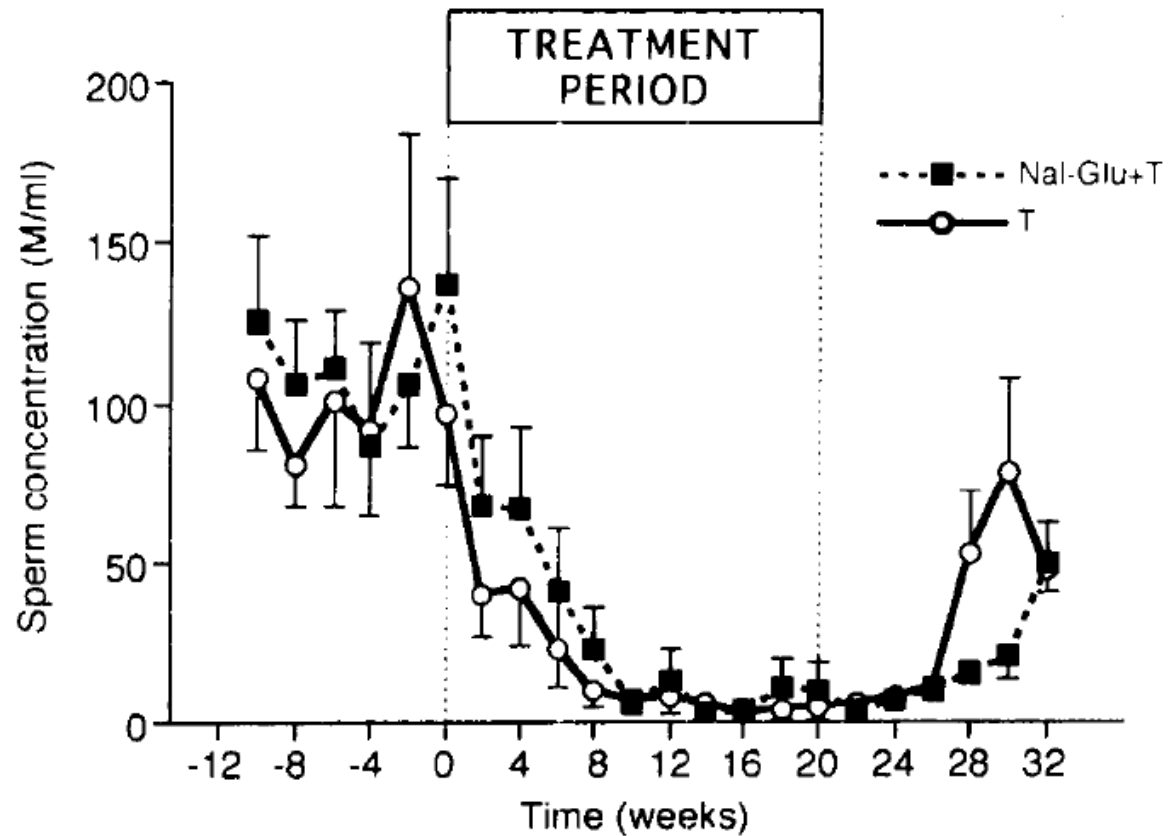


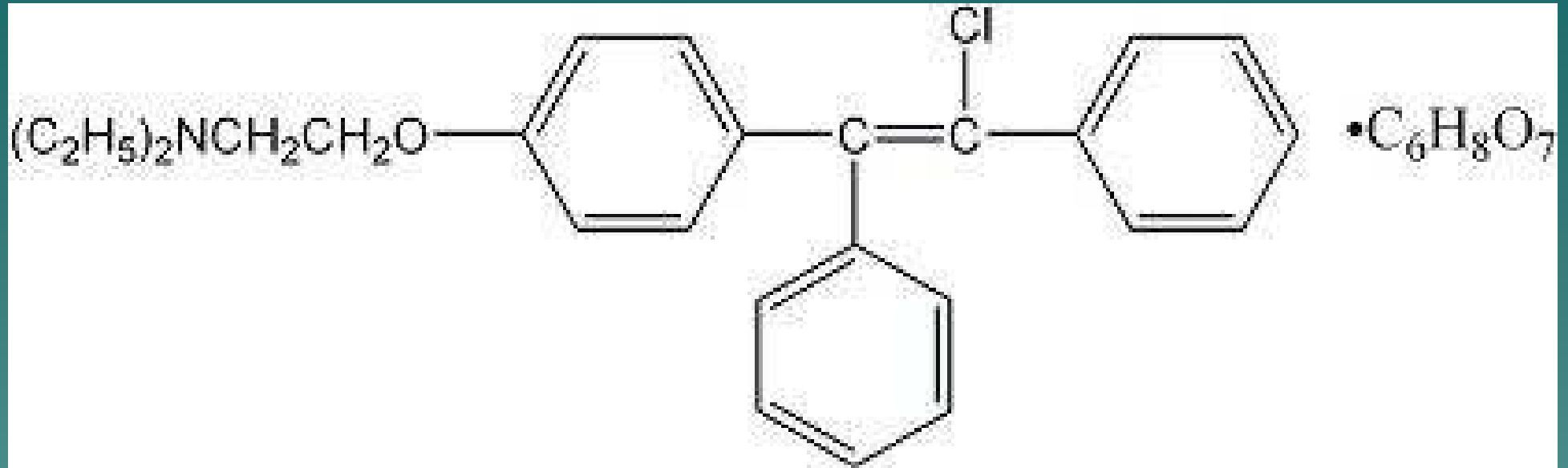
FIG. 1. Mean sperm concentrations (in millions per mL) before, during treatment, and during the first 3 months after treatment in men who received Nal-Glu+T (n = 10, closed squares) and men who received T alone (n = 9, open circles).

- ◆ 30 yo man dx idiopathic hypogonadotropic hypogonadism on T therapy, wishes to conceive.
  - Sx fatigue, mood swings, anxiety, depressed mood; more recently ED, decr libido.
  - T levels 170 – 200 (185-703); SHBG 30, LH 1.4; MRI pituitary - normal.
  - Started on T cypionate injections.
  - Five mos later – pt/wife wish to conceive.

- ◆ Seen in our clinic – on T Rx approx 5 mos.
- ◆ Three prev pregnancies (two with current partner), most recent 3 yrs ago.
- ◆ Exam – nl virilization; testes nl size.
- ◆ T 1320, LH, FSH < 0.1 on therapy.
- ◆ Semen analysis – 4.5 ml, est 20 immotile sperm total in sample.
- ◆ Trial of clomiphene 12.5 mg daily.

- ◆ One month – T 706, LH 14.5
- ◆ 3 months – SA 2.8 ml, 6.7 mil/ml, 79% motility.
- ◆ Shortly after – wife pregnant.
- ◆ After first trimester – stopped clomiphene.
- ◆ 2 months later – T = 662, LH 2.4.
- ◆ 4 months later – T = 306, LH 1.7.

# Clomiphene Citrate



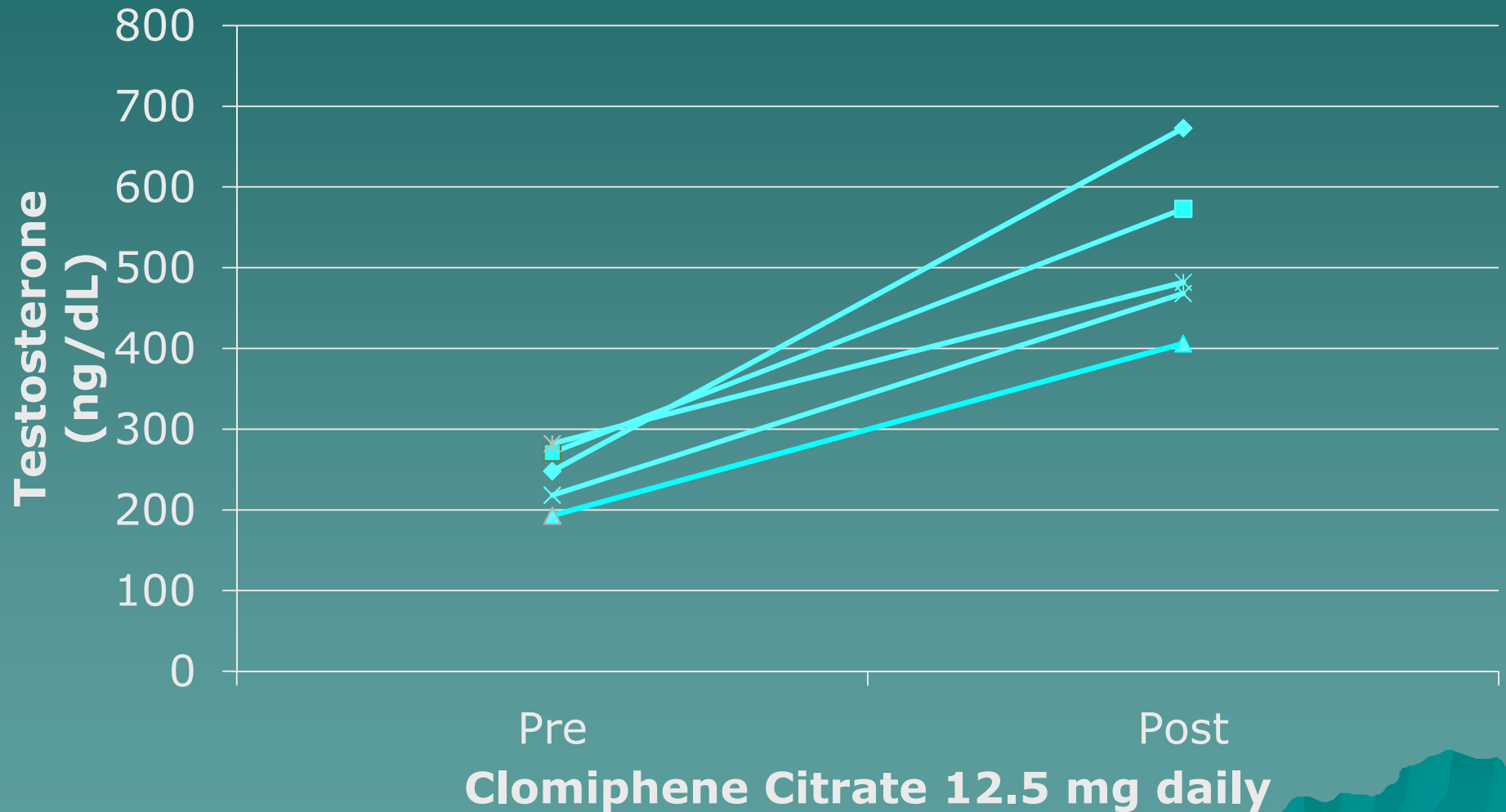
Mixed estrogen agonist/antagonist.

Stimulates gonadotropins.

Off label use in men.

Typical doses 12.5 – 50 mg a day.

# Testosterone Response to Clomiphene



# Aromatase Inhibitors

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## AROMATASE INHIBITORS FOR MALE INFERTILITY

JAY D. RAMAN AND PETER N. SCHLEGEL\*

*From the Department of Urology, James Buchanan Brady Urology Foundation, Center for Male Reproductive Medicine and Microsurgery, New York Presbyterian Hospital, Weill Medical College of Cornell University and The Population Council, Center for Biomedical Research, New York, New York*

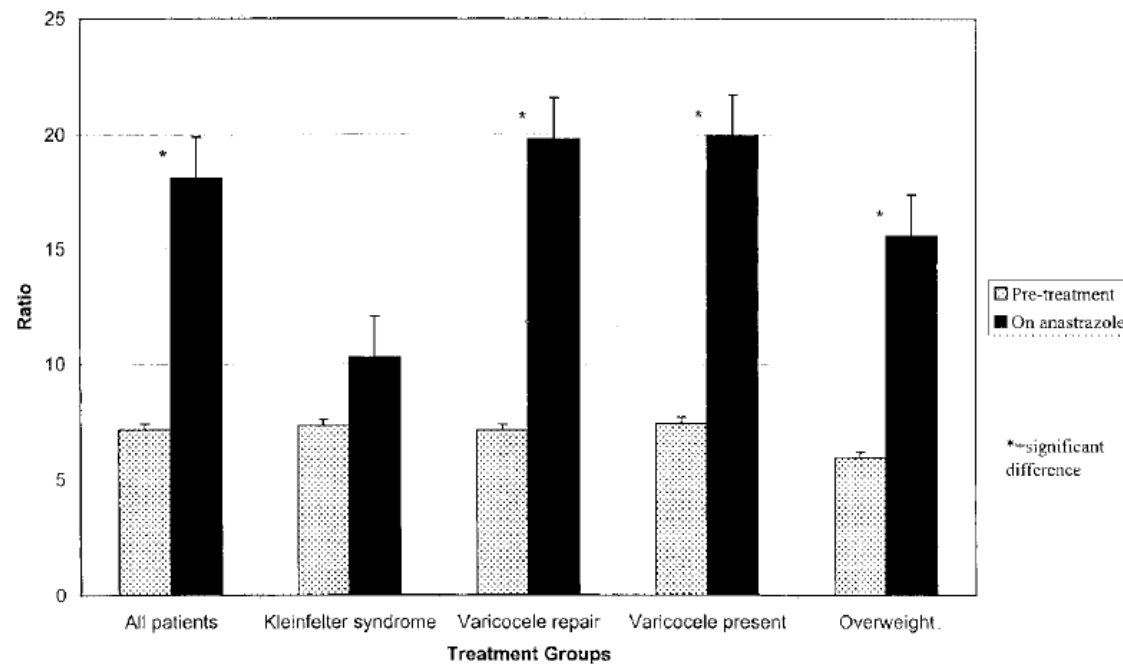
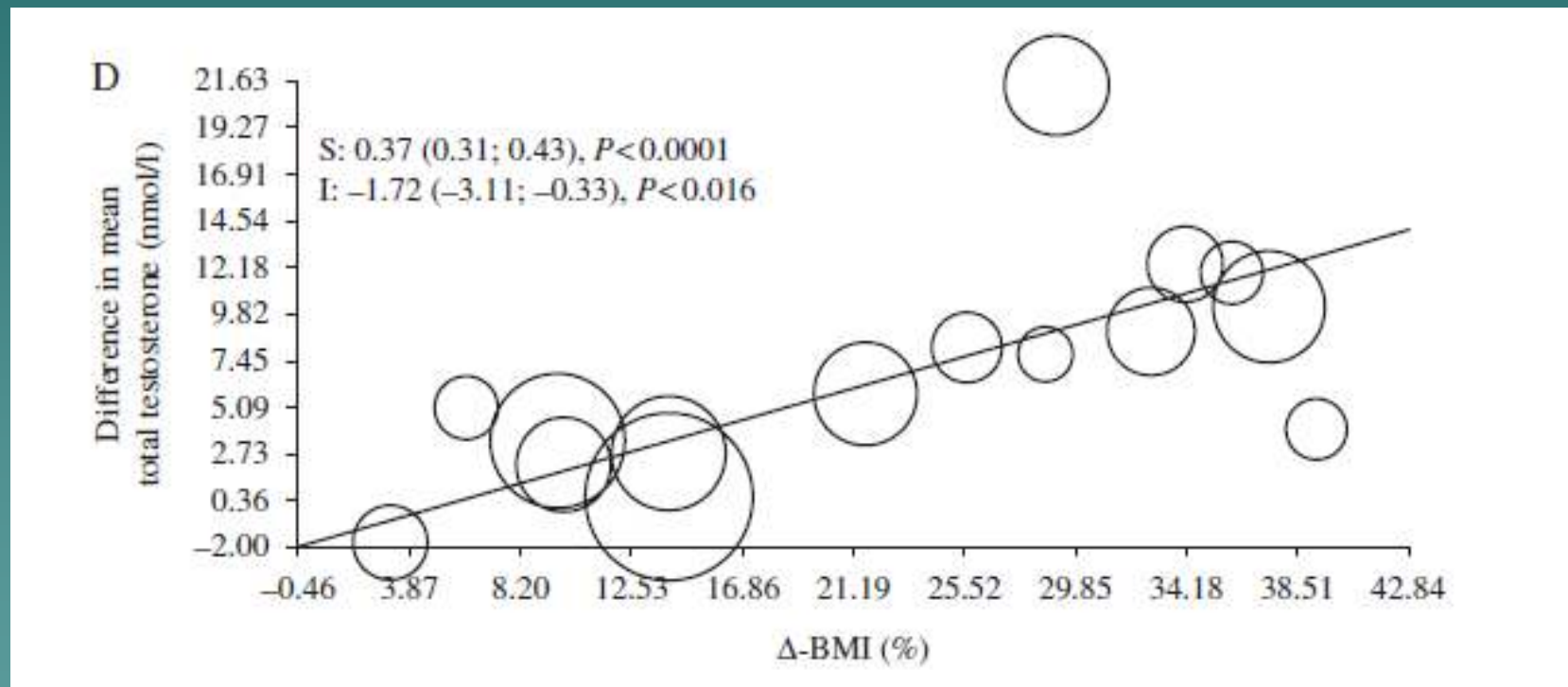


FIG. 5. Changes in testosterone-to-estradiol ratios during treatment with anastrozole are shown for various infertile patients with various clinical conditions as well as all those treated.

# Weight Loss and Testosterone Levels





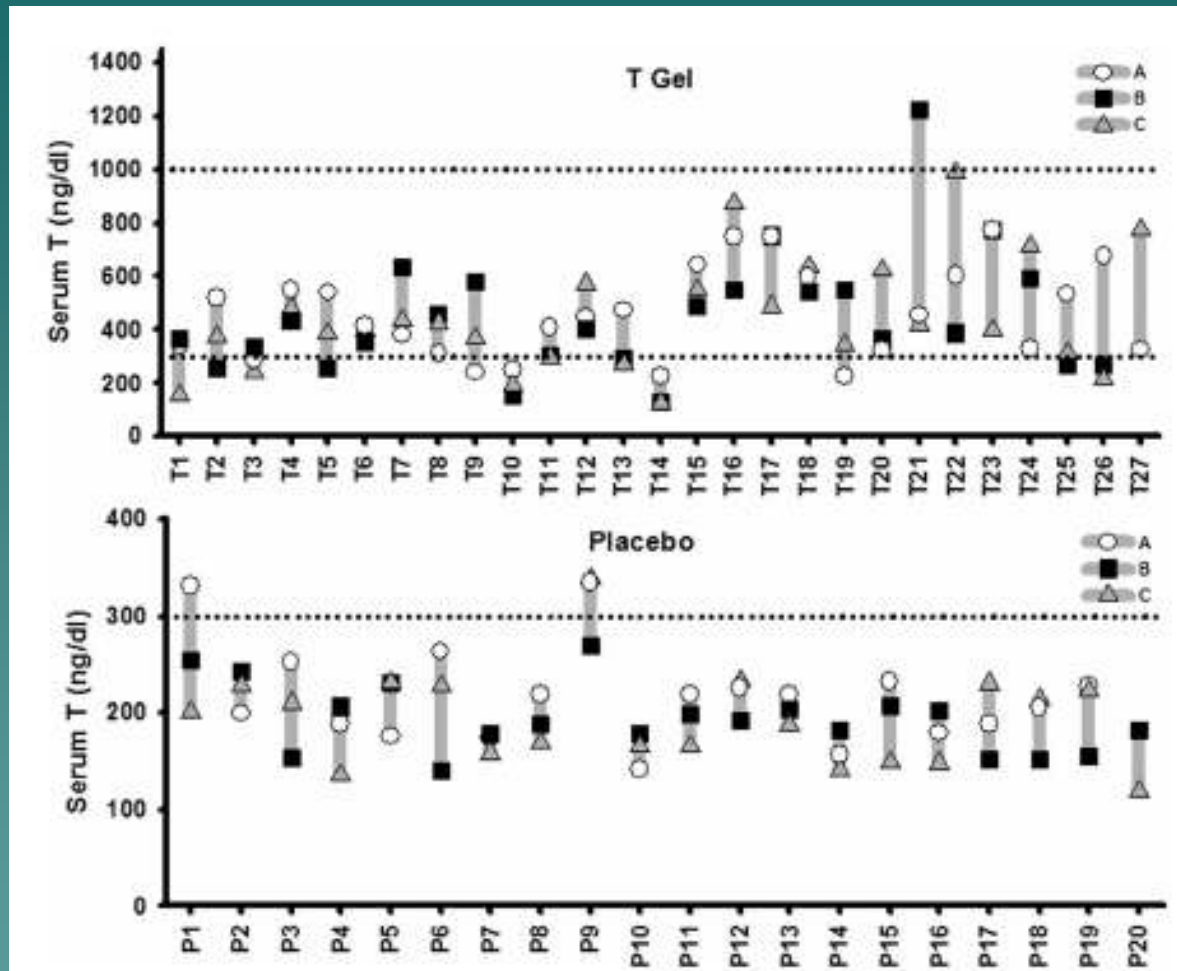
# Testosterone Treatment Options

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# Testosterone Therapy Options

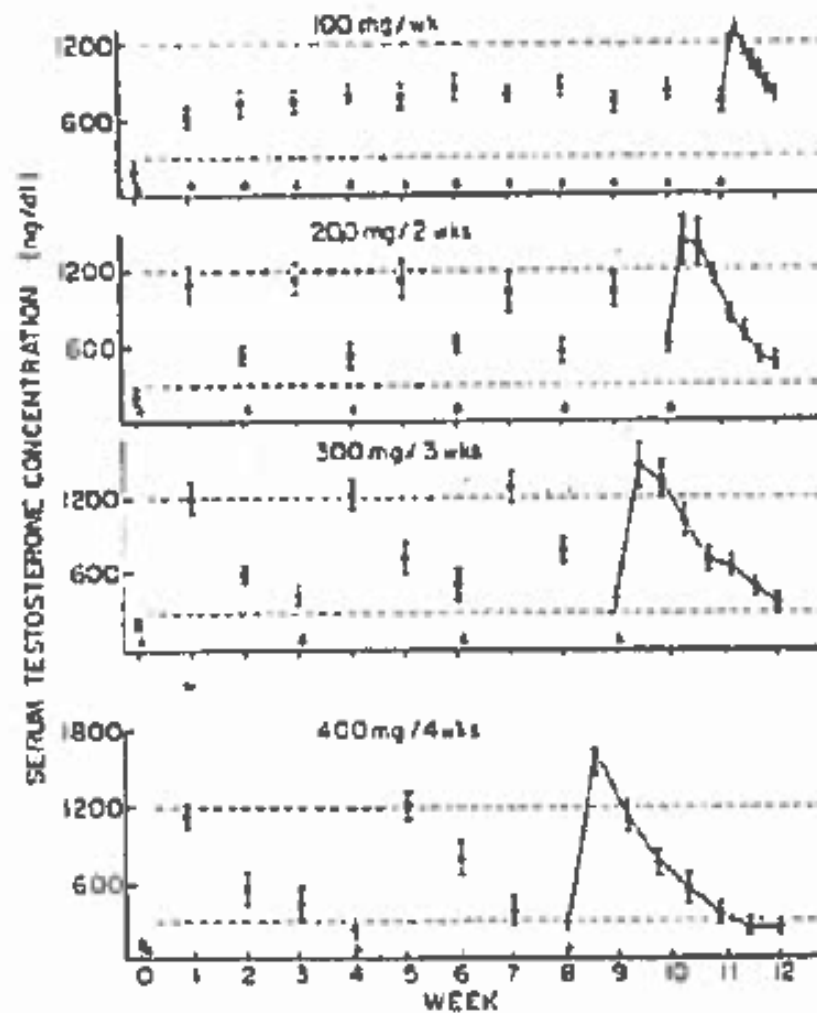
- ◆ Intramuscular T esters
  - T enanthate, T cypionate, 100-300 mg/1-3 wks
  - T undecanoate, 750 mg/10 weeks
- ◆ Transdermal patch – once daily
- ◆ Transdermal gel/spray – once daily
- ◆ Buccal preparation – twice daily
- ◆ Nasal gel – three times daily
- ◆ Subcutaneous testosterone pellets, 3-6 mos

# Variability in T Treatment Levels



**Figure 1.** Large variation of serum T levels 2 hours after gel application at the ambulatory visits (A, open circles, or B, closed squares) and the inpatient day (C, shaded triangle) in the T gel (upper panel, participants T1 to T27) and placebo (lower panel, participants P1 to P20) groups. Note the difference in y-axis scale for serum T concentration in the T vs the placebo group. Shaded vertical lines between highest and lowest T value for each man indicates within-subject variation. The dashed lines represent the adult men reference range of 300–1000 ng/dL (10.4–34.7 nmol/L).

# T Levels after T Ester Injections



# Monitoring Therapy

- ◆ Improvement in symptoms – are they better?
- ◆ Monitor hemoglobin or hematocrit.
- ◆ Prostate monitoring (?)
- ◆ Signs of excess treatment – acne, breast development.
- ◆ Sleep apnea?
- ◆ Dexa

# Conclusions

- ◆ “Unequivocal” hypogonadism is uncommon, generally easy to diagnose as to etiology and treatment appears warranted (if the patient wants it).
- ◆ Most men endocrinologists see for possible hypogonadism probably aren't hypogonadal or have mild idiopathic hypogonadotropic hypogonadism of uncertain clinical significance.
- ◆ We have an increasing number of modalities to treat hypogonadism.
- ◆ The challenges are to better understand the risks/benefits of treatment, how to identify men who benefit from treatment and how to appropriately monitor men on treatment.

