

“Male hypogonadism”

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Definition of male hypogonadism

- ↓ testosterone production
 - prepubertal: small testes
 - postpubertal: normal testes

- ↓ sperm production only
 - Infertile adult man

Common causes of hypogonadism

- **Primary hypogonadism**
 - **Klinefelter's syndrome**
- **Secondary hypogonadism**
 - **Kallmann's syndrome**
 - **Pituitary disease**
 - **Macroadenomas**
 - **Hemochromatosis**
 - **Excessive corticosteroids**
 - **Hyperprolactinemia**

Common symptoms and effects of male hypogonadism

- Weakness
- Fatigue
- Decreased sexual function
- Decreased sense of well-being
- Depression
- Osteoporosis (fractures)
- Loss of facial and body hair

Male hypogonadism: presenting signs

Decreased testosterone production

- small testes (if prepubertal)
- gynecomastia
- loss of facial and body hair
- ↑ skin wrinkling

Decreased sperm production only

- small testes (rare)

Diagnosis of hypogonadism in men

- **Measure total T**
 - Free T by commercial assays underestimate levels
- **Measure FSH and LH**
 - Elevated = primary hypogonadism
 - Low or normal suggests secondary hypogonadism
 - Rule out hemochromatosis, hyperprolactinemia, Cushing's
 - Take drug history
 - Rule out renal or hepatic insufficiency
 - **T < 200 ng/dl-> pituitary imaging**

Favorable effects of androgen replacement for hypogonadal men

– ↑ strength and muscle mass

(Bhasin, *J Clin Endocrinol Metab.* 82:407, 1997)

– ↑ bone mineral density

(Behre, *J Clin Endocrinol Metab.* 82:2386, 1997)

– ↑ sense of well-being and improved mood

(Wang, *J Clin Endocrinol Metab.* 81:3578, 1996)

Effects of exogenous androgens and mood in elderly men

- ↑ sense of well-being improved with transdermal T to older men with serum total < 350

Snyder, JCEM. 1999;84:2647

- Similar findings in testosterone gel (study included older men with low-normal serum T)

Wang, JCEM. 2000;85:2839

Summary of effects of T supplementation for older men

- **↓ lean body mass and ↓ total body and truncal fat**
- **↑ vertebral BMD in older men with total ≤ 350 ng/dL**
- **+/- effects on strength**
- **↑ sense of well-being**

- **Favorable effects of T ↑ with dose**
- **Favorable effects of T ↑ with low basal T level**

Choice of androgen therapy for men

- **Oral testosterone**
 - Alkylated forms
 - Testosterone undecanoate
- **Transdermal testosterone**
 - Scrotal and nonscrotal patches
 - Gel system
- **Intramuscular testosterone**

Choice of androgen therapy for men: oral therapies

Oral testosterone

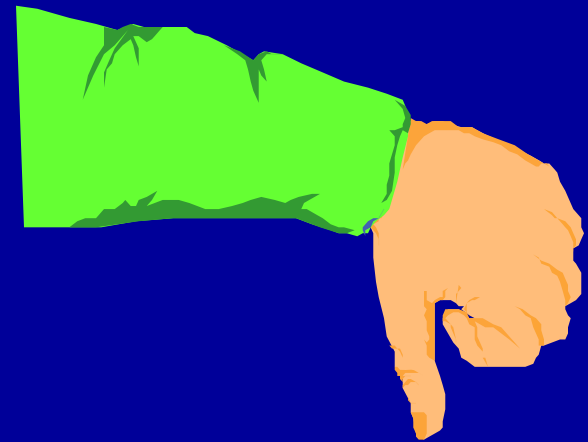
– Alkylated forms-- unsafe

- Lower HDL levels
- Hepatotoxic

» **DON'T USE!**

– Testosterone undecanoate

- Safe (absorbed through lymphatics)
- Frequent dosing (bid or tid)



Choice of androgen therapy for men: transdermal therapies

Transdermal systems

- Patch (scrotal and nonscrotal)
 - reproduce circadian rhythm of T
 - \$\$
 - Cause dermatitis 10-30% of elderly men
 - Inadequate replacement levels for some men
- Gel system
 - reproduce circadian rhythm of T
 - \$\$\$
 - No dermatitis; ? effects on partners
 - Robust levels

Choice of androgen therapy for men: intramuscular T

Intramuscular T esters

- Testosterone cypionate and enanthate (every 10-14 d)
 - Cheap
 - Provide robust levels
 - Nonphysiologic
 - Inconvenient (?)
- Testosterone propionate (shorter half-life)

Monitoring androgen therapy for men

- **Transdermal T**
 - Check T levels
 - Follow hematocrit periodically
 - Prostate cancer screening ??
 - Lipids ??
- **Intramuscular T therapy**
 - Adjust dose or interval based on clinical symptoms
 - Follow hematocrit
 - Prostate cancer screening?
 - Lipids?

Risks of androgen therapy for men

- **Erythrocytosis**
 - More common in the elderly
- **Prostate disease**
 - T necessary but not sufficient for BPH and CaP
- **Cardiovascular disease**
 - Mixed effects on risk factors

Risks of androgen therapy for men: prostate disease

- **Congenital hypogonadism = no prostate disease**
- **Treated hypogonadism restores prostate and PSA to normal**
 - **PSA may double**
- **No correlation between serum T levels and prostate disease**
- **No increase in prostate size or PSA in supraphysiologic T**
- **T deprivation only useful for patients with metastatic cancer**

Risks of androgen therapy for men: cardiovascular disease

- Oral testosterone
 - Decreases HDL
- Transdermal and intramuscular testosterone
 - Decreases HDL
 - Decreases LDL
 - Decreases lipoprotein (a)
- Testosterone may cause vasodilation
- Testosterone decreases visceral fat

Conclusions for androgen therapy for men

- **Candidates for androgen replacement**
 - All men with primary hypogonadism
 - All men with pituitary disease and low T
- **Candidates for androgen supplementation**
 - Older men with total T levels ≤ 350 ng/dL
 - osteopenia, weakness, decreased libido
 - Anemia and renal insufficiency
 - chronic corticosteroid therapy

↑ effect with higher androgen dosage and lower basal T

Case #1

A young couple are having difficulty conceiving a child. On exam, the young man has gynecomastia and very small testes. He is otherwise normal appearing and has a normal sense of smell.

He most likely has

- a. Hemochromatosis**
- b. Hyperprolactinemia**
- c. Klinefelter's syndrome**
- d. Cushing's syndrome**
- e. Kallmann's syndrome**

Case #1 answer

A young couple are having difficulty conceiving a child. On exam, the young man has gynecomastia and very small testes. He is otherwise normal appearing and has a normal sense of smell.

He most likely has **Klinefelter's syndrome (c)**.

Small testes suggest a congenital or prepubertal cause of hypogonadism-- not hemochromatosis, hyperprolactinemia or Cushing's syndrome which are more common in adults than children. Patient could also have Kallmann's syndrome, but this is associated with anosmia and is also rarer than Klinefelter's.

Case #2

An older man complains of decreased libido, weakness and breast tenderness. He has 3 cm gynecomastia bilaterally. He has normal-sized testes. He has normal skin without striae or ecchymoses.

He most likely has

- a. Hyperprolactinemia**
- c. Klinefelter's syndrome**
- d. Cushing's syndrome**
- e. Kallmann's syndrome**

Case #2 answer

An older man complains of decreased libido, weakness and breast tenderness. He has 3 cm gynecomastia bilaterally. He has normal-sized testes. He has normal skin without striae or ecchymoses.

He most likely has **hyperprolactinemia (a)**. Normal-sized testes make Klinefelter's and Kallmann's syndromes *very* unlikely. Cushing's is rarer than hyperprolactinemia plus there are no signs of excessive corticosteroids.

Case #3

The therapy most likely to cheaply and safely provide a 120 kilogram man an adequate level of testosterone is

- a. Transdermal testosterone by patch daily
- b. Oral testosterone daily
- c. Testosterone ester intramuscularly every 14 days
- d. Testosterone gel daily

Case #3 answer

The therapy most likely to cheaply and safely provide a 100 kilogram man an adequate level of testosterone is

Only testosterone intramuscularly and testosterone gel will reliably provide a large man an adequate level of testosterone. Intramuscular testosterone is by far the cheapest mode of therapy.

Hypogonadism references

Review

Bhasin, et al. Therapeutic perspective: issues in testosterone replacement in older men. J Clin Endocrinol Metab. 1998;83:3435-3448.

Testosterone and bone mineral density

Snyder PJ, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. 1999;84:1966-74.

Behre HM, et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab. 1997;82:2386-2390.

Testosterone and lean body mass/strength

Wang C, Swerdloff RS, Irnamanesh A, Dobs A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength in hypogonadal men. J Clin Endocrinol Metab. 2000;85:2839-2853.

Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab. 1999;84:2647-2653.v

Hypogonadism references

Testosterone and cardiovascular disease

Webb, CM, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 1999;100:1690-1696.

Bagatell CJ and Bremner WJ. Androgen and progestagen effects on plasma lipids. *Progress in cardiovascular diseases*. 1995;38(3):255-271. *Excellent review of the effects of androgens on lipids.*

Testosterone replacement and mood

Wang C, Alexander G, Berman N, et al.: Testosterone replacement therapy improves mood in hypogonadal men-a clinical research study. *J Clin Endocrinol Metab* 1996;81:3578-3583.

Snyder PJ, Peachey H, Berlin JA, Hannoush P, et al. Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab* 2000;85:2670-2677.