

Androgen deficiency

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Outline

- Pathological androgen deficiency
 - Background, causes, interpretation
 - Indications for treatment
- Androgen deficiency in older men
 - Evidence for T treatment in older men

Background

- Testis as a source of virility known for centuries
- Castration of men and animals
- Chinese eunuch system
- Castration of boys to preserve high pitched voice for opera singing

Iyer and Handelsman, Testosterone misuse and abuse In: Testosterone: basic to clinical aspects (in press)

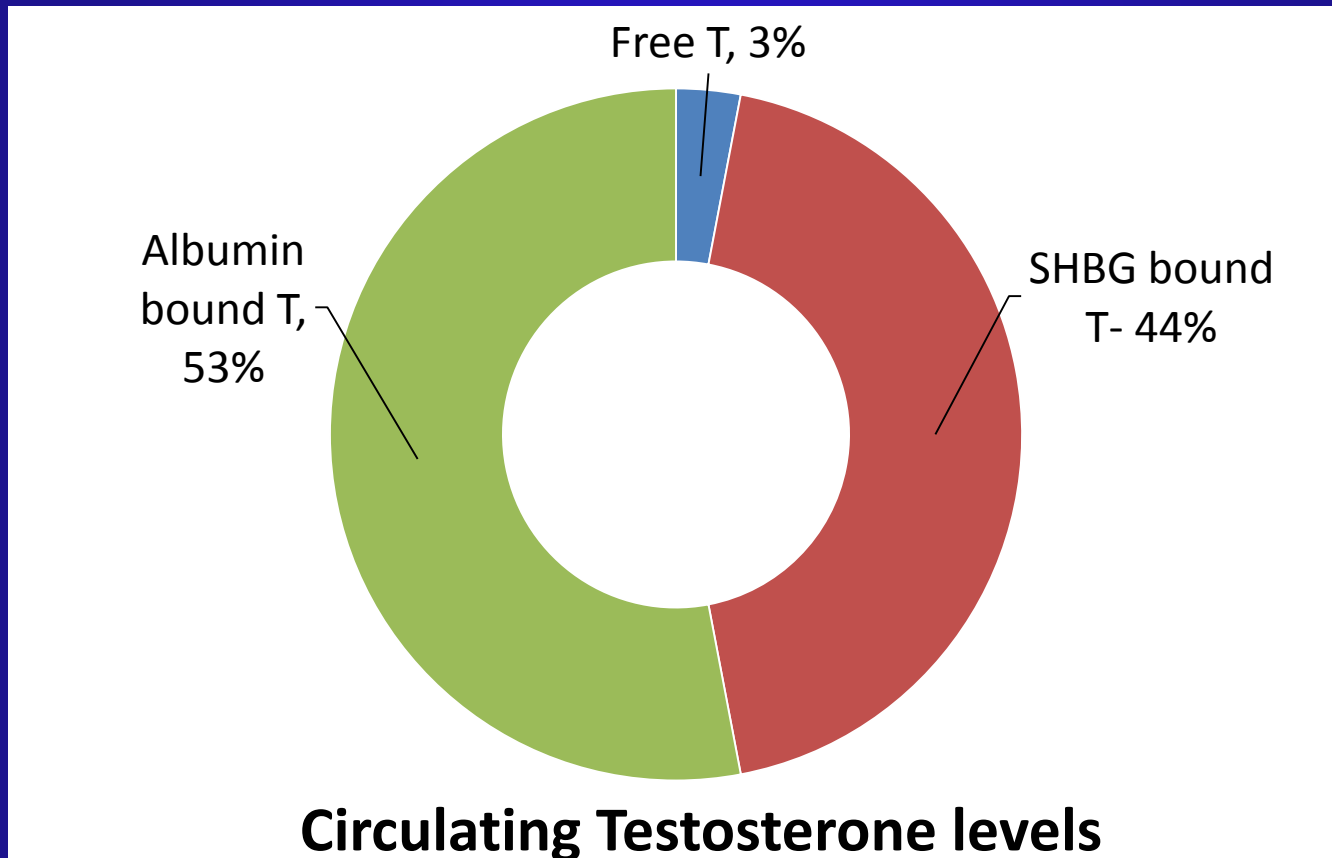
Testosterone (T)

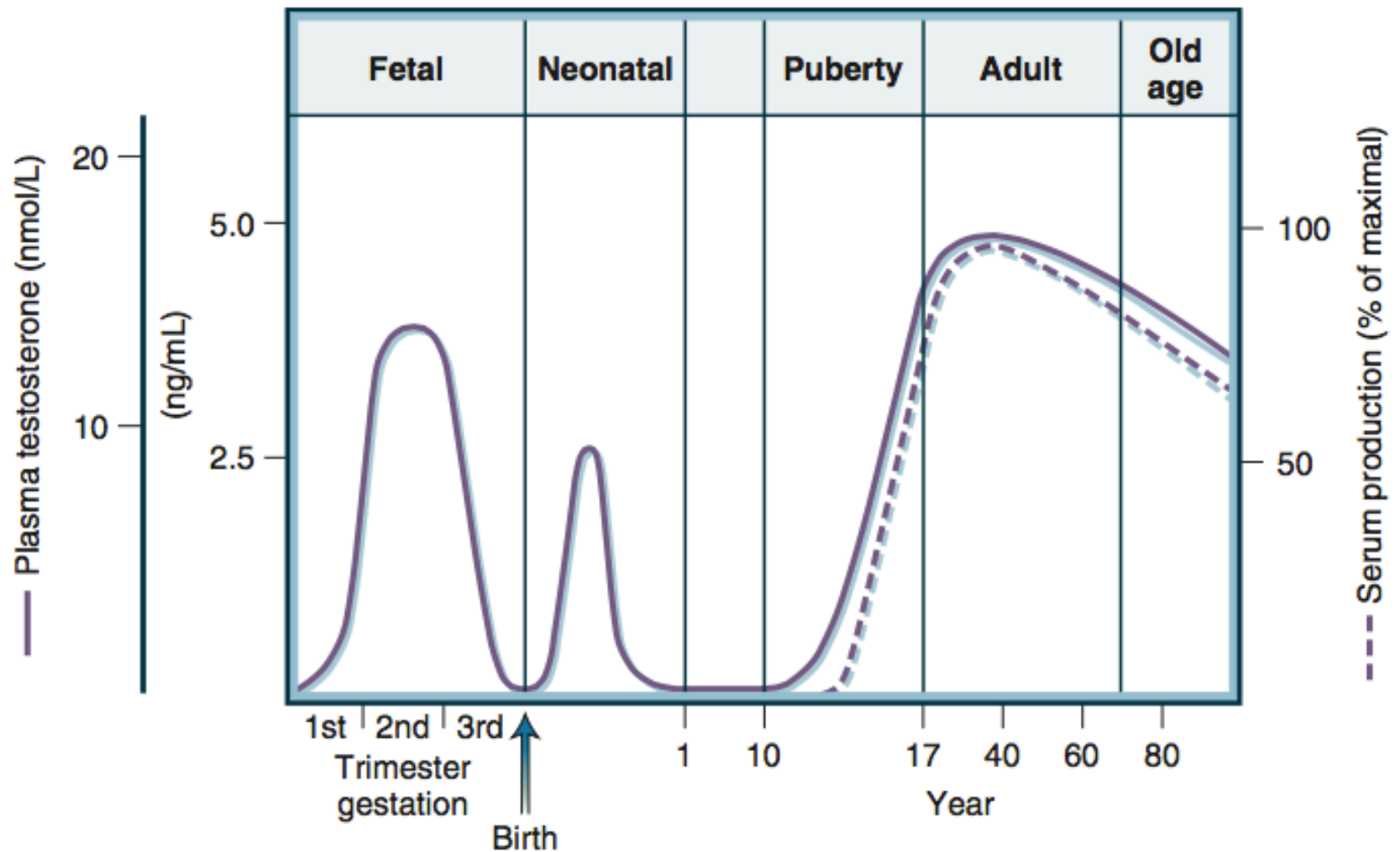
- T was characterized as a principal circulating androgen in 1935*
- Usage of T proliferated in the post war decades
- One of the oldest marketed drugs in use
- Appropriate use remains pathological androgen deficiency (prevalence 0.5%)

*David K, Über krystallinisches männliches Hormon aus 837 Hoden (Testosteron), wirksamer als aus Harn oder aus Cholestrin bereitetes Androsteron. 838 Hoppe Seylers Zeischrift Physiologische Chemie. 1935;233:281–2

Testosterone

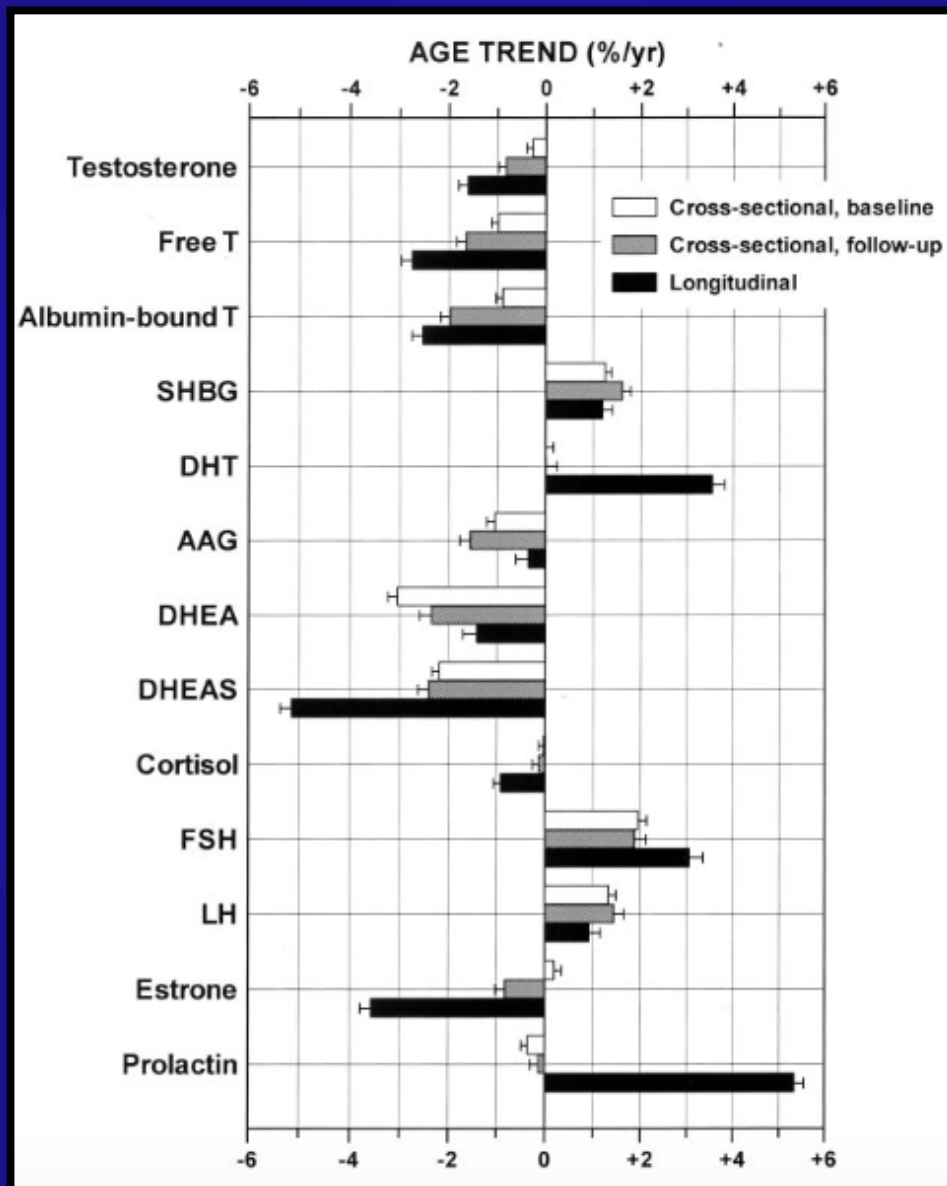
- Synthesized and secreted from Leydig cells
- Available bound and free in circulation





Serum testosterone concentrations in different phases of life

Androgens in aging



Hypogonadism

- Pathological disorder of hypothalamo-pituitary-testicular axis resulting in impaired production of testosterone (androgen) and spermatogenesis
- Hypogonadism and androgen deficiency used interchangeably

Hypogonadism Causes

Primary

- Klinefelter syndrome
- Testicular failure

Secondary

- Kallmann's syndrome
- Pituitary disease: pituitary adenomas, hypopituitarism, infiltrative disorders
- Hemochromatosis
- Hyperprolactinemia
- Drugs: anabolic and corticosteroids, opioids, others
- Chronic Liver Disease
- Acute illness
- Other

Symptoms and signs

Symptoms	Signs
Incomplete sexual development	Eunuchoidism
Lack of libido	Small/shrinking testis
Reduced night time or morning erections	Loss of axillary or pubic hair
Breast enlargement or tenderness	Gynaecomastia
infertility	Azoospermia/oligospermia
Height loss, fragility fracture	Osteopenia, osteoporosis
Hot flushes, sweats	Vertebral compression #
Reduced shaving frequency	

Symptoms and signs

Less specific Symptoms	Less specific Signs
Decreased energy, vitality	Normochromic, normocytic anaemia
Decreased motivation or self confidence	Mood disorders, depression
Feeling sad, blue, irritability	Reduced muscle bulk, strength
Weakness, decreased work performance	Increased fat mass, BMI
Poor concentration, memory	Fine facial skin wrinkling
Increased sleepiness	

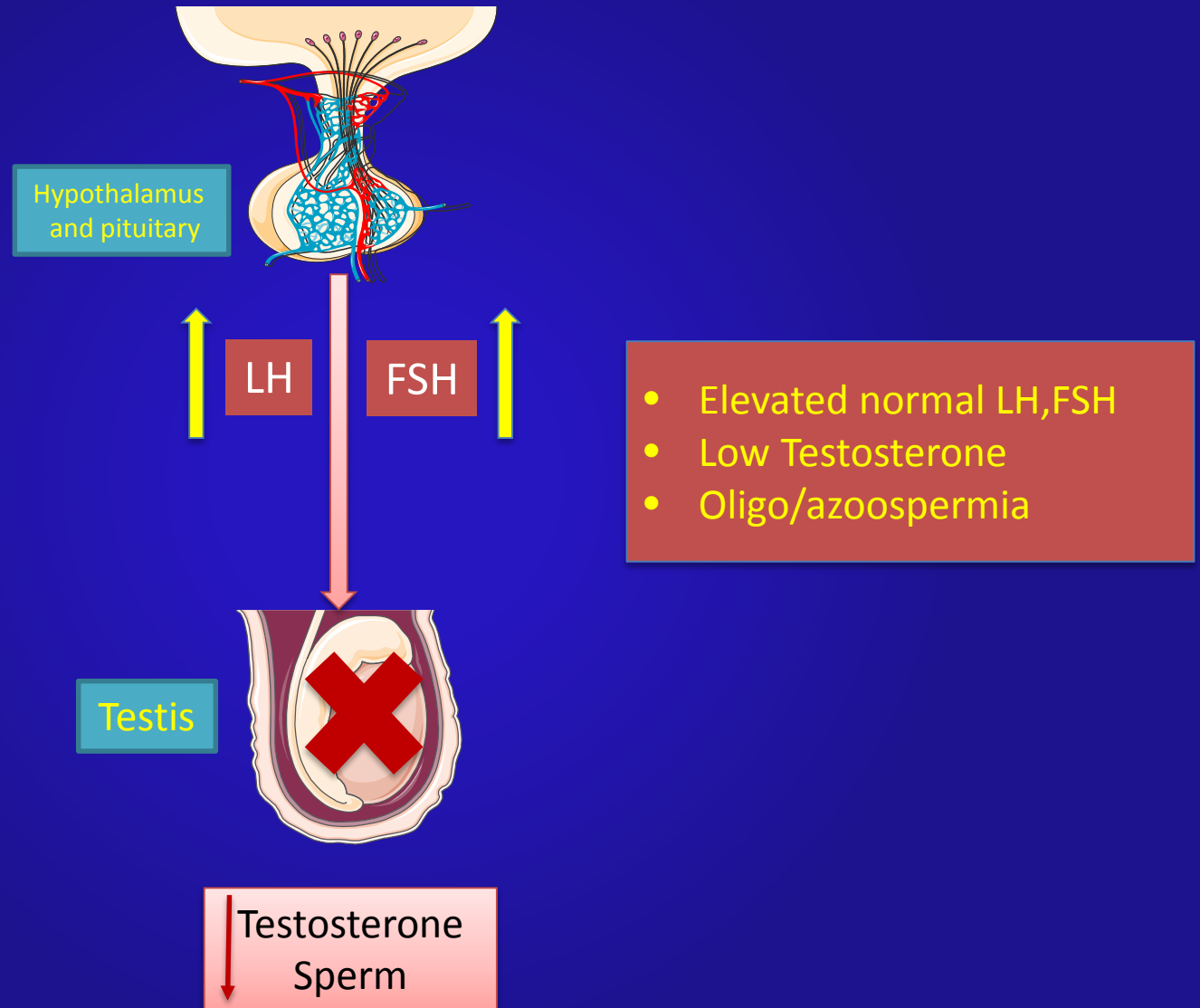
Examination

- General- congenital defects, eunuchoidal habitus, gynaecomastia, anosmia
- BMI
- Testicular volume
- Visual fields if indicated

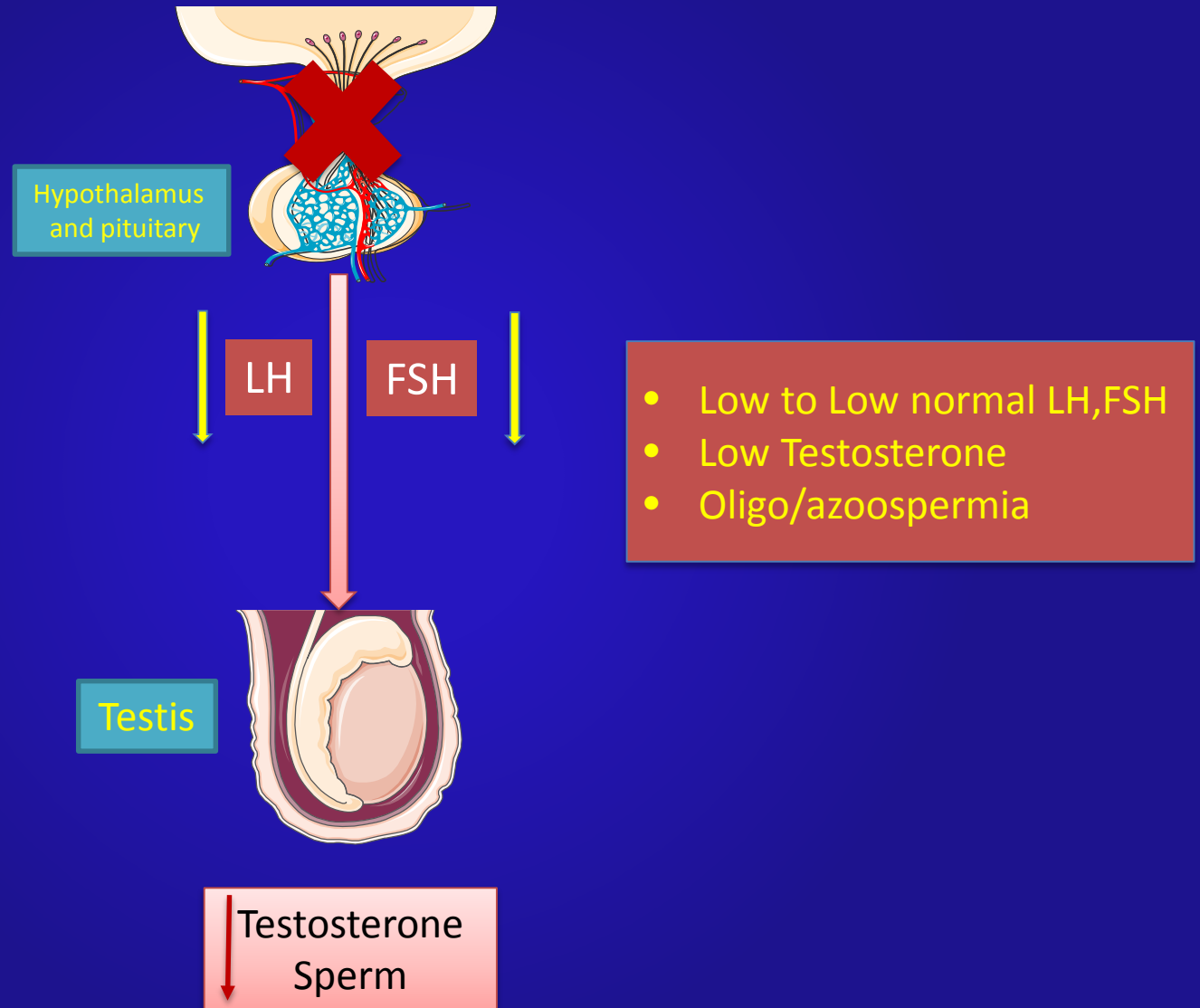
Investigations

- Initial hormone assessment
 - Serum Total T, LH, FSH, SHBG 08:00-10:00
(age appropriate reference intervals for T)
 - Prolactin, Fe studies, anterior pituitary testing, karyotyping, MRI Sella
 - Sleep studies if indicated

Primary hypogonadism



Secondary hypogonadism



Valid indications

Primary testicular failure

- Klinefelter syndrome
- Testicular trauma, torsion, removal
- Infection
- Testicular atrophy of any cause

Hypogonadotropic hypogonadism

- Congenital- IHH, Kallman
- Acquired- Prolactinoma, pituitary tumour, surgery, RTx
- Delayed puberty

Subject of ongoing research

- Middle aged and older men
- Chronic disease and ill health
- Hormonal male contraception

PBS criteria

- Pubertal induction
 - Constitutional delay in growth and puberty
 - Established pituitary or testicular disorder
 - Androgen deficiency
 - >40 years
 - No established pituitary or testicular disorder
 - and must not be due to age, obesity, CVS disease, infertility, drugs
- (AD-- T <6 nmol/L or T 6-15 nmol/L with LH >1.5 times the upper limit of normal or >14 IU/L whichever is higher)

Treatment

Testosterone preparations

- Oral
- Topical- gel, cream, pumps
- Buccal
- Patches
- Implants
- Intramuscular- long acting and extra long acting

Treatment

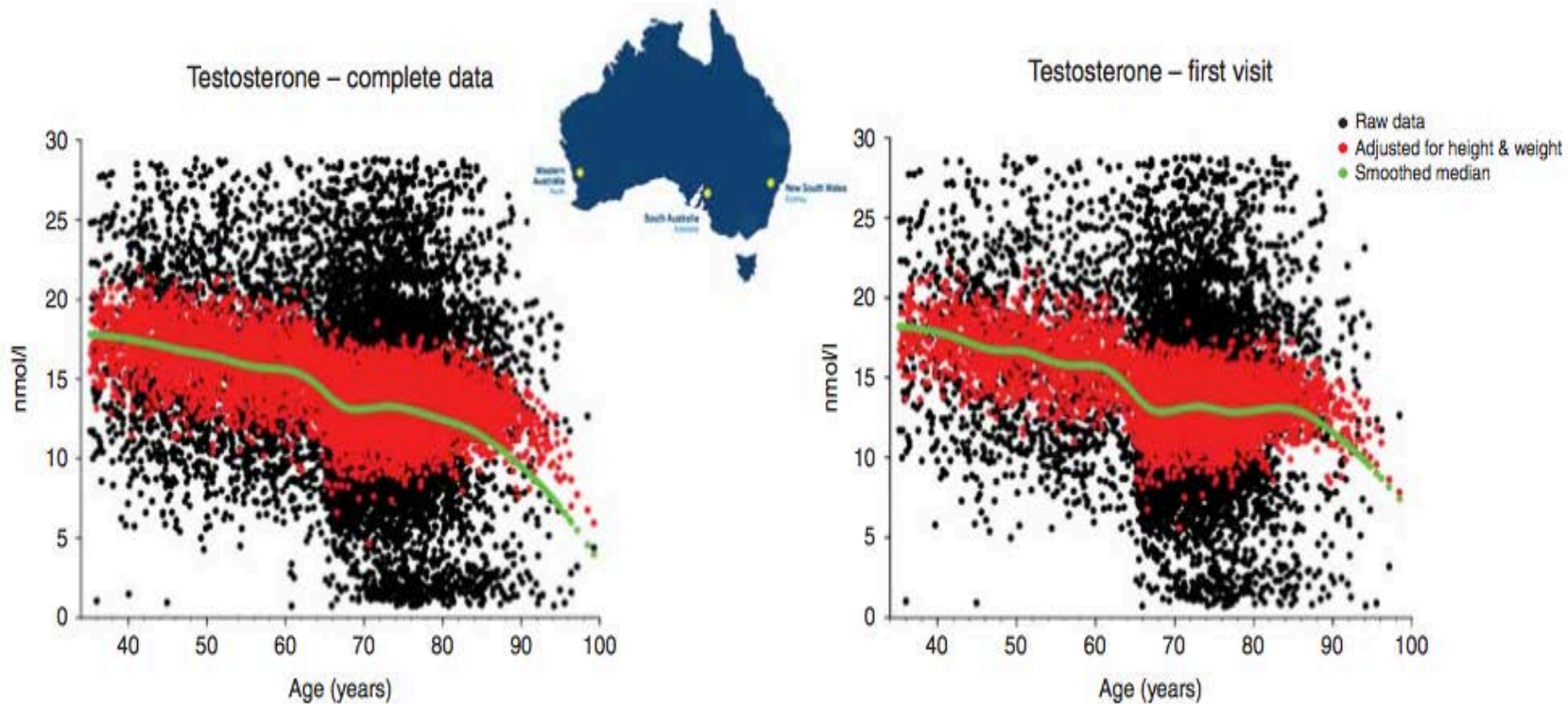
- Testosterone undecanoate- 1000mg 0,6, every 12 weeks thereafter
- Monitoring- trough testosterone levels, blood count, PSA

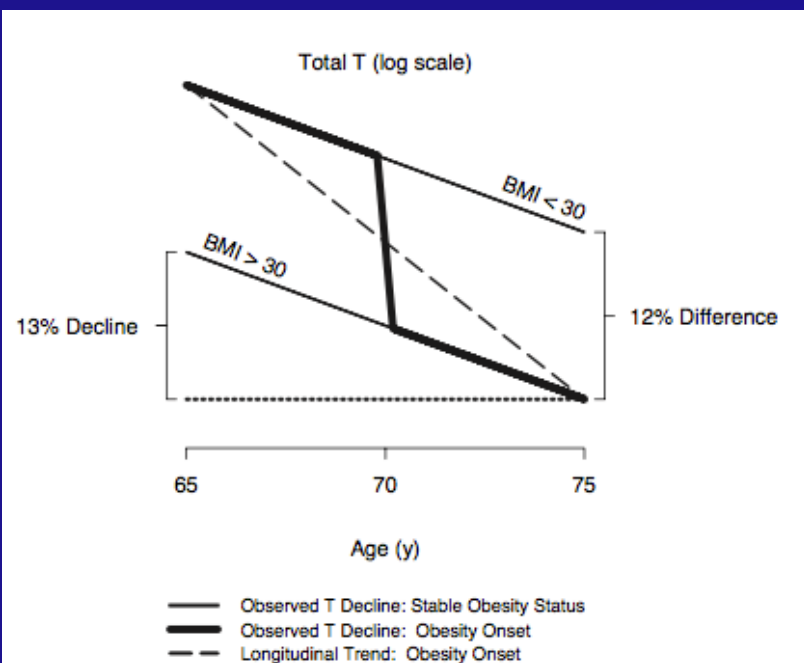
Low T in older men

Low T in older men

- Older men with non specific symptoms and low testosterone level
 - Andropause
 - Late onset hypogonadism (LOH)
 - Androgen deficiency in aging male (ADAM)
 - sHG
- Renewed attempt at rejuvenation??

Androgens in aging





- Accelerated T decline on jumping tracks

Travison (MMAS) JCEM2007

Health/lifestyle factor	N ^b	Mean decline (%) ^c	
		TT	FT
Increased chronic illness			
No illness T1 and T2	382	-4.0	-7.3
No illness T1, one or more illnesses T2	162	-6.3	-13.1
Increased use of medications			
Fewer than six medications T1 and T2	889	-5.0	-9.6
Fewer than six medications T1, six or more T2	49	-9.9	-13.4
Smoking cessation			
Smoker T1 and T2	112	1.6	-6.9
Smoker T1, nonsmoker T2	93	-7.6	-11.0
Loss of spouse			
Married T1 and T2	680	-6.0	-12.0
Married T1, widowed T2	25	-16.9	-21.2

Covariate predictor	Outcome measurement								
	TT			FT			SHBG		
	% Difference ^a	95% confidence interval	P	% Difference ^a	95% confidence interval	P	% Difference ^a	95% confidence interval	P
Age and aging ^b									
Cross-sectional (10 yr)	-1.0	(-2.9 to 1.0)	0.33	-8.8	(-10.9 to -6.7)	<0.001	15.1	(12.9 to 17.3)	<0.001
Longitudinal (10 yr)	-10.1	(-12.5 to -7.9)	<0.001	-23.8	(-26.3 to -21.3)	<0.001			
Health									
Diabetes ^c	-4.9	(-9.8 to 0.1)	0.05	-5.8	(-11.1 to -0.5)	0.03	-0.7	(-7.3 to 6.0)	0.84
Hypertension ^c	-4.7	(-7.7 to -1.6)	0.002	-2.8	(-6.1 to 0.5)	0.09	-2.3	(-6.3 to 1.7)	0.25
Medications ^c									
1-2	-1.5	(-4.3 to 1.4)	0.31	-2.3	(-5.7 to 1.0)	0.16	-0.9	(-2.9 to 3.9)	0.61
3-5	-1.8	(-5.4 to 1.9)	0.34	-2.2	(-6.4 to 2.0)	0.29	-1.8	(-3.9 to 4.8)	0.45
6+	-6.0	(-12.1 to -1.0)	0.03	-8.8	(-15.0 to -2.6)	0.003	-1.3	(-9.2 to 6.6)	0.73
Lifestyle									
Cigarette smoking ^c	8.6	(5.2 to 11.9)	<0.001	7.8	(4.1 to 11.5)	<0.001	3.7	(-0.6 to 7.9)	0.09
BMI (kg/m ²)	-1.9	(-2.2 to -1.6)	<0.001	-0.6	(-0.9 to -0.2)	0.002	-2.9	(-3.3 to -2.5)	<0.001
Employment ^c	3.2	(0.3 to 6.5)	0.04	3.7	(0.2 to 7.3)	0.04	-1.5	(-5.5 to 2.6)	0.48
Widowed ^c	-11.1	(-17.3 to -4.6)	<0.001	-9.3	(-16.3 to -2.3)	0.005	-9.2	(-18.0 to -0.4)	0.03

Travison (MMAS) JCEM2007

TABLE 5. Associations of low T, DHT, and E2 levels with frailty, diabetes, and CVD in 3690 community-dwelling older men

Variable	Frailty (n = 563) OR (95% CI) P value	Diabetes (n = 571) OR (95% CI) P value	CVD (n = 1, 362) OR (95% CI) P value
T ≤ 12.1 nmol/liter (348 ng/dl) (n = 1673)	1.82 (1.51, 2.19) <0.001	2.22 (1.85, 2.67) <0.001	1.23 (1.08, 1.41) <0.001
T ≤ 6.40 nmol/liter (184 ng/dl) (n = 190)	2.70 (1.94, 3.74) <0.001	2.76 (2.00, 3.81) <0.001	1.61 (1.20, 2.17) <0.001
DHT ≤ 0.49 nmol/liter (14.2 ng/dl) (n = 204)	1.67 (1.18, 2.37) <0.001	2.50 (1.82, 3.43) <0.001	1.47 (1.10, 1.97) 0.01
E2 ≤ 27.55 pmol/liter (7.5 pg/ml) (n = 126)	1.16 (0.73, 1.84) 0.54	0.88 (0.52, 1.47) 0.62	0.97 (0.67, 1.41) 0.89
Low T (≤6.40 nmol/liter) and DHT (≤0.49 nmol/liter) (n = 74)	3.28 (2.01, 5.36) <0.001	2.77 (1.69, 4.56) <0.001	1.78 (1.11, 2.85) 0.02
Low T (≤6.40 nmol/liter) and E2 (≤27.55 pmol/liter) (n = 51)	1.44 (0.75, 2.77) 0.27	1.09 (0.51, 2.34) 0.83	1.69 (0.96, 2.97) 0.07
Low DHT (≤0.49 nmol/liter) and E2 (≤27.55 pmol/liter) (n = 27)	2.30 (1.00, 5.26) 0.05	0.72 (0.21, 2.39) 0.59	3.48 (1.51, 8.03) <0.001

OR, Age-adjusted odds ratio; CI, confidence interval.

Summary

- T declines with aging
- Accelerated decline with incident chronic illness

Potential benefits of T treatment in
older men with Low T?

Recent studies

The Testosterone trials

- Test the efficacy of T treatment in older men with Low T and one or more clinical abnormalities
- **Specific trials**
 - Physical function trial
 - Sexual function trial
 - Vitality trial
 - Cognitive function trial
 - Anemia trial
 - Cardiovascular trial
 - Bone trial

Participants

Inclusion criteria

- >65 years
- Serum T < 275ng/dl (9.5 nmol/L)

Exclusion criteria

- Prostate Ca
- > risk of prostate ca
- Other causes of hypogonadism
- Medications, high CVS risk

Sexual function trial

- Self reported decreased libido
- <20 DISF-M-II
- Partner willing to have intercourse twice a month
- Primary: change in PDQ Q4
- Secondary: higher scores in IIEF and DISF-M-II

Physical function trial

- Self reported difficulty in walking and a gait speed $<1.2\text{m/s}$ in 6MWT
- Primary: % men who increased walking distance by 50m
- Secondary: higher scores in PF domain of SF-36

Vitality trial

- Self reported low vitality <40 in FACIT fatigue scale
- Primary: % of men with increase in FACIT fatigue scale by 4 points
- Secondary: Change in FACIT 4 scale, PANAS scale, PHQ9 depression scale

Treatment

- T gel 1% or placebo
- Initial dose 5g/day
- Serum T measured at 1,2,3,6,9 months and increased to maintain the concentration within the normal range for young men 19-40 years of age

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*

Testosterone Treatment and Sexual Function in Older Men With Low Testosterone Levels

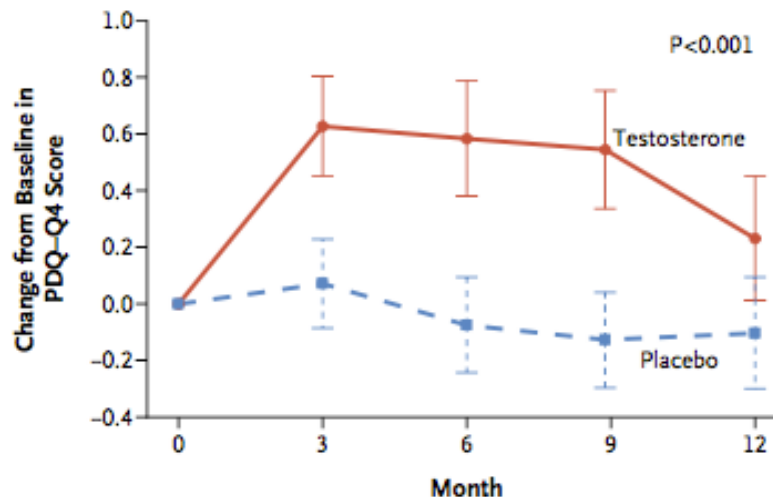
Glenn R. Cunningham, Alisa J. Stephens-Shields, Raymond C. Rosen, Christina Wang, Shalender Bhasin, Alvin M. Matsumoto, J. Kellogg Parsons, Thomas M. Gill, Mark E. Molitch, John T. Farrar, David Cella, Elizabeth Barrett-Connor, Jane A. Cauley, Denise Cifelli, Jill P. Crandall, Kristine E. Ensrud, Laura Gallagher, Bret Zeldow, Cora E. Lewis, Marco Pahor, Ronald S. Swerdloff, Xiaoling Hou, Stephen Anton, Shehzad Basaria, Susan J. Diem, Vafa Tabatabaie, Susan S. Ellenberg, and Peter J. Snyder*

Sexual function trial

Table 1. Sexual Function Trial Outcomes.*

Cohort and Outcome	No. of Men	Baseline Value	Change from Baseline Value				Treatment Effect (95% CI) [†]	Effect Size (95% CI) [‡]	P Value [§]
			Month 3	Month 6	Month 9	Month 12			
Men enrolled in Sexual Function Trial									
Primary outcome: PDQ-Q4 score¶									
Testosterone	230	1.4±1.3	0.6±1.3	0.6±1.5	0.5±1.5	0.2±1.6	0.58 (0.38–0.78)	0.45 (0.30–0.60)	<0.001
Placebo	229	1.4±1.3	0.1±1.1	–0.1±1.2	–0.1±1.2	–0.1±1.4			
Secondary outcomes									
DISF-M-II sexual desire score									
Testosterone	234	11.9±6.7	3.5±6.3	3.5±6.0	4.0±7.4	2.6±6.5	2.93 (2.13–3.74)	0.44 (0.32–0.56)	<0.001
Placebo	236	11.6±6.6	0.7±5.8	0.8±5.6	0.9±5.5	0.0±5.0			
IIEF erectile function score**									
Testosterone	234	8.0±8.2	3.4±6.1	3.3±6.5	3.4±6.9	3.1±6.9	2.64 (1.68–3.61)	0.32 (0.20–0.44)	<0.001
Placebo	236	7.7±8.2	1.0± 5.3	0.5±6.1	0.5±7.1	1.0±6.0			
All Testosterone Trials participants††									
PDQ-Q4 score¶									
Testosterone	387	1.5±1.3	0.7±1.3	0.6±1.6	0.6±1.6	0.3±1.7	0.62 (0.45–0.79)	0.45 (0.33–0.58)	<0.001
Placebo	384	1.5±1.4	0.0±1.2	–0.1±1.3	–0.1±1.3	–0.1±1.4			

A Sexual Activity



No. at Risk

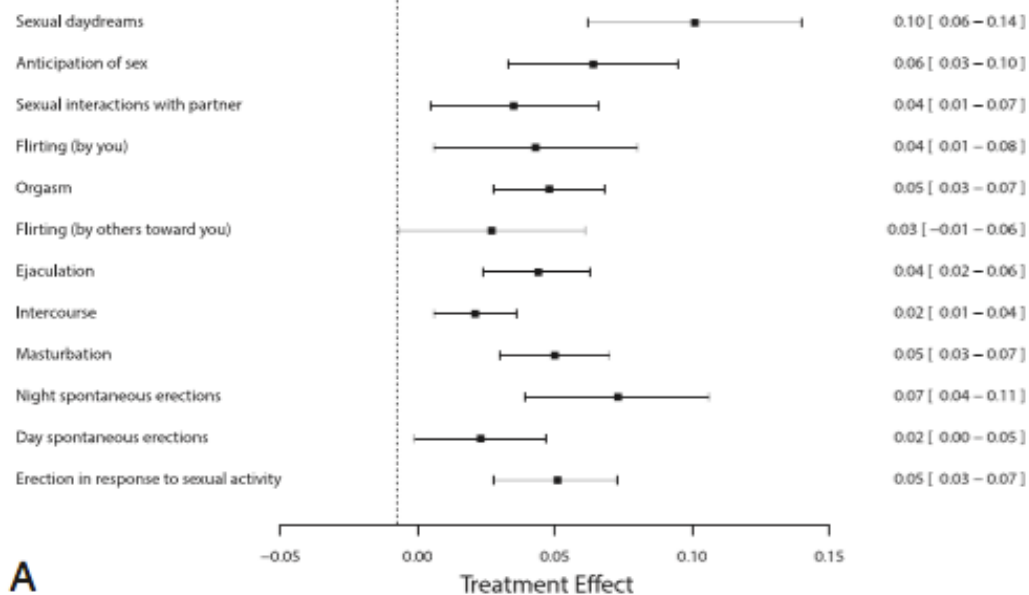
Testosterone	230	205	208	205	193
Placebo	229	198	189	190	193

- Sexual activity increased with T Rx
- Greater T \rightarrow Greater increment in PDQ Q4
- Increased sexual desire
- Increased erectile function

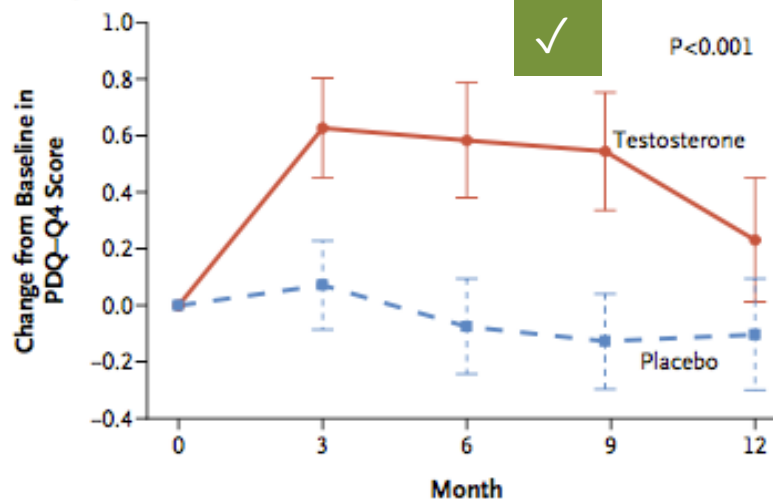
- 10/12 measures in PDQ Q4 improved

PDQ-Q4 Item

Treatment Effect [95% CI]



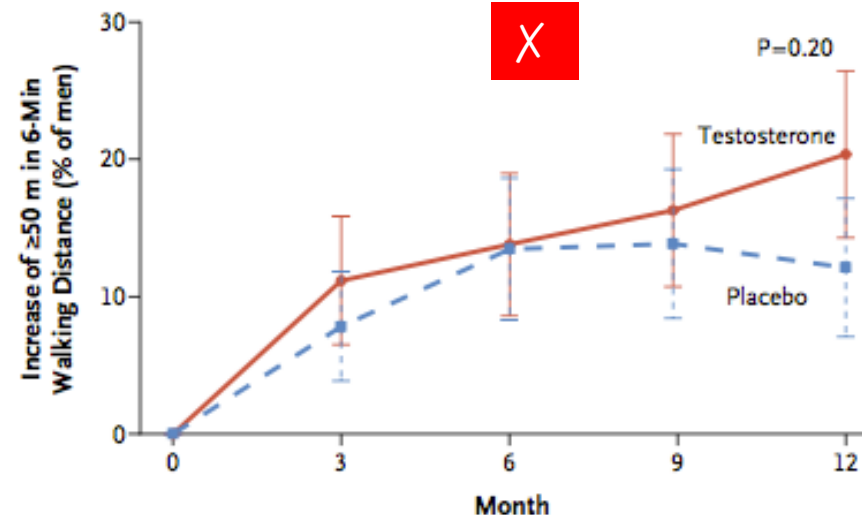
A Sexual Activity



No. at Risk

Testosterone	230	205	208	205	193
Placebo	229	198	189	190	193

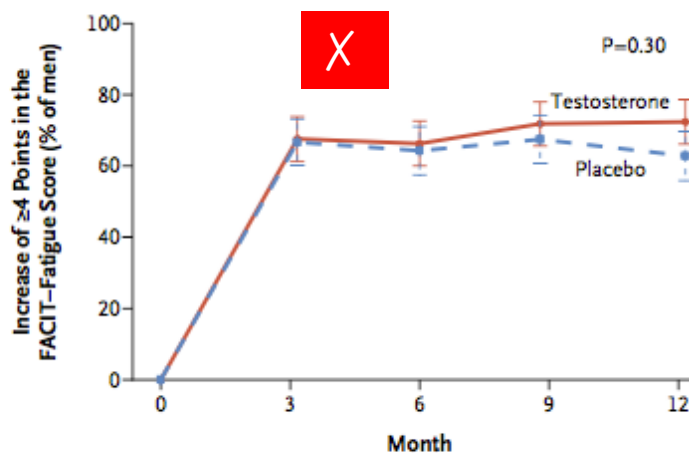
B Walking Ability



No. at Risk

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

C Vitality



No. at Risk

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

Summary

- T treatment
 - increases sexual function in “short term”- but long term effects unknown
 - No improvement in vitality and physical function
- Future- Wait for “The Testosterone trials” long term data

In the interim?

- Trial of Testosterone?
- Address modifiable risk factors

Conclusion

- Pathological androgen deficiency
 - Clinical diagnosis confirmed by hormonal evaluation
 - T replacement at physiological doses
- T treatment in older men is controversial
 - Trial of T for limited period maybe warranted