

Men Getting Older – Will Testosterone Keep Him Young?

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Disclosures

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- Royalties
 - UpToDate

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Charles Edouard Brown-Séquard



- Rejuvenating effects of self-injecting aqueous extracts (*inactive*) from dog and guinea pig testes
- ↑ “strength... expulsion of fecal matters... intellectual labour”

Brown-Séquard CE, Lancet 2: 105-107, 1889

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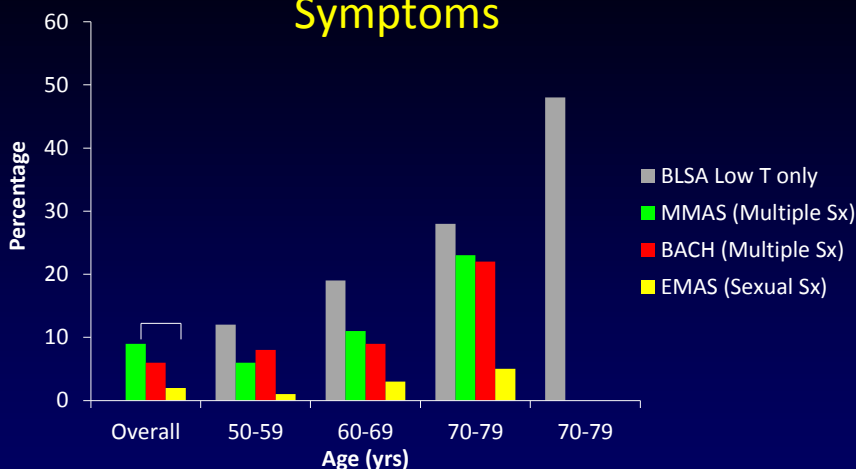
Male Hypogonadism Diagnosis

- Clinical manifestations of androgen deficiency AND consistently low T level
 - Symptoms & signs
 - T @ least x 2, preferably in morning, fasting
- Symptoms alone or low T level alone \neq hypogonadism
 - Result in over-diagnosis

Bhasin S, et al, J Clin Endocrinol Metab 95:2536-2559, 2010

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Prevalence of Low T Alone vs Low T with Symptoms



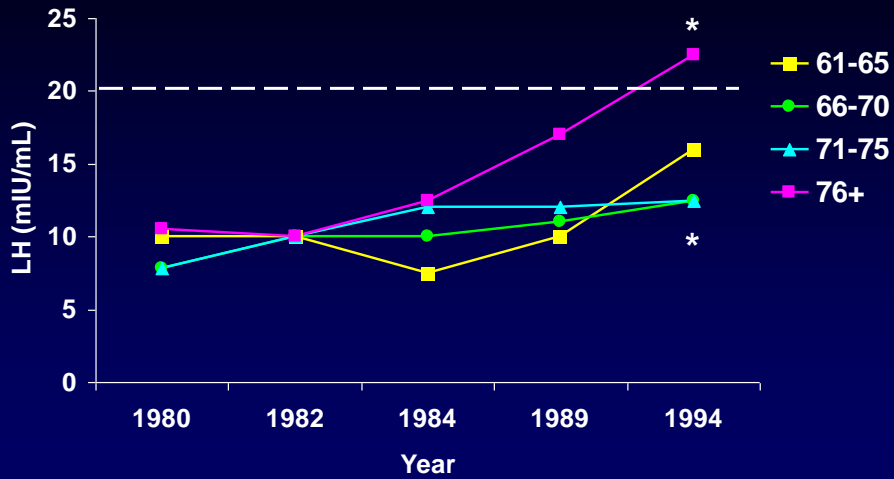
Harman SM, et al, J Clin Endocrinol Metab 86:724-731, 2001; Araujo A, et al, J Clin Endocrinol Metab 89:5920-5926, 2004; Araujo A, et al, J Clin Endocrinol Metab 92:4241-4247, 2007; Wu FC, et al, N Engl J Med 363:123-135, 2010

Age-Related Hypogonadism

- Symptoms non-specific
- Modest ↓ T levels may not be hypogonadism
- Combined 1° and 2° hypogonadism
 - 1° hypogonadism – organic (age)
 - ↓ Leydig cell number and T response to hCG
 - 2° hypogonadism – functional (comorbidity)
 - Obesity, co-morbid illness, medications
 - FSH and LH normal (2° – most common) or slightly ↑ (1° – advanced old age)
- High prevalence CV and prostate disease

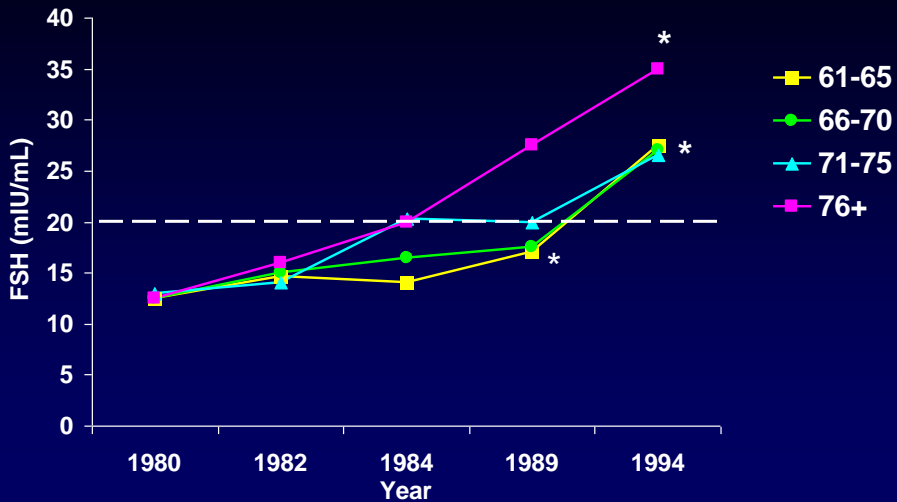
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Longitudinal Changes in Serum LH Levels in Older Men



Morley JE, et al, Metabolism 46:410-413, 1997

Longitudinal Changes in Serum FSH Levels in Older Men



Morley JE, et al, Metabolism 46:410-413, 1997

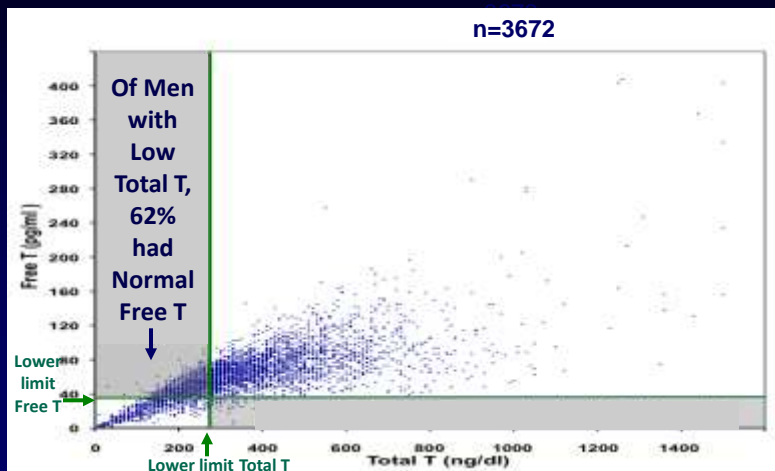
Causes of Symptoms or Low T Level Other Than Hypogonadism

- Symptoms & signs not caused by low T level
 - Depression, medications, comorbidities
- Low T level not caused by hypogonadism
 - Transient ↓T (illness, drugs, malnutrition)
 - Biological T variability (lower T in PM and non-fasting; day-to-day variation 30%)
 - Low SHBG (obesity) → ↓ total T but normal free T

Matsumoto AM, Endocrinol Metab Clin N Am 42:271-286, 2013

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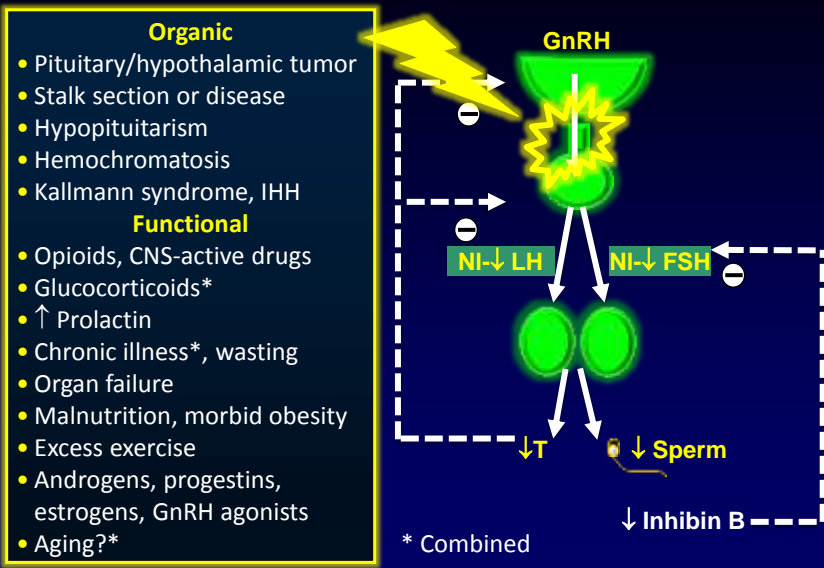
Performance of Total T to Predict Calculated Free T in Veterans



Anawalt BD, et al, J Urol 187:1369-1373, 2012

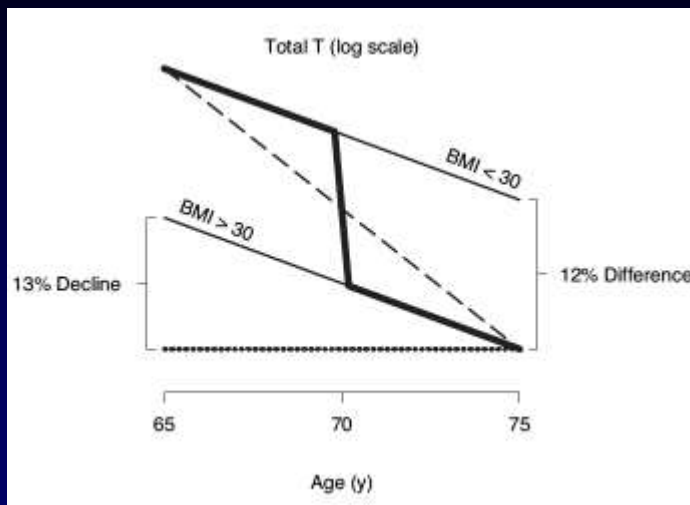
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Causes of 2° Hypogonadism



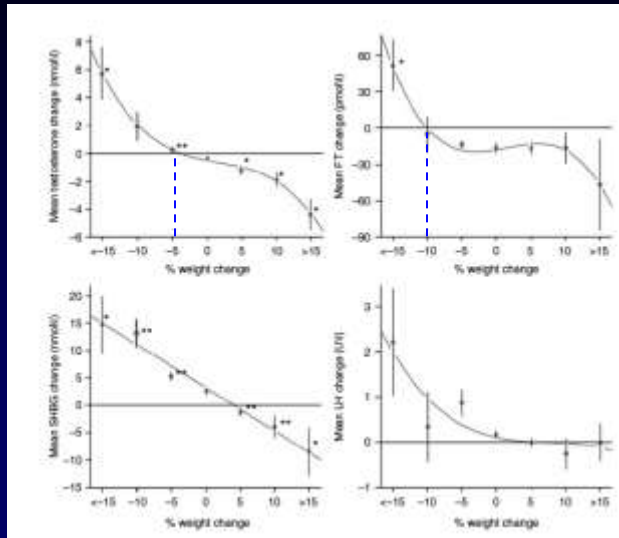
Matsumoto AM, Endocrinol Metab Clin N Am 42:271-286, 2013

Effect of Obesity Onset on Decline in T Levels MMAS



Travison T, et al, Eur J Endocrinol 92:549-555, 2007

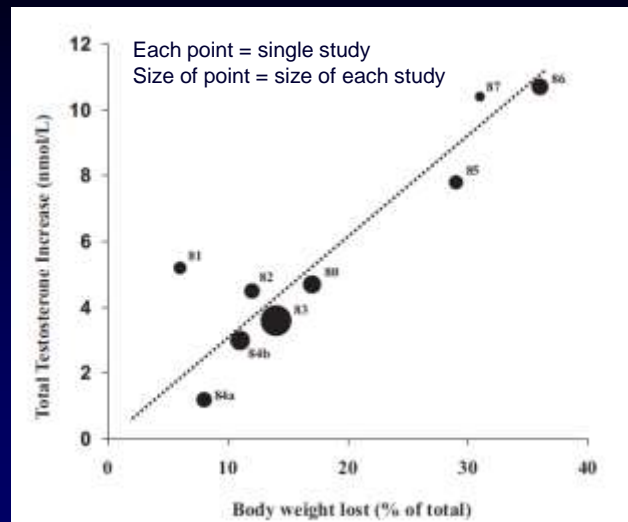
Longitudinal Δ in Weight vs. Δ in Hormones EMAS



Comacho EM, et al, Eur J Endocrinol 168:445-455, 2013

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Effect of Weight Loss on T Levels



Grossmann M, J Clin Endocrinol Metab 96:2341-2353, 2011

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Limitations of Previous T Treatment Trials in Older Men

- Heterogenous
 - Healthy without symptoms/signs
 - Men with normal T levels
- Short-term
- T Rx → T levels too low or high
- Small n's (under-powered)
- Surrogate, not optimal measures

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The Testosterone Trials

- Randomized, double-blind, placebo-controlled trial of T vs. placebo x 1 yr
- 790 men \geq 65 yrs, symptoms/signs, T \leq 275 ng/dL x 2, low risk prostate cancer
- 7 coordinated trials (12 sites):
 - Physical function, sexual function, vitality
 - Cognitive function, anemia, cardiovascular, bone
- T gel 5 g/d → adjusted to T 500-800 ng/dL

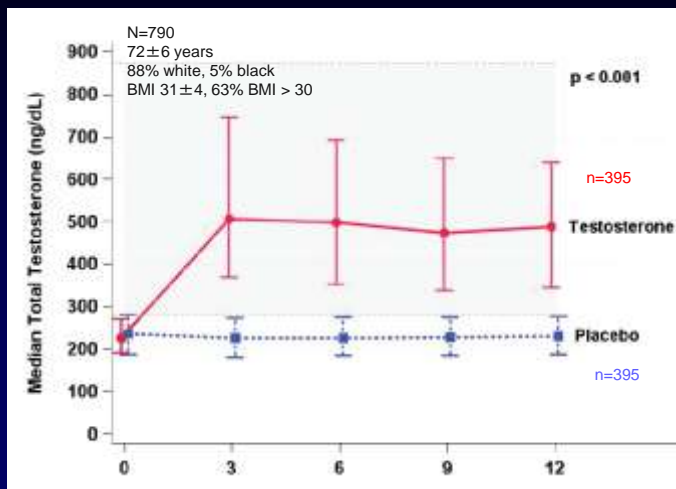
The T Trials Screening and Recruitment

- 51,085 screened
- 4700/21,940 low T on 1st blood sampling (21%)
- 1490/2163 low T on 2nd blood sampling (69%)
- Overall inclusion by T level 14.7%

Cauley JA et al, J Gerontol A Biol Sci Med Sci 70:1105-1111, 2015

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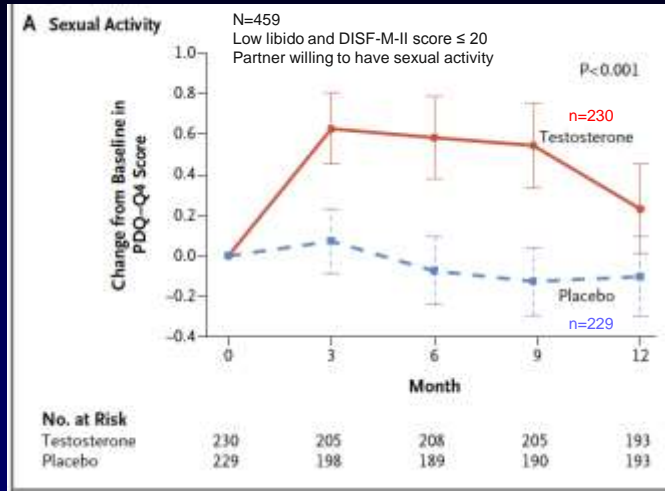
The T Trials Total Testosterone in All Men



Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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The T Trials Sexual Function Trial



Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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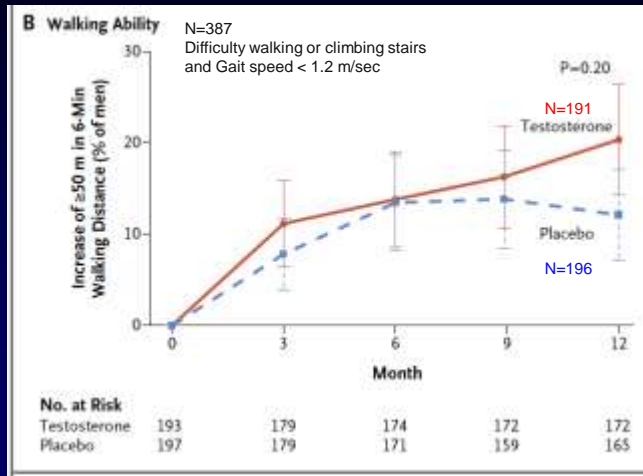
The Testosterone Trials T vs. Placebo in Sexual Function Trial

- 1^o in Sexual Function Trial men
 - Moderate \uparrow sexual activity by PDQ-4
- 2^o in Sexual Function Trial men
 - Moderate \uparrow libido by DISF-M-II and erectile function by IIEF
- 2^o in All T Trials men
 - Moderate \uparrow sexual activity by PDQ-4
- Global impression of improved libido

Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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The Testosterone Trials Physical Function Trial



Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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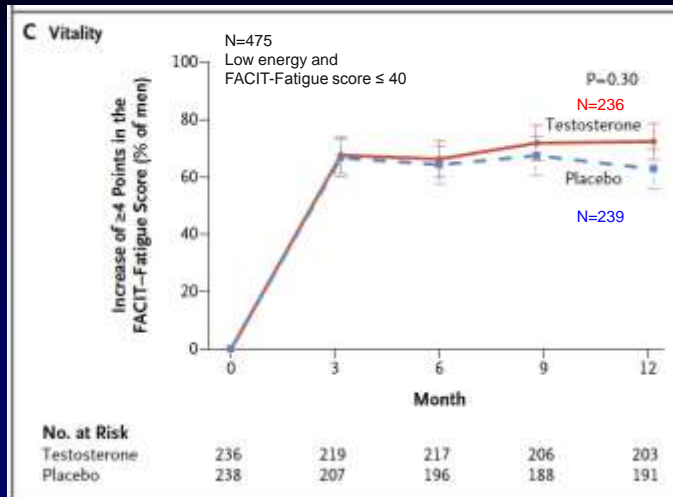
The Testosterone Trials T vs. Placebo in Physical Function Trial

- 1^o in Physical Function Trial men
 - No $\uparrow \geq 50$ m on 6 minute walk
- 2^o in All T Trials men
 - Small $\uparrow \geq 50$ m and total on 6 minute walk
 - Small \uparrow physical function by $\uparrow \geq 8$ and total score on PF-10
- Global impression of improved walking ability

Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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The Testosterone Trials Vitality Trial



Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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The Testosterone Trials T vs. Placebo in Vitality Trial

- 1^o in Vitality Trial men
 - No $\uparrow \geq 4$ m on FACIT-Fatigue
- 2^o in Vitality T Trial men
 - Small \uparrow positive and \downarrow negative affect by PANAS
 - Small \downarrow depression symptoms by PHQ-9
- 2^o in All T Trials men
 - Small \uparrow in FACIT-Fatigue score
- Global impression of improved energy

Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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The Testosterone Trials T vs. Placebo Adverse Events

Event	Placebo (N= 394)	Testosterone (N= 394)
	<i>no. of participants</i>	
Prostate-related event		
Increase in PSA level by ≥ 1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS > 19 †	26	27
Hemoglobin ≥ 17.5 g/dl	0	7
Cardiovascular event‡		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other§	6	7

Snyder PJ, et al, N Eng J Med 374:611-624, 2016

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Low T Levels in Older Men Take Homes

- Consider other causes of symptoms and low T
 - Depression, medications, comorbidities
 - Transient \downarrow T, biological T variability, low SHBG
- Age-related hypogonadism 1° and 2°
 - Potentially reversible functional 2° causes of low T
- T treatment in older men with hypogonadism
 - \uparrow Sexual function and may \uparrow physical function, mood, depressive symptoms (The Testosterone Trials)
 - Effects on cognitive function, cardiovascular disease, bone and anemia forthcoming

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