Testosterone Deficiency Syndrome in Older Adult Males

FEBRUARY 12, 2025

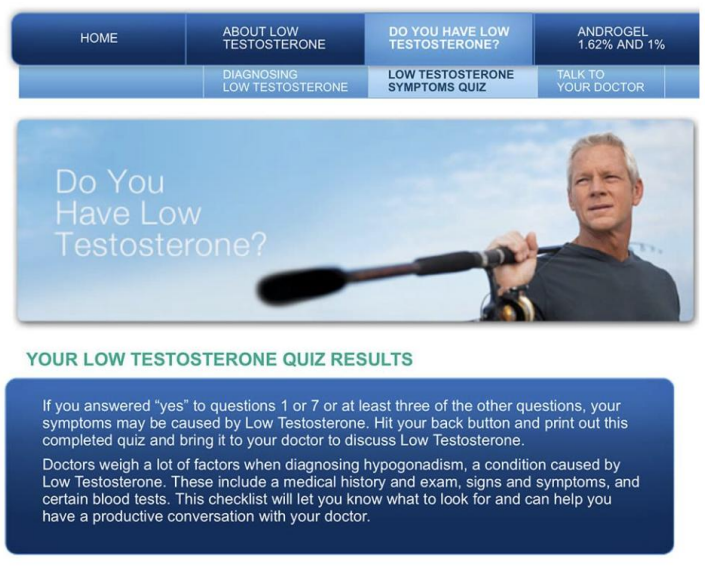
Objectives

- Review the HPG pathway of testosterone production in primary and secondary hypogonadism
- Understand the investigation of testosterone deficiency and its limitations
- Review the potential benefits and risks of testosterone deficiency in older adult males

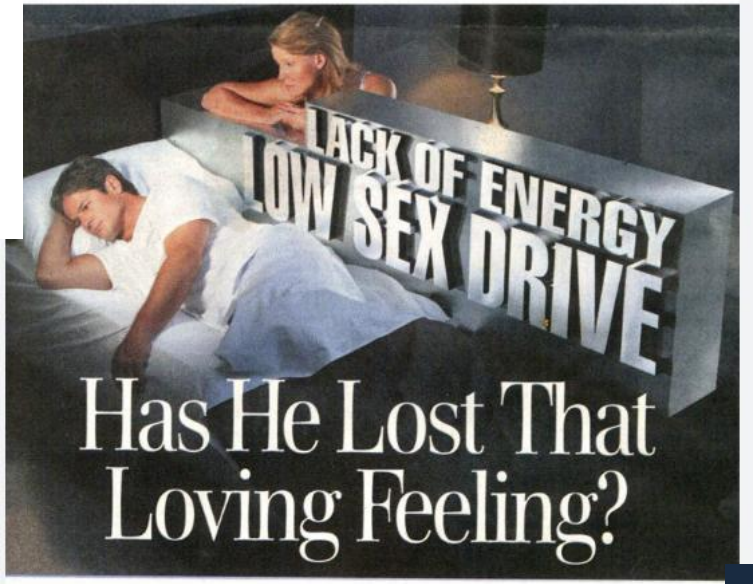
- Bayer Video.

Case: Mr. T

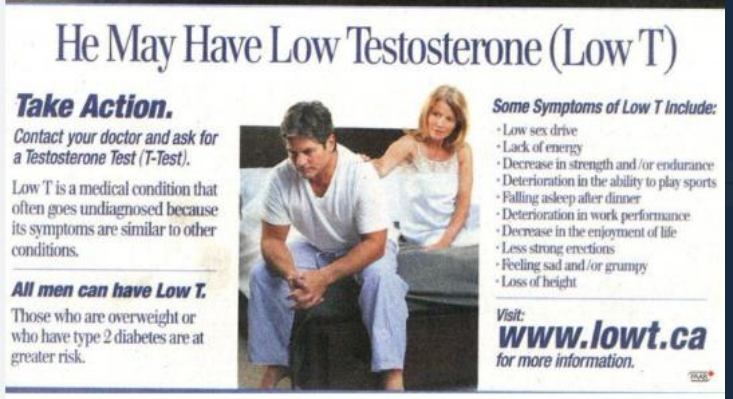
- 65 yr old new patient
- Taking Androgel 10 g daily since the age of ? 50 yrs for low libido
- No documentation in his prior chart on diagnosis, testing , testosterone levels being monitored
- NSTEMI 2021 with 100% thrombus to RCA
- Atrial fibrillation
- Quit smoking age 44, no diabetes, no obesity
- Meds: Rosuvastatin, Apixaban, Perindopril, Bisoprolol, Androgel
- “Please refill my testosterone….”


HOME
ABOUT LOW TESTOSTERONE
DO YOU HAVE LOW TESTOSTERONE?
ANDROGEL 1.62% AND 1%
DIAGNOSING LOW TESTOSTERONE
LOW TESTOSTERONE SYMPTOMS QUIZ
TALK TO YOUR DOCTOR
Do You Have Low Testosterone?
YOUR LOW TESTOSTERONE QUIZ RESULTS
If you answered "yes" to questions 1 or 7 or at least three of the other questions, your symptoms may be caused by Low Testosterone. Hit your back button and print out this completed quiz and bring it to your doctor to discuss Low Testosterone.
Doctors weigh a lot of factors when diagnosing hypogonadism, a condition caused by Low Testosterone. These include a medical history and exam, signs and symptoms, and certain blood tests. This checklist will let you know what to look for and can help you have a productive conversation with your doctor.


Testosterone Pellets for Low-T
GET BACK IN THE GAME
ENERGY. FOCUS. LIBIDO.


LACK OF ENERGY
LOW SEX DRIVE
Has He Lost That Loving Feeling?


BE A MAN!
T BOOSTER
ENHANCE!
HERBAL T


He May Have Low Testosterone (Low T)
Take Action.
Contact your doctor and ask for a Testosterone Test (T-Test).
Low T is a medical condition that often goes undiagnosed because its symptoms are similar to other conditions.
All men can have Low T.
Those who are overweight or who have type 2 diabetes are at greater risk.
Some Symptoms of Low T include:
• Low sex drive
• Lack of energy
• Decrease in strength and/or endurance
• Deterioration in the ability to play sports
• Falling asleep after dinner
• Deterioration in work performance
• Decrease in the enjoyment of life
• Less strong erections
• Feeling sad and/or grumpy
• Loss of height
Visit:
www.lowt.ca
for more information.

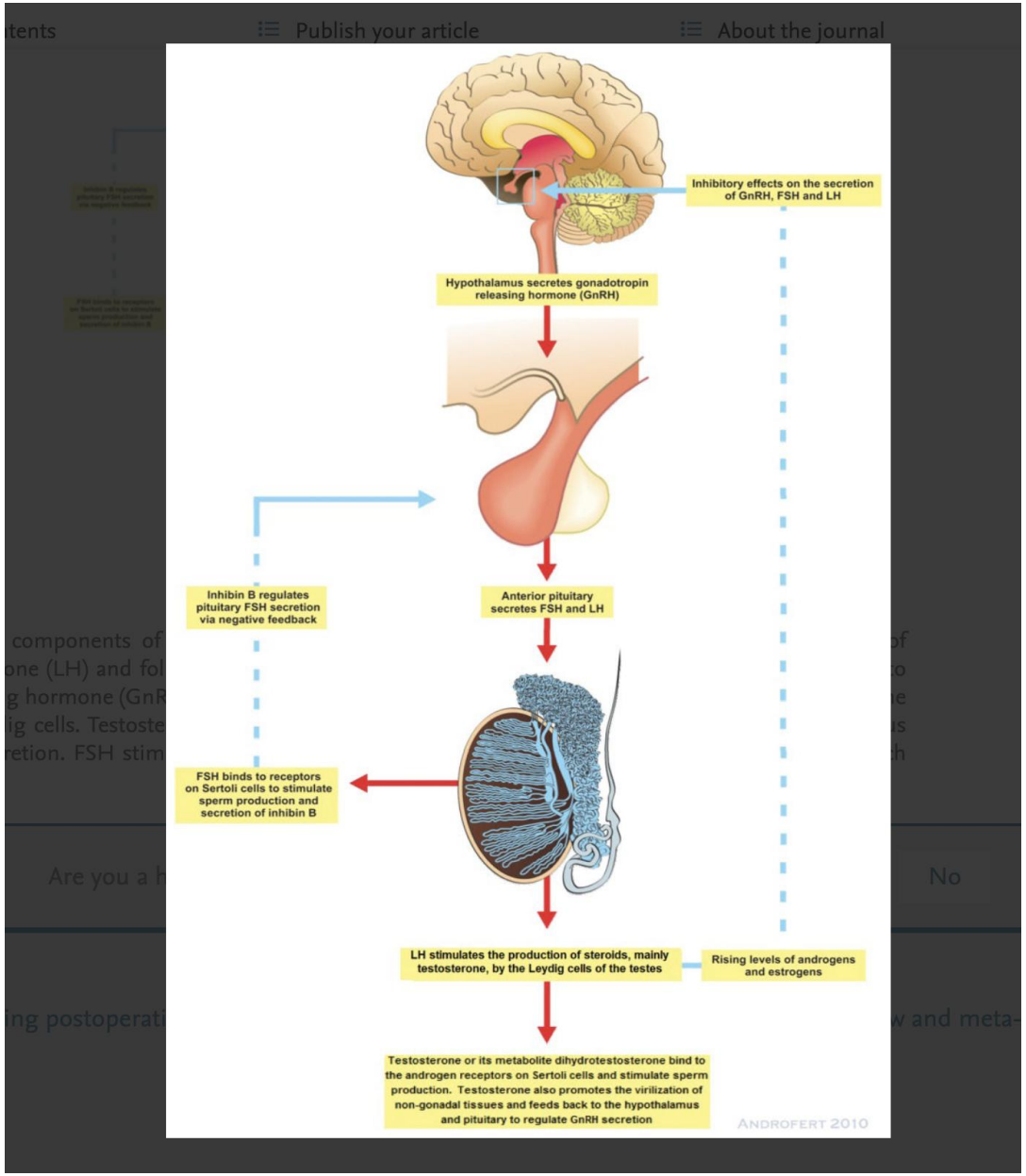

2013 All-Star Large Pharma Marketing Team of the Year: AndroGel
Vim, vigor and sales drive: Uncovering the market for what has been a taboo topic is a tricky goal, but this brand did it. Larry Dobrow reports
Larry Dobrow | January 2, 2013 | 5:00 AM
5 POINT TUNE UP
ALL-STAR LARGE PHARMA MARKETING TEAM OF THE YEAR: ANDROGEL

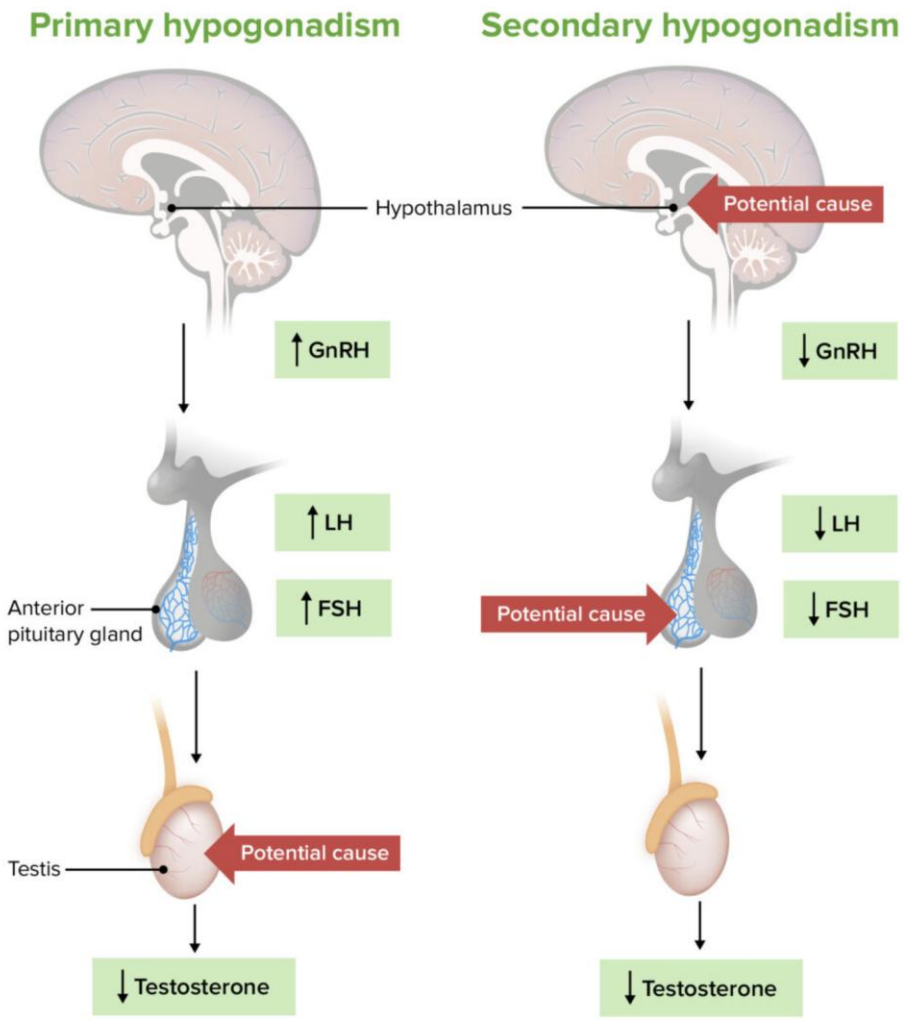

Low T
What Is Low T
Do You Have Low T
What You Can Do
Partner
TALK TO YOUR DOCTOR
TAKE THE LOW T QUIZ
Français
-A | A | +A
DO YOU HAVE
Low T

Why is this so confusing?

- Varying definitions of testosterone deficiency
- Variable onset, degree and relevance of T decline amongst men
- Contributing variables – ethnicity, fat, stress, medications, diet, environment, comorbidity
- No valid symptom score
- Variability in assays and lack of validated reference ranges for testosterone (T)
- Misinterpretation of diagnostic tests and what to order
- Controversy regarding T and cardiovascular health and other risks

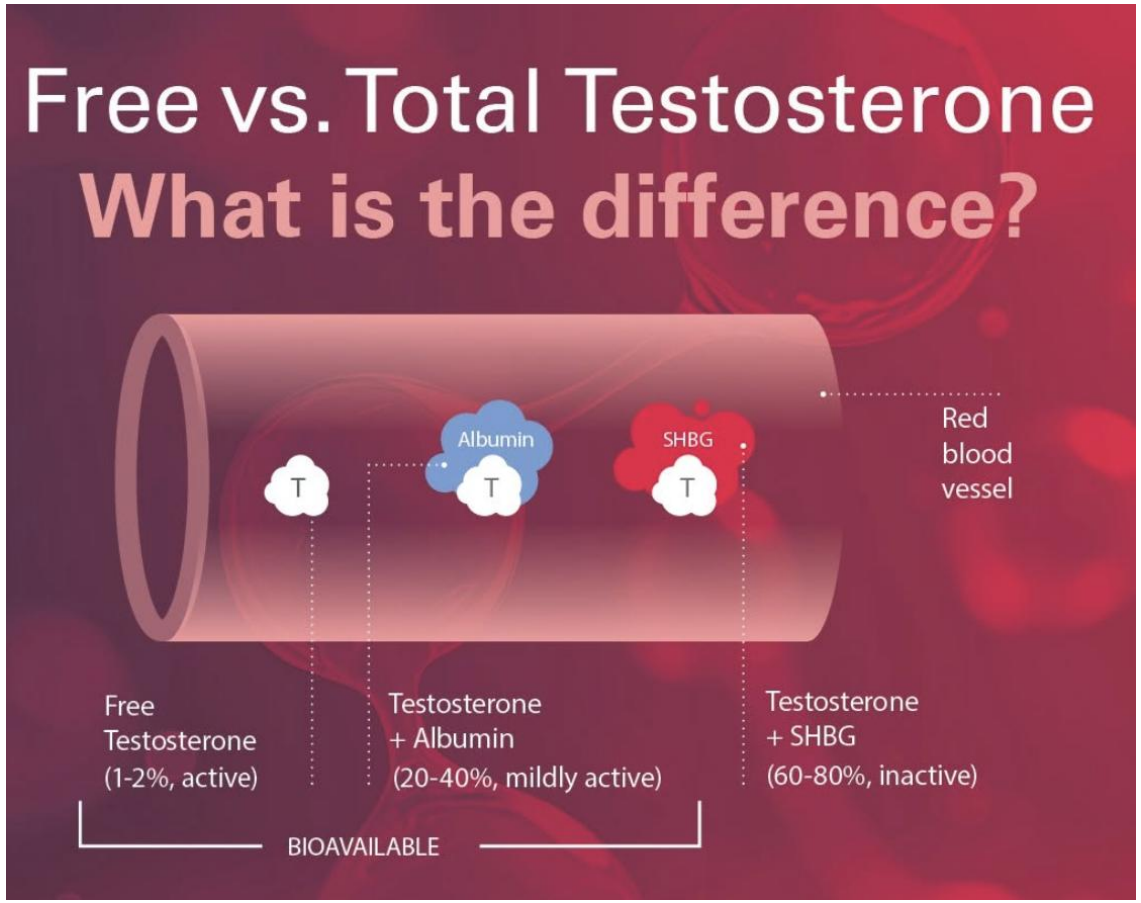
Hypothalamic-Pituitary-Gonadal Axis




Primary hypogonadism
Secondary hypogonadism
Hypothalamus
Potential cause
GnRH
GnRH
LH
LH
Anterior pituitary gland
FSH
Potential cause
FSH
Testis
Potential cause
Testosterone
Testosterone

Testosterone

- Total Testosterone
- Bioavailable Testosterone
- Free Testosterone
- Sex Hormone Binding Globulin



Testosterone Deficiency Syndrome in Older Adult Males (Late-Onset Hypogonadism)

- **Documented low Total Testosterone (TT) + Clinical symptoms**

- Prevalence[2]:
  - Estimated at 25% of M (40-62y)
    - 4-12% (age 50-59)
    - 9-23% (age 60-69)
    - 28-49% (age 70+)

Etiology of Testosterone Deficiency

Primary Hypogonadism	Secondary Hypogonadism
Orchitis (mumps)	Hypothalamic or pituitary tumor
Klinefelters	Hemochromatosis
Cryptorchidism	Radiation/infiltrative disease of the H/P
Testicular torsion	Kallman's
Testicular chemo/radiation	
Advanced age	

Etiology of Testosterone Deficiency: Associated Diseases

- Diabetes
- Obesity
- Metabolic syndrome
- HIV
- Hyperprolactinemia
- ESRD
- Liver disease
- COPD
- Sleep apnea
- Severe hypothyroidism
- Nutritional deficiency/excessive exercise

Causes of Testosterone Deficiency Medications/Substances

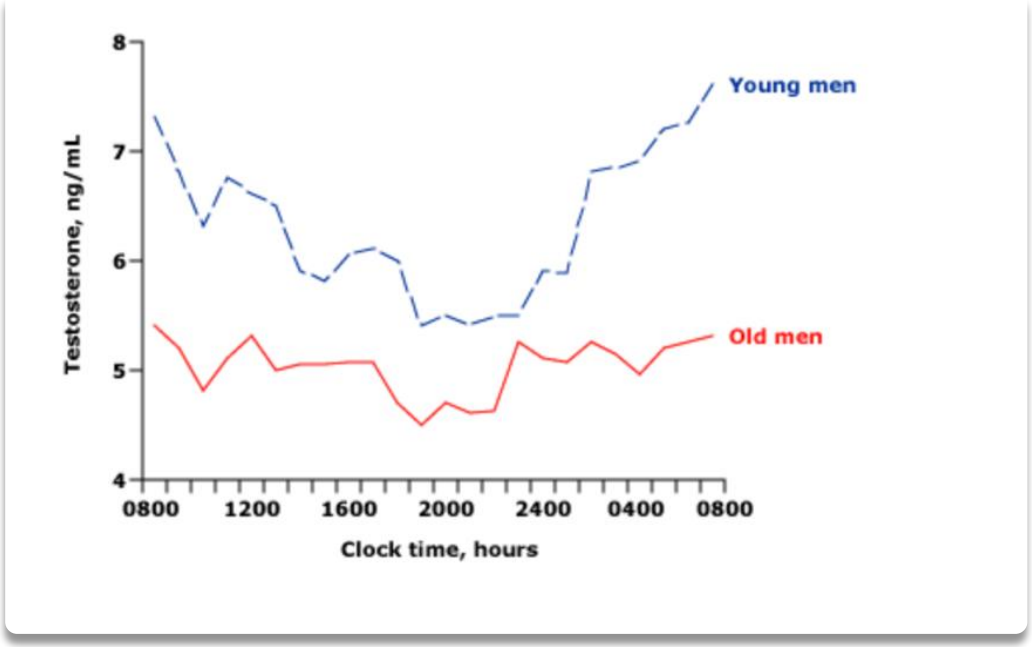
- Opioids
- Glucocorticoids
- Anabolic steroids
- Estrogens
- Marijuana
- Alcohol
- Anticonvulsants (valproic acid, phenytoin)
- Androgen deprivation (finasteride, bicalutamide)

Testosterone Deficiency Syndrome in Older Adult Males

- Total T declines by 0.5% / yr starting at age 35
- Approx 50% of men > 80 have T < 12
- Increase SHBG
- Dec GnRH
- Dec Leydig cells and function (ischemic)

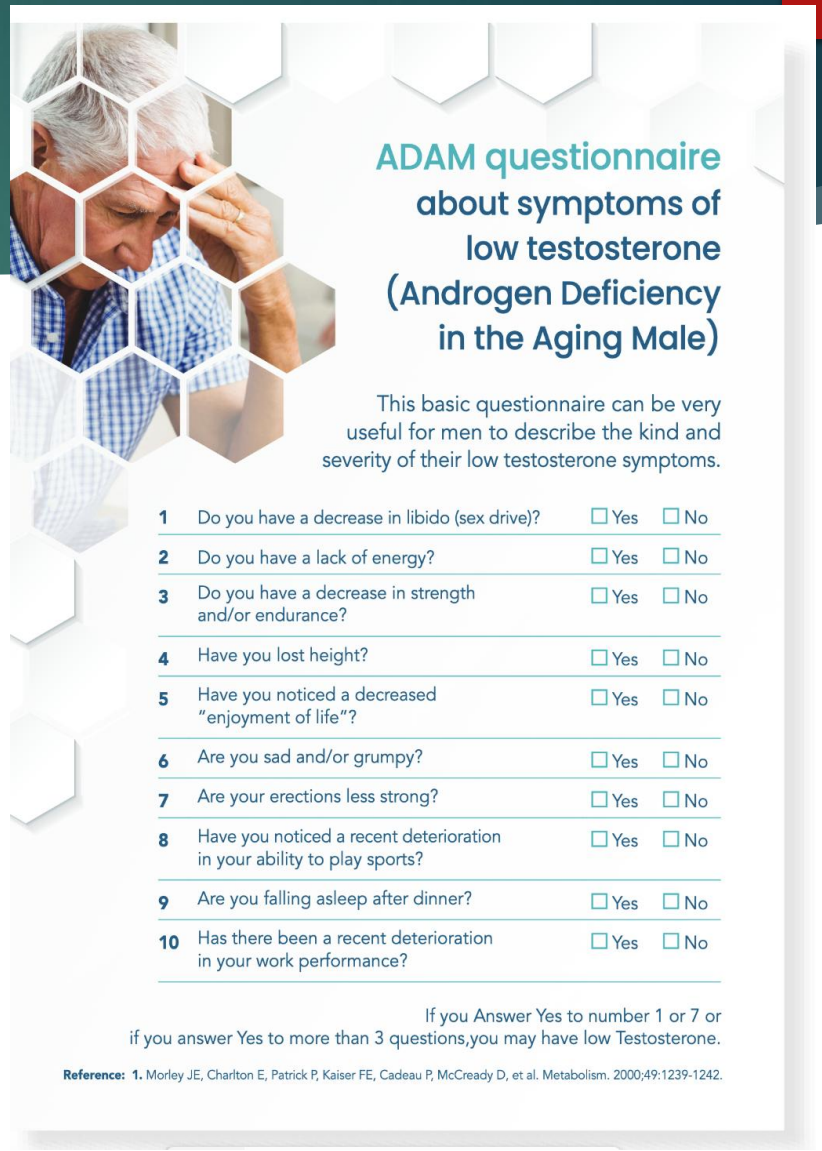
BUT

- European Male Aging Study[3]
  - Only 2.5% of males 40-79 had low T < 11 nmol/L + 3 sexual symptoms
  - Only 0.9% had T < 8 nmol/L



History

- Symptoms:
  - Sexual
    - Reduced libido (most specific)
    - Erectile dysfunction
    - Decreased performance
  - Fatigue
  - Psychiatric
    - Depression
    - Irritability
    - Insomnia
  - Hot flashes



ADAM questionnaire about symptoms of low testosterone (Androgen Deficiency in the Aging Male)

This basic questionnaire can be very useful for men to describe the kind and severity of their low testosterone symptoms.

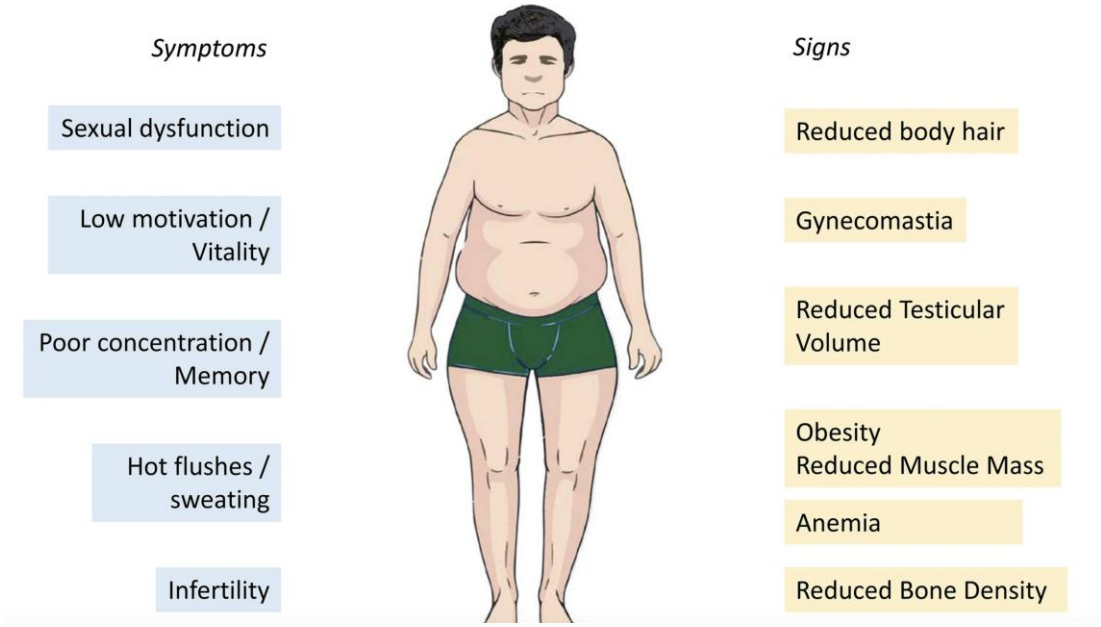
1	Do you have a decrease in libido (sex drive)?	☐ Yes	☐ No
2	Do you have a lack of energy?	☐ Yes	☐ No
3	Do you have a decrease in strength and/or endurance?	☐ Yes	☐ No
4	Have you lost height?	☐ Yes	☐ No
5	Have you noticed a decreased "enjoyment of life"?	☐ Yes	☐ No
6	Are you sad and/or grumpy?	☐ Yes	☐ No
7	Are your erections less strong?	☐ Yes	☐ No
8	Have you noticed a recent deterioration in your ability to play sports?	☐ Yes	☐ No
9	Are you falling asleep after dinner?	☐ Yes	☐ No
10	Has there been a recent deterioration in your work performance?	☐ Yes	☐ No

If you Answer Yes to number 1 or 7 or if you answer Yes to more than 3 questions,you may have low Testosterone.

Reference: 1. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, et al. Metabolism. 2000;49:1239-1242.

Physical Exam

- Increased visceral fat
- Decreased muscle bulk and strength
- Gynecomastia
- Hair loss – facial, axillary, pubic
- Gonadal atrophy
  - Testes < 6 mL
- Decreased bone density/osteopenia
- Anemia

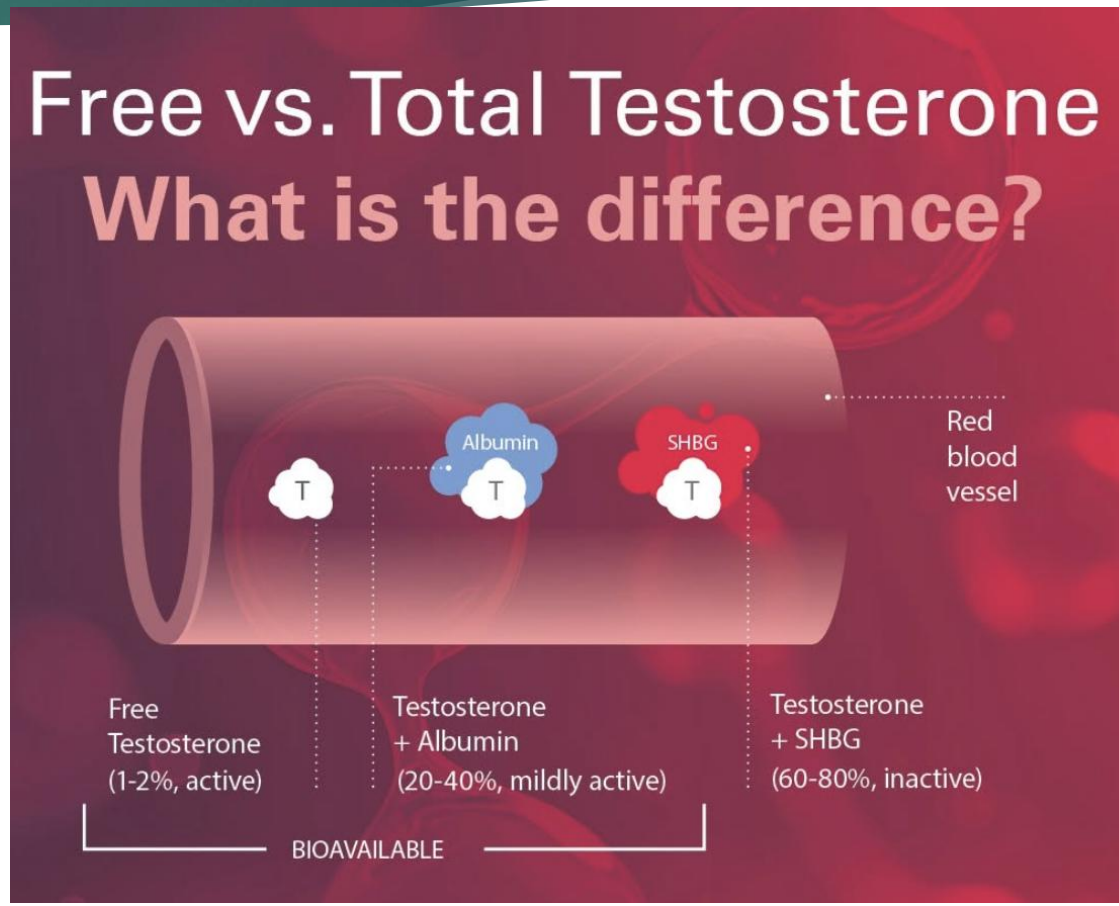


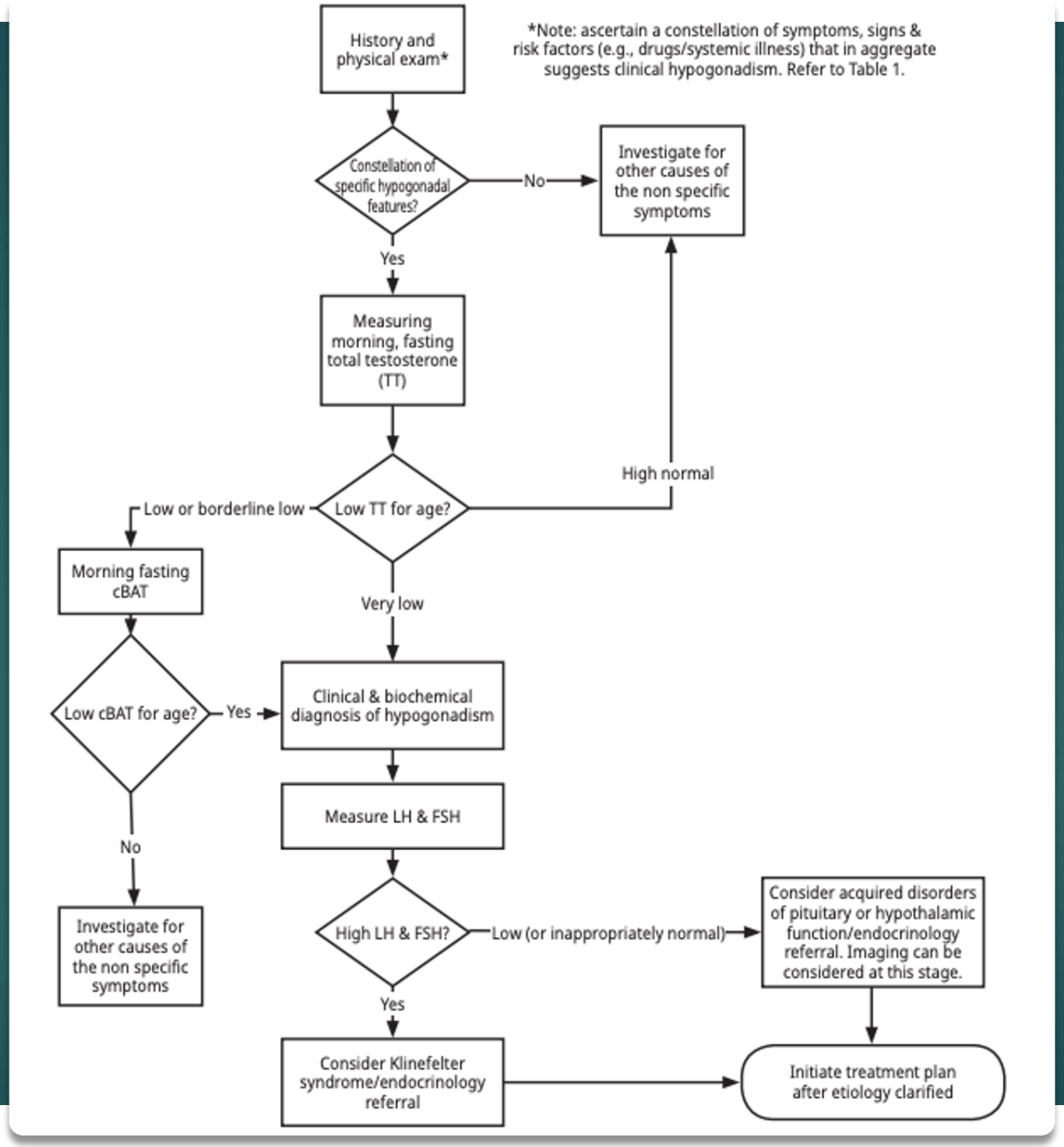
Investigation:

- Testosterone
  - Total Testosterone (TT)
    - Serum
    - Fasting
    - Within 3 hours of waking (7-11 am)
    - Not when acutely ill or hospitalized
  - Deficiency:
    - TT < 6 nmol/L (> 50 yrs old) (2015)
    - TT < 10 nmol/L (Canadian Urologic Association, 2021)

Investigation

- If borderline or equivocal Total Testosterone:
  - Repeat TT
  - Bioavailable Testosterone
  - Free Testosterone




History and physical exam*
*Note: ascertain a constellation of symptoms, signs & risk factors (e.g., drugs/systemic illness) that in aggregate suggests clinical hypogonadism. Refer to Table 1.
Constellation of specific hypogonadal features?
No
Investigate for other causes of the non specific symptoms
Yes
Measuring morning, fasting total testosterone (TT)
Low TT for age?
High normal
Low or borderline low
Morning fasting cBAT
Very low
Low cBAT for age?
Yes
Clinical & biochemical diagnosis of hypogonadism
Measure LH & FSH
No
Investigate for other causes of the non specific symptoms
High LH & FSH?
Low (or inappropriately normal)
Consider acquired disorders of pituitary or hypothalamic function/endocrinology referral. Imaging can be considered at this stage.
Yes
Consider Klinefelter syndrome/endocrinology referral
Initiate treatment plan after etiology clarified

Additional Investigations

Tests for Etiology/Associated conditions	Baseline Tests for TRT
SHBG	PSA
FSH & LH	Hct
Cr	
ALT, ALP	
A1C & lipids	
Hb	
Prolactin	
TSH, free T4	
Ferritin (hemochromatosis, anemia)	
Urine for opiates	

Treat Associated Comorbidities:

- Type 2 diabetes
- Obesity
- Sleep apnea
- Hemochromatosis
- Medications
- Extreme nutritional deficiencies and anorexia

Obesity and hypogonadism

- Obesity lowers T by:
  - lowers LH
  - Increased aromatization of T to estrogen in adipose
  - Lowers SHBG
  - Higher resistance to leptin
- Weight loss, bariatric surgery, exercise can increase T
  - > 10% wt loss can inc T over 2-4 yrs

Treatment

Who to treat:

- Only with low T AND symptomatic
- Target mid-normal range (T = 14-17 nmol/L) weak recommendation
- Treat symptoms
- Consider 3m trial of treatment in those with symptoms but borderline T level
- Anemic – low T and no other etiology
- Chronic glucocorticoids or opioids

Contraindications:

- Allergy/hypersensitivity
- Unstable cardiovascular disease
- Metastatic or high risk prostate Ca
- Breast cancer
- Desiring fertility preservation

Testosterone Formulations

Generic	Trade	Dosage	Comments
INJECTABLE			
Testosterone Enanthate	Delatestryl	100-200 mg IM q2 weeks OR 50-100 mg IM q1 week	Cost effective Wide fluctuations higher risk for polycythemia
Testosterone Cypionate	Depo-testosterone	100-200 mg IM q2 weeks OR 50-100 mg IM q1 week	Cost effective Wide fluctuations higher risk for polycythemia
ORAL			
Testosterone Undecanoate	Andriol	120-160 mg/d divided BID	Short half life Clinical and biochemical variability
TRANSDERMAL			
Patch	Androderm	2.5 – 5 mg/d	Rash Variable absorption $$
Gel	Androgel Testim	5-10 g/day	Rash; Risk of transfer; $$
NASAL GEL	Natesto	5.5 mg BID	$$

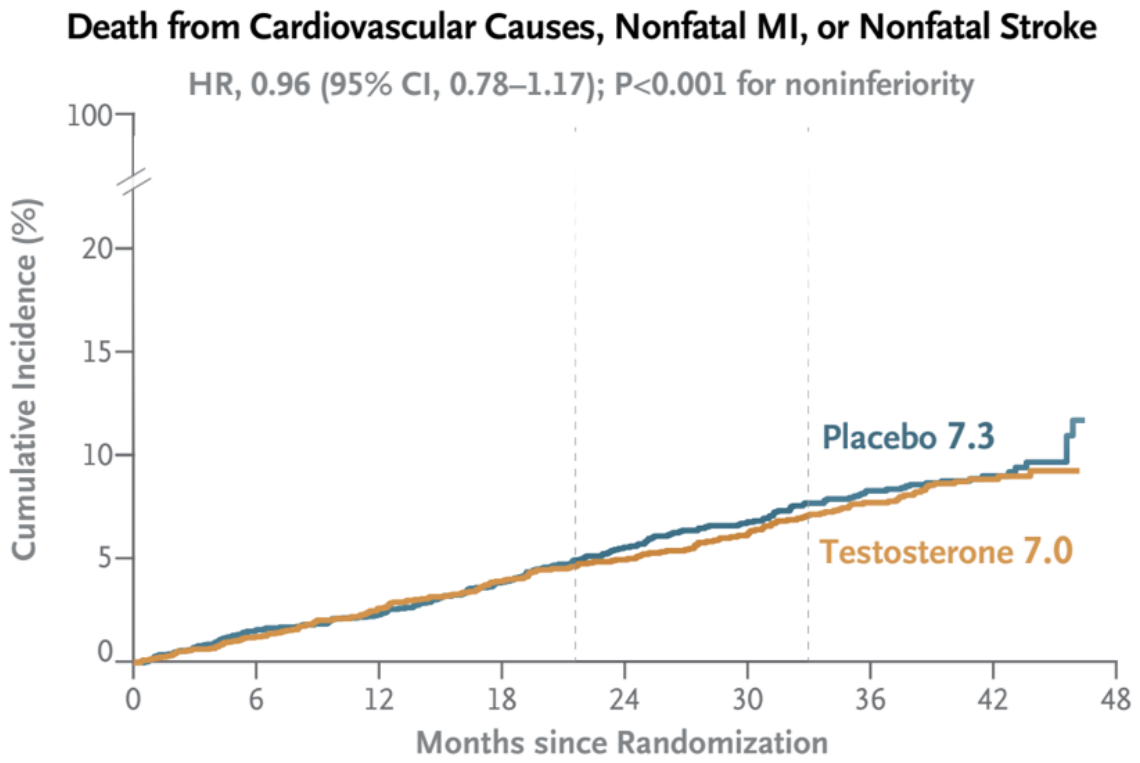
Treatment Risks?
Testosterone and Cardiovascular events

- Traverse Trial [3]
  - 2018-2023
  - RCT, double blind, placebo controlled
  - N = 5204
  - Mean age = 63.3 y
  - Included subjects at high CV risk
  - Randomized to 1.62% T gel (40.5 mg) vs. placebo for 33 months
  - Goal was T titrate to 12-26 nmol/L **(avg T achieved = 12.8)**
  - Assess risk for MACE
  - Primary outcome of CV event (non-fatal MI, non-fatal CVA or CV death)

Treatment Risks?
Testosterone and Cardiovascular events

No increased risk of major

Adverse CV event

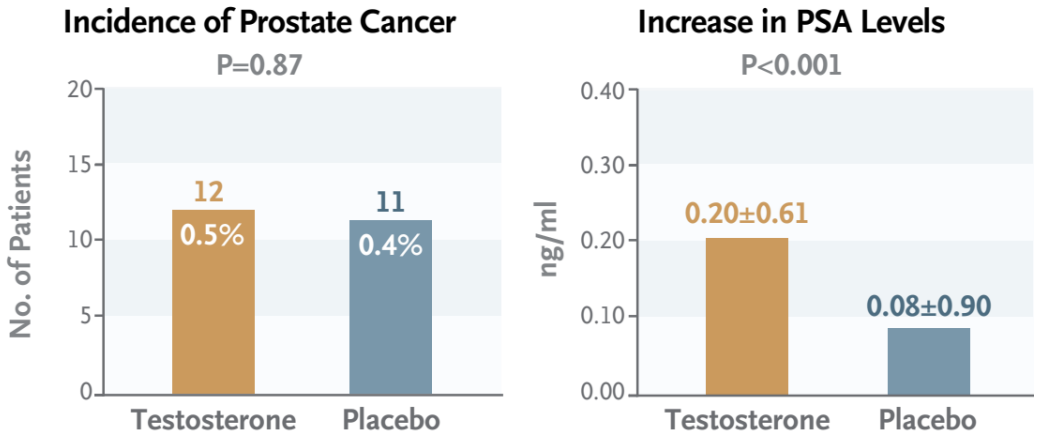


Treatment Risks?
Testosterone & Prostate Cancer

- Testosterone Trials (2016)
  - 65 yrs +
  - N = 790
  - 12 mths of treatment
  - 1 Prostate Ca

No increased risk of prostate Cancer

- Traverse Trial (2018-2023)
  - N = 5204
  - 63.3 yrs
  - 22 mths of T gel vs placebo

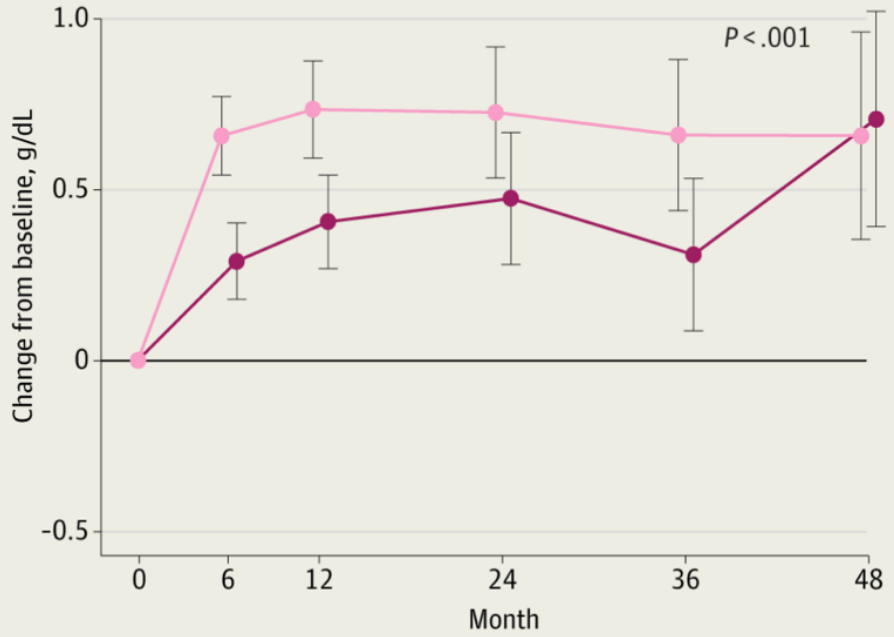


Additional Treatment Benefits

- Traverse Trial Benefits
  - Anemia corrected
  - Reduced depression
  - Improved mood and energy
  - Libido
- No Benefits:
  - Cognition
  - Sleep quality
  - Diabetes
  - Fracture

FINDINGS

The proportion of participants whose anemia was corrected was significantly greater in the testosterone replacement therapy (TRT) than the placebo group



TRT group: 143/349 (41.0%) at 6 mo, 152/338 (45.0%) at 12 mo

Placebo group: 122/360 (27.5%) at 6 mo, 122/360 (33.9%) at 12 mo

Traverse Trial

TRAVERSE Trials Summary

Trial	Risks	Benefits
CV	MACE- No	
Prostate	Cancer- No BPH/LUTS- No	
Sexual Function		ED - No Libido- Yes
Depression		Yes
Bone Fracture		No
Anemia		Yes
Diabetes		No

Limitations to Traverse Trial

- ? Bias
- Trial ended at 21.7 mths
- High drop out rate
- Avg T level reached was 12.8 nmol/L

PROCEED with CAUTION….

Treatment Monitoring

Testosterone therapy monitoring schedule

	Baseline	3 months	6 months	Yearly
Symptom evaluation	×	×	×	×
Adverse event monitoring		×	×	×
Serum testosterone	×	×	×	×
Hematocrit	×	×		×
Prostate-specific antigen (PSA)	×	×	×	×
Digital rectal examination (DRE)	×			×

Testosterone levels:

- IM – midway between injections
- Gel - 2-8 h after
- Patch – 3-12 h after
- Oral – 3-5 hrs after fat containing meal

Case: Mr. T

- No events since 2021
- Feels “great”
- He went off T for 2 weeks and c/o low energy, low mood and low libido
- Total Testosterone 18 ng/mL
- LDL 0.86
- A1C 5.4%
- PSA 0.94
- Hct. 49%

Key points:

- Don't prescribe testosterone unless there is biochemical evidence of T deficiency (Choosing Wisely)
- Check Total Testosterone and if needed repeat it and/or a free or bioavailable T
- Determine if primary or secondary hypogonadism
- Address contributing cases like obesity, sleep apnea
- Treat based on a low Total Testosterone level AND clinical symptoms
- [Target mid-normal range (T = 14-17 nmol/L) weak recommendation
- Traverse Trial
  - No increased risk for MACE or prostate cancer
  - Improved depression, libido, anemia

References:

1. Piszczek, J et al. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. PLoS ONE 2014; 9; e98003

2. Canadian Urological Association Guideline on Testosterone Deficiency in Men: Evidence-based Q&A. Canadian Urol Association Journal. 2021 Feb 23; 15(5) E234-243

3. Lincoff et al. Cardiovascular safety of testosterone replacement therapy . New England Journal of Medicine. 2023. Jun3 16; 389 (2)

4. BC Health: Testosterone testing protocol. BCGuidelines.ca. Oct 27, 2022

5. Morales et al. Diagnosis and management of testosterone deficiency syndrome in men: Clinical practice guidelines. CMAJ. 2015. Dec 8; 187 (18).

6. Mulhall, J. Et al. Evaluation and management of testosterone deficiency: AUA Guideline. The journal of Urology. 2018, Aug.