Role of Testosterone in Treatment of Male Disorders

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Faculty Disclosures

8/13/16

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- Off-Label Usage: None

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Objectives

- 1. Describe physiology of testosterone axis in men
- 2. Review roles played by testosterone in men: prostate health, erectile function, well-being, skeleton, and red blood cell production
- 3. Discuss treatment of male disorders with testosterone

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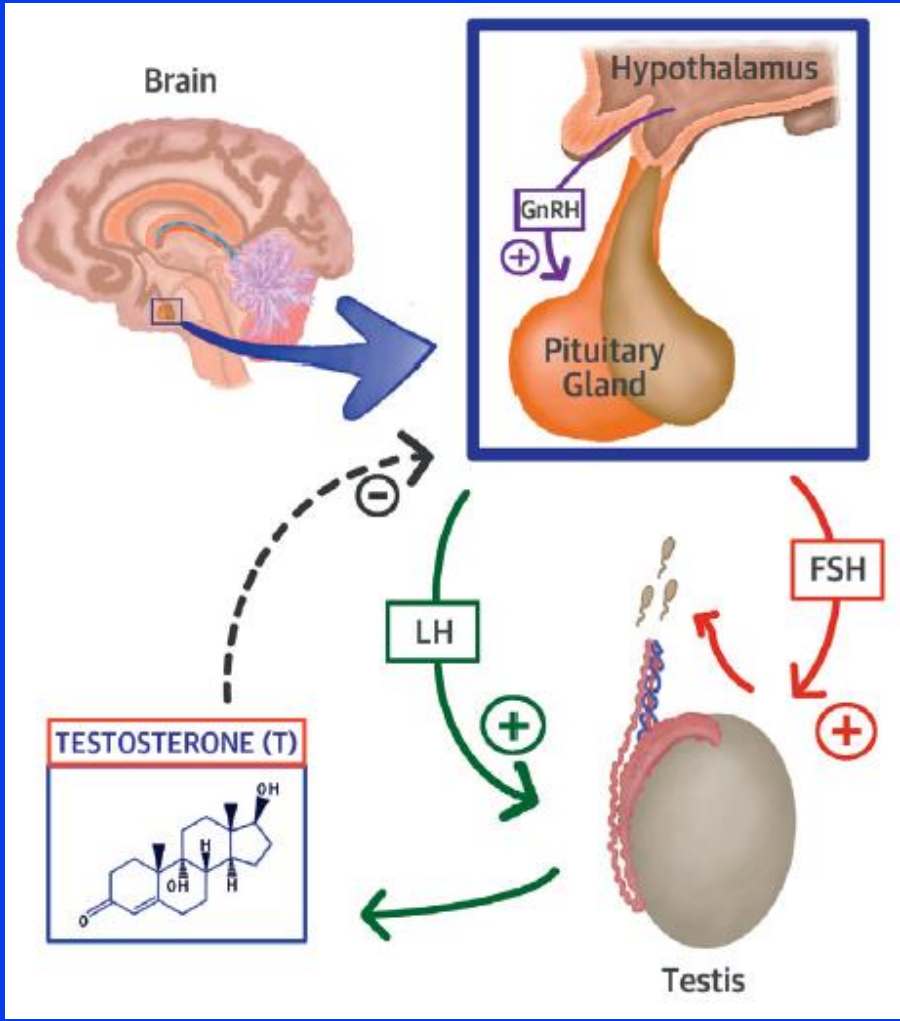
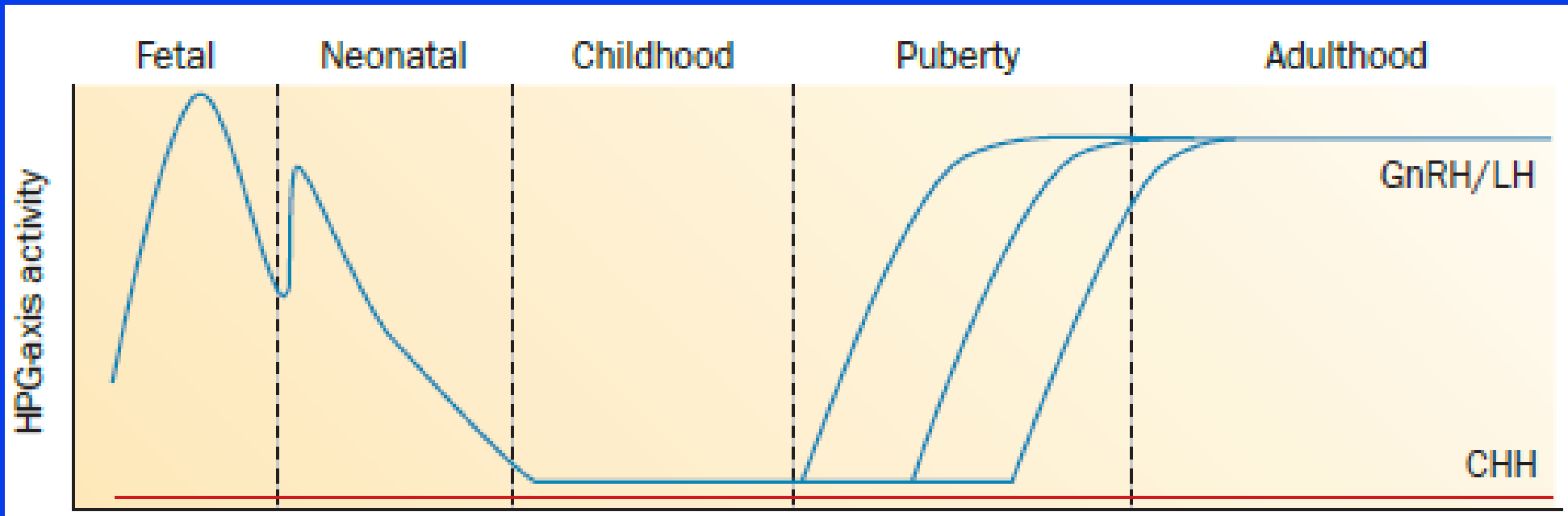
Hypothalamic-Pituitary-Gonadal Axis

Kloner RA et al. J Am Coll Cardiol. 2016;67:545-557.



Hypothalamic-Pituitary-Gonadal Axis Across the Lifespan

Boehm U et al. Nat Rev Endocrinol. 2015;11:547-564.



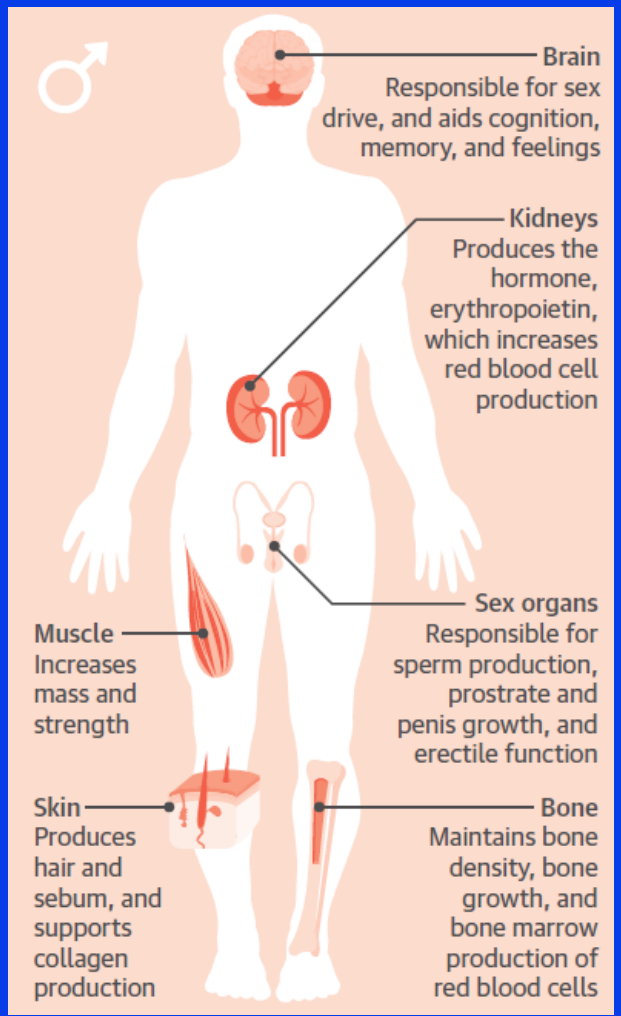
- Cryptorchidism (M)
- Micropenis (M)

- Prepubertal testes (M)
- Undervirilization (M)
- Absent breast development (F)
- Primary amenorrhoea (F)

- Infertility (M and F)

Multiple Effects of Testosterone on Body Tissues

Kloner RA et al. J Am Coll Cardiol. 2016;67:545-557.



Causes of Testosterone Deficiency in Adult Men

Dean JD et al. J Sex Med. 2015;12:1660-1686

Table 2 Testosterone deficiency because of hypergonadotropic (primary) hypogonadism

Congenital		Klinefelter's syndrome (47XXY)
		Androgen receptor defects
		Noonan syndrome
		Cryptorchidism
Acquired	Autoimmune	Mumps orchitis
	Metabolic	Hemachromatosis
	Trauma	Testicular trauma or torsion
		Testicular infarction
	Iatrogenic	Testicular irradiation
		Drugs
		Surgery
	Aging (mixed hypogonadism)	

Table 3 Testosterone deficiency because of hypogonadotropic (secondary) hypogonadism

Congenital		Isolated hypogonadotropic hypogonadism
		Kallmann's syndrome
		Prader–Willi syndrome
		Pasqualini syndrome
Acquired	Neoplasia	Primary and secondary central nervous system tumors
	Endocrine/ metabolic disorder	Diabetes
		Obesity
		Hyperprolactinemia
	Iatrogenic	Hypothalamic–pituitary irradiation
		Drugs
		Surgery
	Aging (mixed hypogonadism)	

Causes of 2º Hypogonadism in 4220 Men with Sexual Dysfunction

Corona G, Maggi M. J Sex Med. 2015;12:1690-1693.

- Only 11% had diagnosable classical secondary cause:
  - Surgery 3.4%
  - Drugs 2.4% (Opioids, glucocorticoids, cimetidine, TCAs, nicotine, marijuana)
  - Empty sella 1.7%
  - Genetic 1.1%
  - Radiotherapy 1.1%
  - Pituitary prolactinoma 1.1%
  - Trauma 0.1%
  - Comorbidites: Obesity, central adiposity, metabolic syndrome, HIV, untreated sleep apnea, medical stress
- 70.7% of subjects had metabolic disease: obesity, DM2, or metabolic syndrome

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Symptoms of Testosterone Deficiency in Adult Men

Dean JD et al. J Sex Med. 2015;12:1660-1686

Table 4 Symptoms of testosterone deficiency

	Symptoms of testosterone deficiency
Physical function	Reduced muscle strength
	Impaired physical coordination
	Impaired balance
	Physical frailty
Cognitive function	Impaired concentration
	Impaired verbal memory
	Impaired visual-spatial awareness
Sleep	Fatigue, tendency to fall asleep during the day
	Insomnia
	Falling asleep
	Staying asleep
Affect	Reduced sense of general well-being
	Reduced energy and motivation
	Anxiety
	Depression
	Irritability
Sexual function	Reduced sexual desire
	Infrequent or absent nocturnal erection and erection on wakening
	Impaired erectile function
	Impaired ejaculatory function
	Impaired orgasmic function

Causes of Increased SHBG

Dean JD et al. J Sex Med. 2015;12:1660-1686

Table 5 Causes of raised and decreased sex hormone binding levels (SHBG)

Conditions that decrease SHBG	Conditions that increase SHBG
Anabolic steroids	Aging men
Polycystic ovary syndrome	Oral contraceptives
Hypothyroidism	Pregnancy,
Obesity	Hyperthyroidism,
Cushing's syndrome	Cirrhosis,
Acromegaly	Anorexia nervosa
	Long-term calorie restriction
	Carbamazepine

Studies of Hypogonadism in Aging Men

Dean JD et al. J Sex Med. 2015;12:1660-1686.

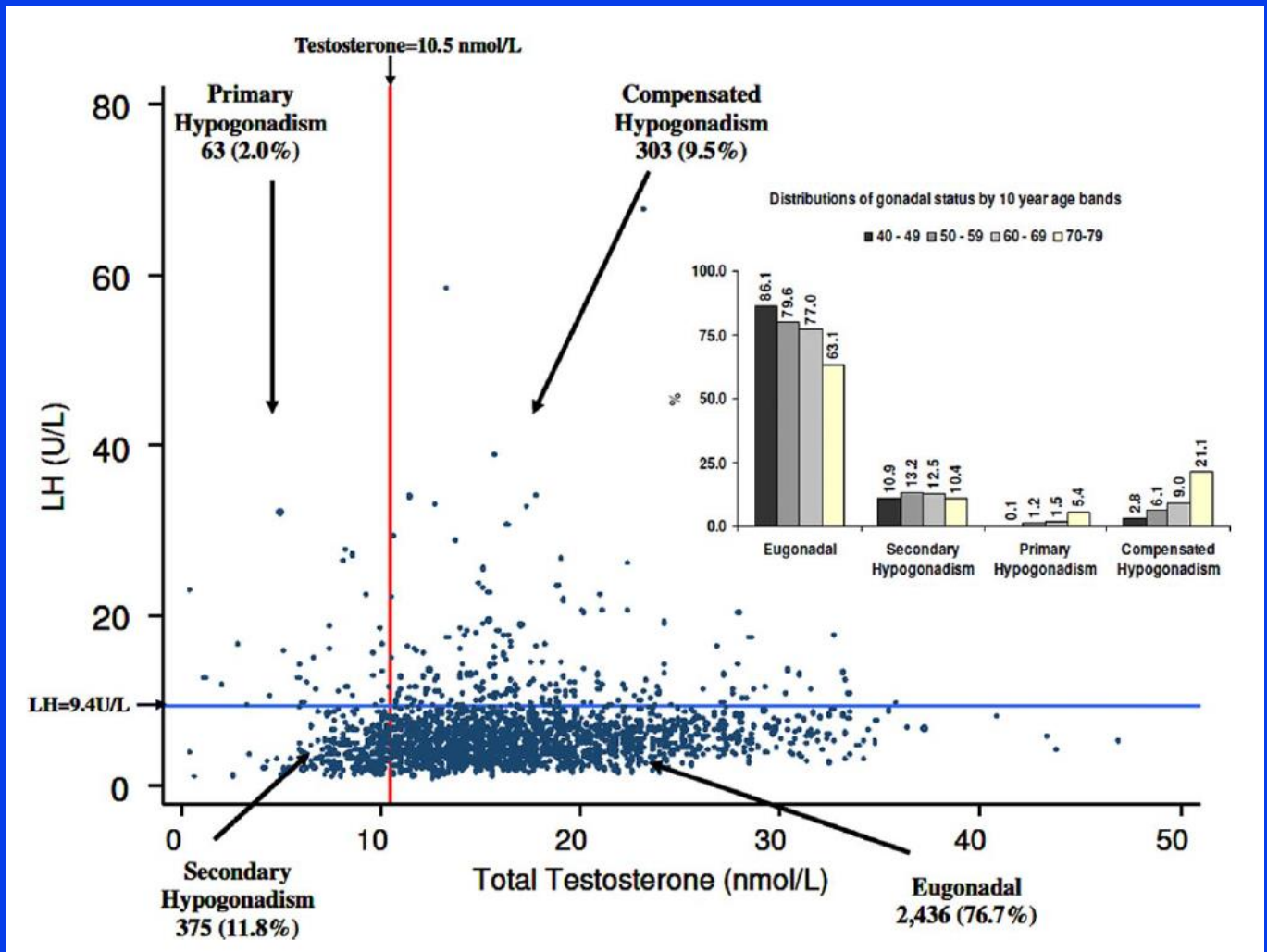
Table 1 Cross-sectional and longitudinal studies of hypogonadism in aging men

Study	n	Age at Baseline (years)	Diagnosis of hypogonadism	Results
The Massachusetts Male Aging Study [4]	1667	40–70	≥3 signs or symptoms associated with low T (hypoactive sexual desire, ED, depression, lethargy, inability to concentrate, sleep disturbance, irritability and depressed mood) and total T <6.9 or 6.9–13.88 nmol/L (200–400 ng/dL) with free T <300 pmol/L (8.9 ng/dL)	Crude prevalence of androgen deficiency at baseline and follow-up was 6.0% and 12.3%
Boston Area Community Health Survey [5]	1475	30–79	One specific symptom (hypoactive sexual desire, ED, osteoporosis), or ≥2 nonspecific symptoms (sleep disturbance depressed mood, lethargy or low physical performance) and total T <10.4 nmol/L (300 mg/dL) and free T < 170 pmol/L (5 ng/dL)	Crude prevalence of symptomatic androgen deficiency was 5.6%
European Male Aging Study [6]	3219	40–79	≥3 sexual symptoms in a male with a total T <11 nmol/L (320 ng/dL) and a free T <220 pmol/L (6 ng.dL)	Overall prevalence of hypogonadism was 2.1%
Hypogonadism in Male [7]	2162	>45	Total T <10.4 nmol/L (300 mg/dL)	Crude prevalence rate of hypogonadism was estimated as 38.7%

ED = erectile dysfunction; T = testosterone.

Gonadal Status and Age in 3119 Community-Dwelling Men Aged 40-79 Years

Tajar A et al. J Clin Endocrinol Metab. 2010;95:1810-1818.



Gonadal Status and Age in 3119 Community-Dwelling Men Aged 40-79 Years

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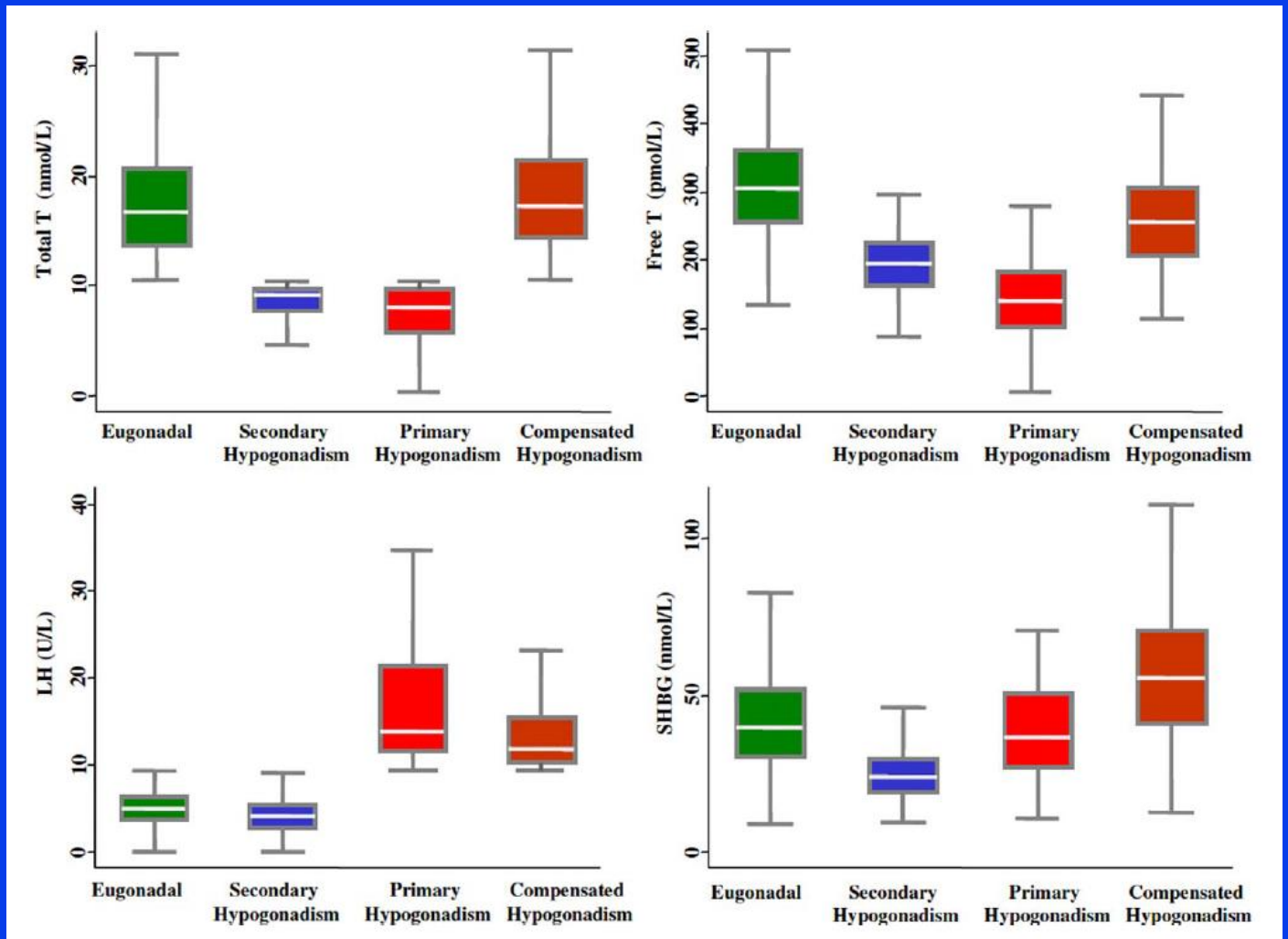


Gonadal Status and Age in 3119 Community-Dwelling Men Aged 40-79 Years

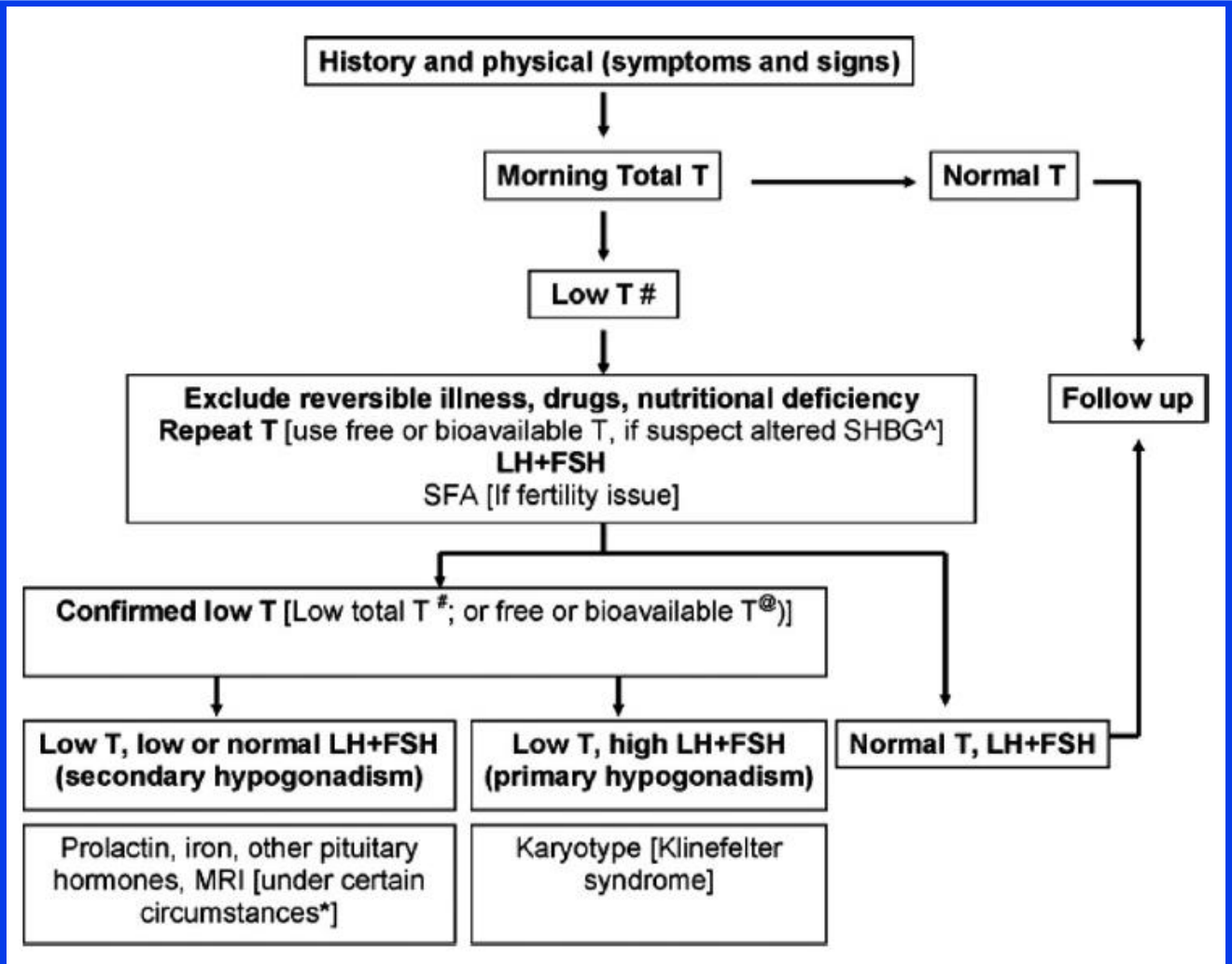
Tajar A et al. J Clin Endocrinol Metab. 2010;95:1810-1818.

TABLE 3. Symptoms association (sexual and physical) with hypogonadal status

Dependent variables	OR (95% CI) Secondary hypogonadism	Primary hypogonadism	Compensated hypogonadism
Sexual symptoms			
Unadjusted			
Decreased morning erections	1.57 (1.25–1.98)[d]	3.77 (2.14–6.64)[d]	2.17 (1.68–2.78)[d]
Erectile dysfunction	1.38 (1.08–1.77)[b]	3.83 (2.18–6.73)[d]	2.97 (2.30–3.83)[d]
Decreased frequency of sexual thoughts[a]	1.10 (0.85–1.44)	3.50 (2.03–6.02)[d]	2.14 (1.65–2.78)[d]
Adjusted for age			
Decreased morning erections	1.55 (1.21–1.98)[d]	1.85 (1.01–3.38)[b]	1.21 (0.92–1.58)
Erectile dysfunction	1.34 (1.01–1.77)[b]	1.39 (0.73–2.63)	1.35 (1.01–1.81)[b]
Decreased frequency of sexual thoughts[a]	0.97 (0.71–1.32)	3.78 (1.61–8.86)[c]	0.64 (0.39–1.06)
Adjusted for age, BMI, smoking status, alcohol intake, comorbidity, and marital/partner status			
Decreased Morning erections	1.42 (1.09–1.86)[c]	1.76 (0.93–3.32)	1.18 (0.89–1.56)
Erectile dysfunction	1.15 (0.85–1.56)	1.38 (0.71–2.70)	1.34 (0.99–1.82)
Decreased Frequency of sexual thoughts[a]	0.97 (0.70–1.35)	3.68 (1.44–9.42)[c]	0.63 (0.38–1.06)

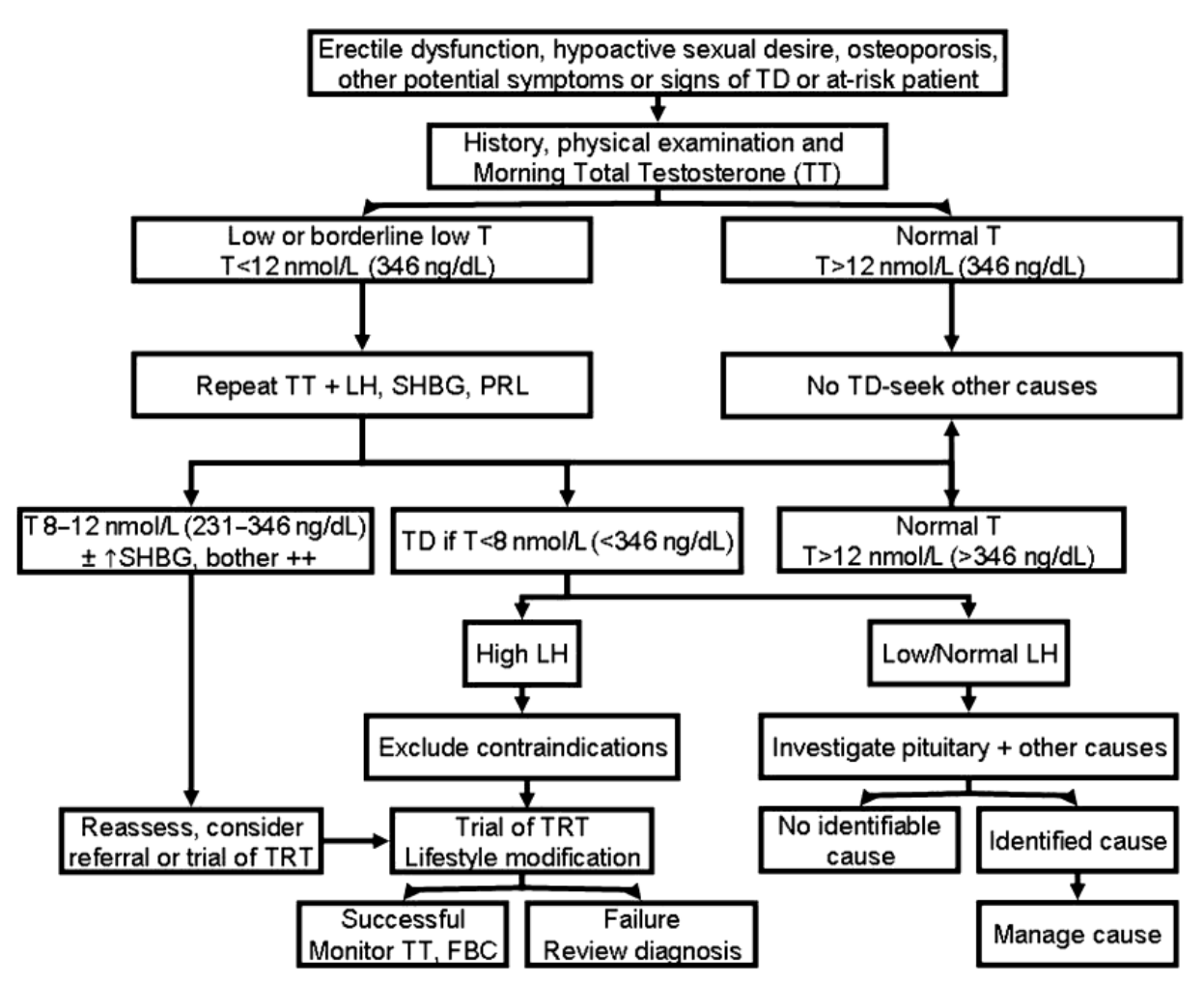
Evaluation of Men Suspected of Androgen Deficiency

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



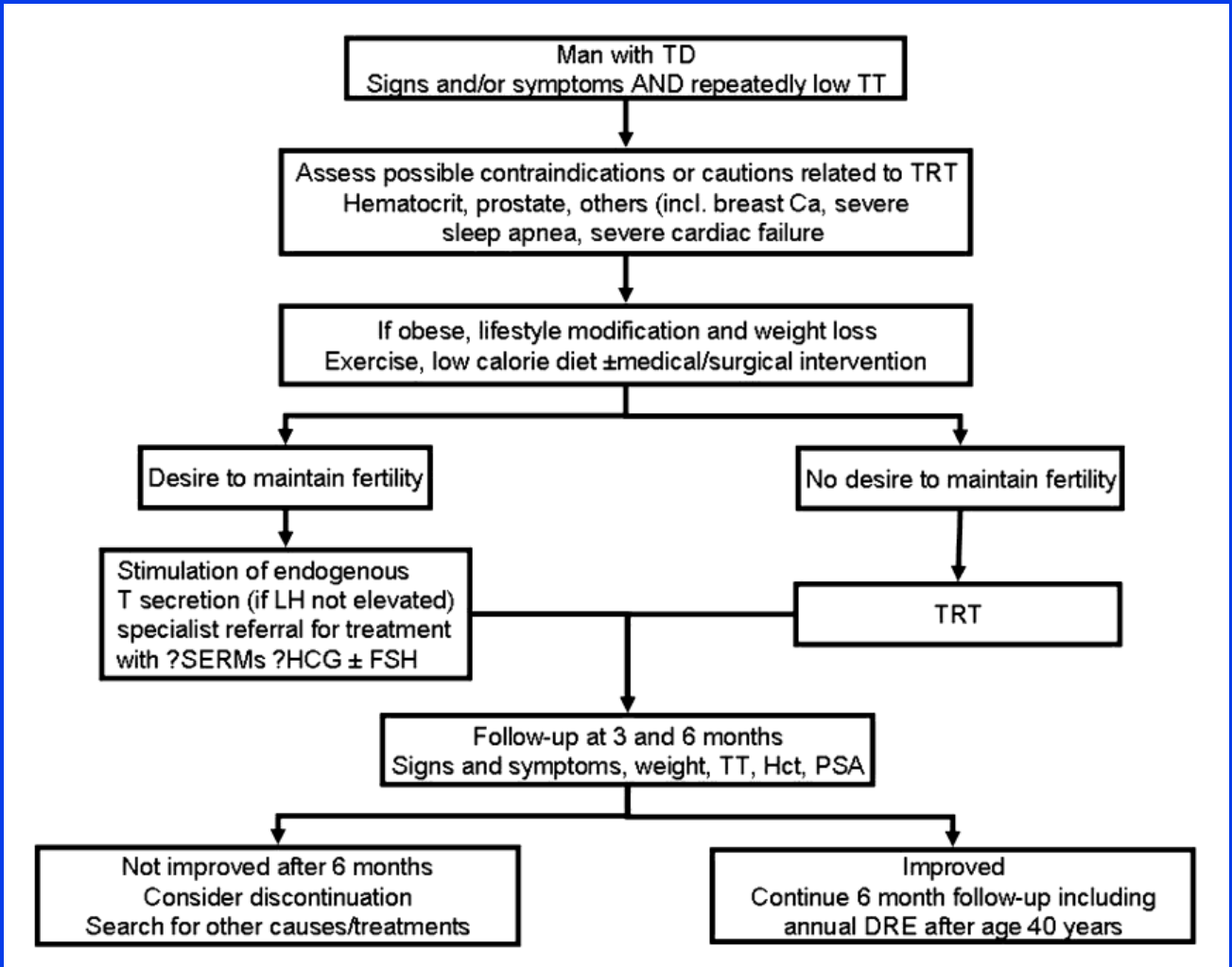
Assessment and Management of Testosterone Deficiency in Adult Men

Dean JD et al. J Sex Med. 2015;12:1660-1686



Assessment and Management of Testosterone Deficiency in Adult Men Wishing to Maintain Fertility

Dean JD et al. J Sex Med. 2015;12:1660-1686



Clinical Practice Guideline on Diagnosis and Management of T Deficiency Syndrome in Men

Morales A et al. CMAJ 2015;187:1369-1377.

KEY POINTS

- Diagnosis of testosterone deficiency syndrome requires the presence of the clinical manifestations of testosterone deficiency, together with documented testosterone levels below the local laboratory ranges.
- Treatment is recommended for testosterone deficiency syndrome; the choice of treatment is based on product safety, efficacy, tolerability, cost and the absence of contraindications.
- Testosterone replacement therapy is appropriate in men with testosterone deficiency syndrome who have cardiovascular disease or are at risk of cardiovascular disease.
- Hypogonadal men with successfully treated prostate cancer may be candidates for testosterone supplementation; these patients require referral to a specialist, because treatment involves close monitoring by a physician with expertise in the risks and benefits of testosterone therapy.
- Regular monitoring for clinical and biochemical response, and for adverse effects, to testosterone replacement therapy is essential, particularly during the first year of treatment.

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Clinical Practice Guideline on Diagnosis and Management of T Deficiency Syndrome in Men

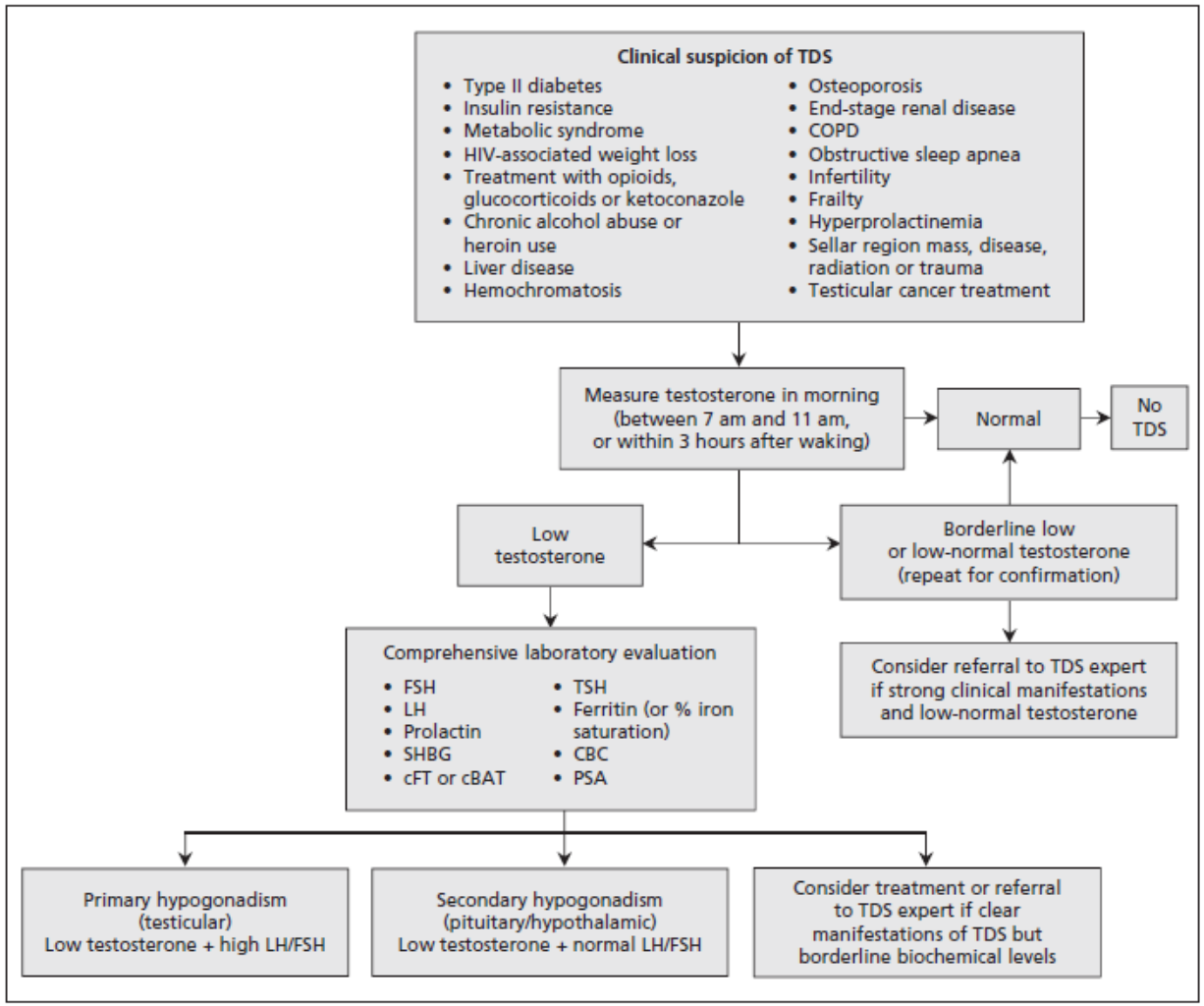
Morales A et al. CMAJ 2015;187:1369-1377.

Box 3: Signs and symptoms associated with testosterone deficiency syndrome[1]

- *Sexual:* Decreased libido; erectile dysfunction; decreased frequency of morning erections; decreased performance
- *Somatic:* Increased visceral body fat/obesity; decreased lean muscle mass; decreased strength; fatigue/loss of energy; decreased physical activity/ vitality; low bone mineral density; anemia; flushes; loss of facial, axillary and pubic hair/slow beard growth; decline in general feeling of well-being
- *Psychological:* Depression/depressed mood; mood changes; irritability; inability to concentrate; insomnia/sleep disturbances

Clinical Practice Guideline on Diagnosis and Management of T Deficiency Syndrome in Men

Morales A et al. CMAJ 2015;187:1369-1377.



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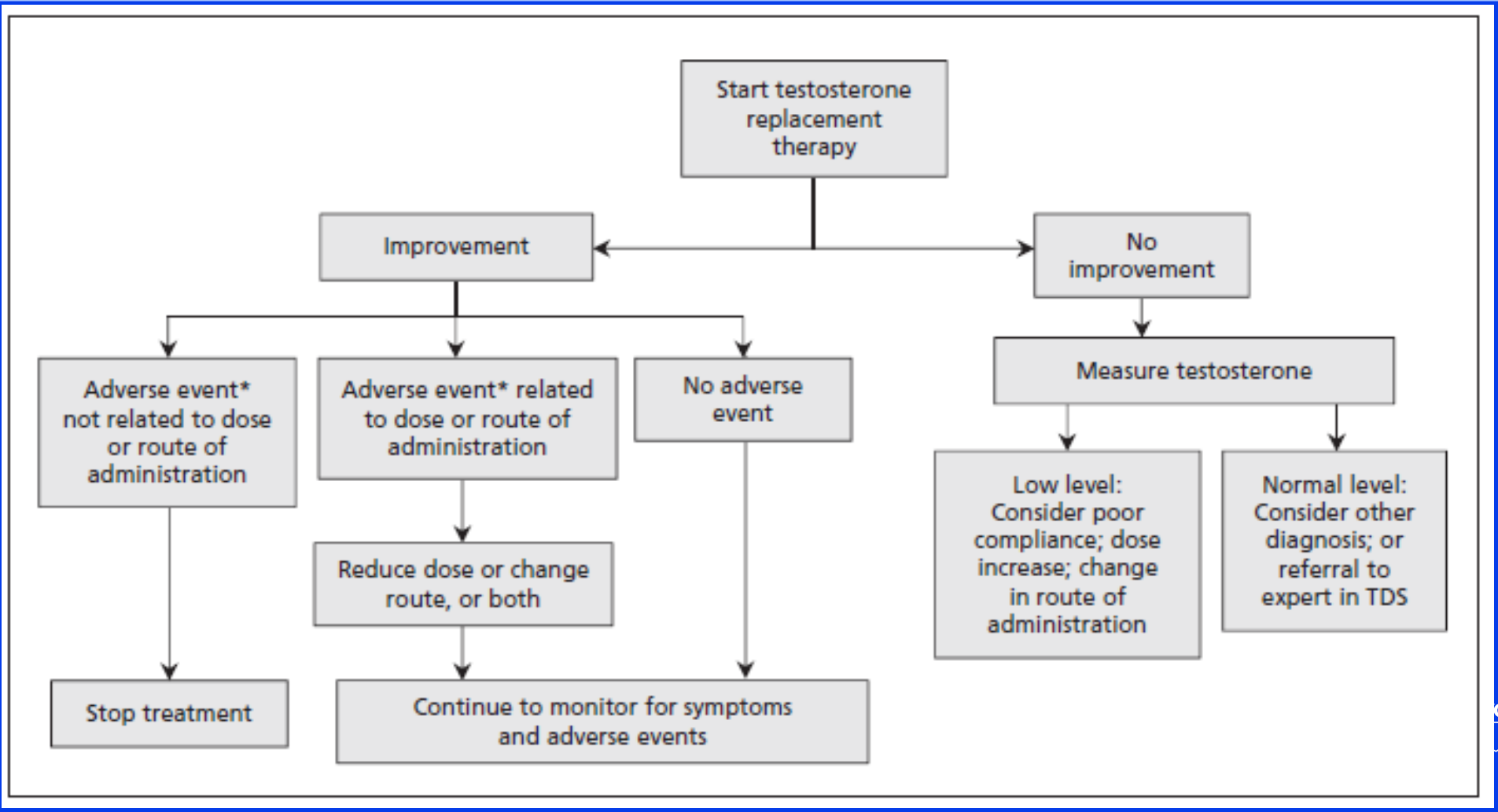


Clinical Practice Guideline on Diagnosis and Management of T Deficiency Syndrome in Men

Morales A et al. CMAJ 2015;187:1369-1377.

Table 1: Potential benefits and harms of testosterone supplementation in men with testosterone deficiency syndrome*[17,18]

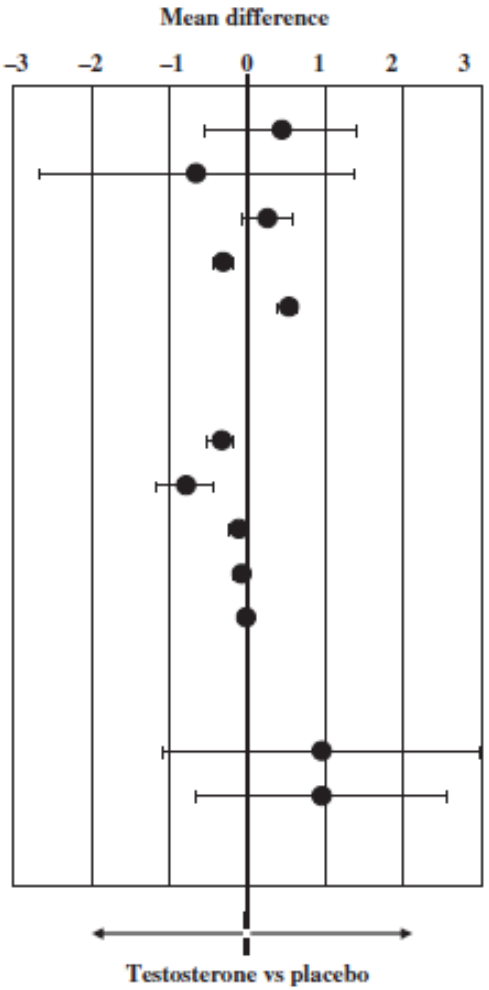
Organ system	Benefits	Harms
Erectile function/libido	Improvement	None
Depression/mood/fatigue	Improvement	Aggressive behaviour
Erythropoiesis	Increase in hematocrit	Increased risk of polycythemia, embolism
Skeletal muscle	Increase in fat-free mass	None
Bone metabolism	Prevention of osteoporosis	None
Cardiovascular system	Improvement in congestive heart failure, exercise capacity	Increased risk of thromboembolic cardiovascular events
Prostate		
Benign prostatic hyperplasia	None beyond manifestations of testosterone deficiency syndrome	Marginal increase in volume and prostate-specific antigen level
Cancer (metastatic or high risk of recurrence)	Absolute contraindication	Recurrence and rapid progression
Cancer (localized and treated)	None beyond manifestations of testosterone deficiency syndrome	Potential exacerbation of subclinical residual cancer
Testicle	None beyond manifestations of testosterone deficiency syndrome	Atrophy or impairment of spermatogenesis

*For additional details on the strength of the evidence, see Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150033/-/DC1).

Meta-Analysis of Testosterone Supplementation and Body Composition

Corona G et al. Eur J Endocrinol. 2016;174:R99-R116.

Source	Number of trials	Diff in mean	LL	UL	*P*	I^2
Bodycomposition						
Weight (kg)	32	0.43	–0.54	1.39	0.39	35.85
Waist circumference (cm)	17	–0.66	–2.66	1.35	0.52	76.05
BMI (kg/m^2)	29	0.25	–0.09	0.58	0.15	68.86
Fat mass*	42	–0.32	–0.44	–0.19	0.00	68.20
Lean mass*	40	0.51	0.37	0.66	0.00	74.68
Glyco-metabolic profile						
Fasting glycemia (mM)	23	–0.34	–0.51	–0.17	0.00	56.49
HOMA index	16	–0.80	–1.16	–0.45	0.00	59.25
Total cholesterol (mM)	42	–0.12	–0.25	0.01	0.08	73.59
Triglycerides (mM)	33	–0.08	–0.18	0.01	0.09	66.80
HDL (mM)	40	–0.03	–0.08	0.01	0.18	93.17
Blood pressure						
SBP (mmHg)	17	0.94	–1.08	2.96	0.36	53.81
DBP (mmHg)	16	0.95	–0.66	2.54	0.25	70.42



Underdiagnosis of Male Osteoporosis

- Under-recognized and under-treated
- Projections from NHANES III and the 2000 U.S. Census suggest that:
  - About 2 million men have osteoporosis (T-score less than -2.5)
  - About 12 million men have osteopenia (National Osteoporosis Foundation, 2002)
- Fracture risk increases exponentially with age in men, beginning about a decade later than in women

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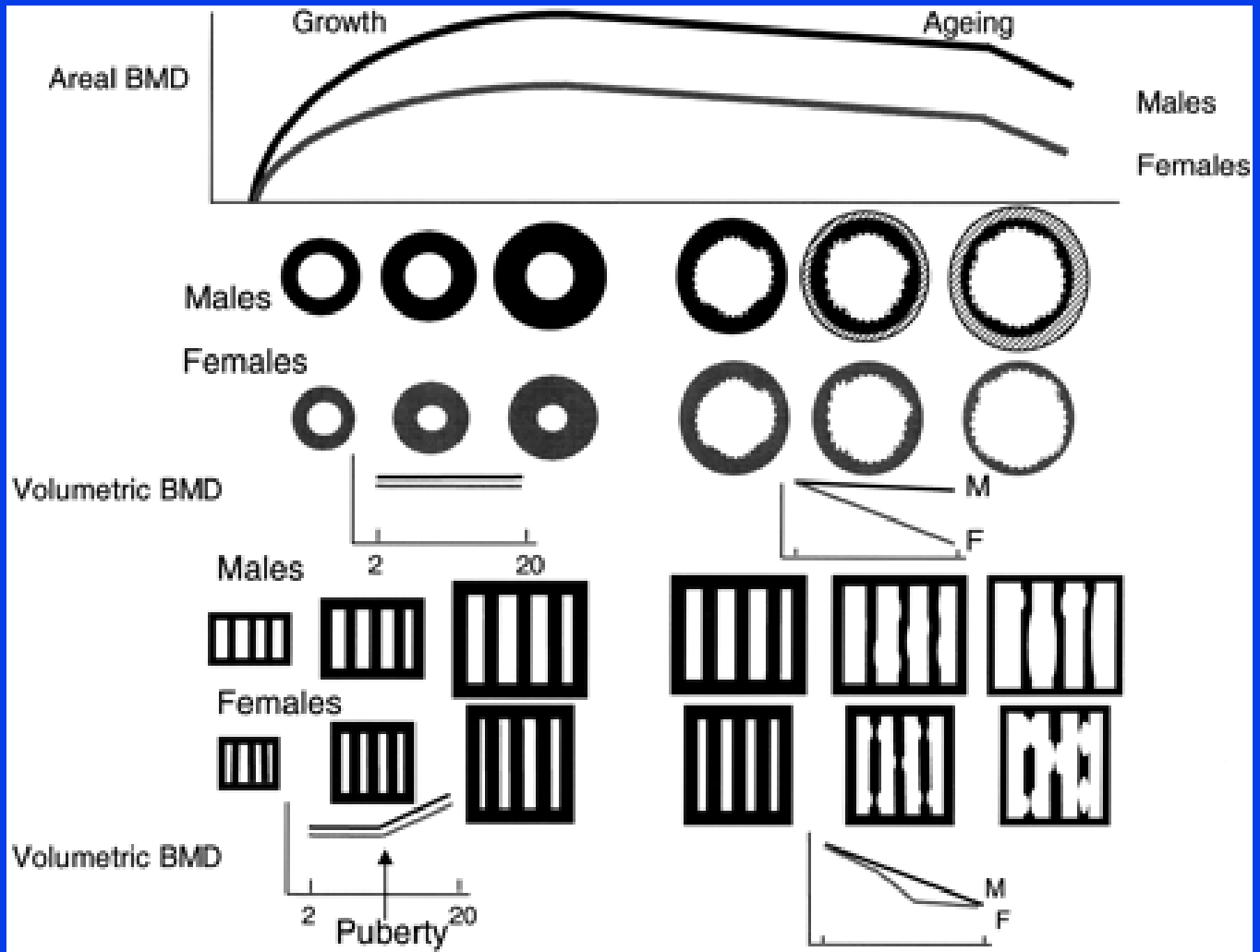
Underdiagnosis of Male Osteoporosis

- Estimated that:
  - 13% of Caucasian men over age 50 will sustain an osteoporosis-related fracture
  - 30% of all hip fractures occur in men
- Men twice as likely to die in hospital after a hip fracture as women
- One-year mortality rate after hip fracture is higher in men compared to women (31% vs. 17%)
- Fractures increase dramatically in men after age 70

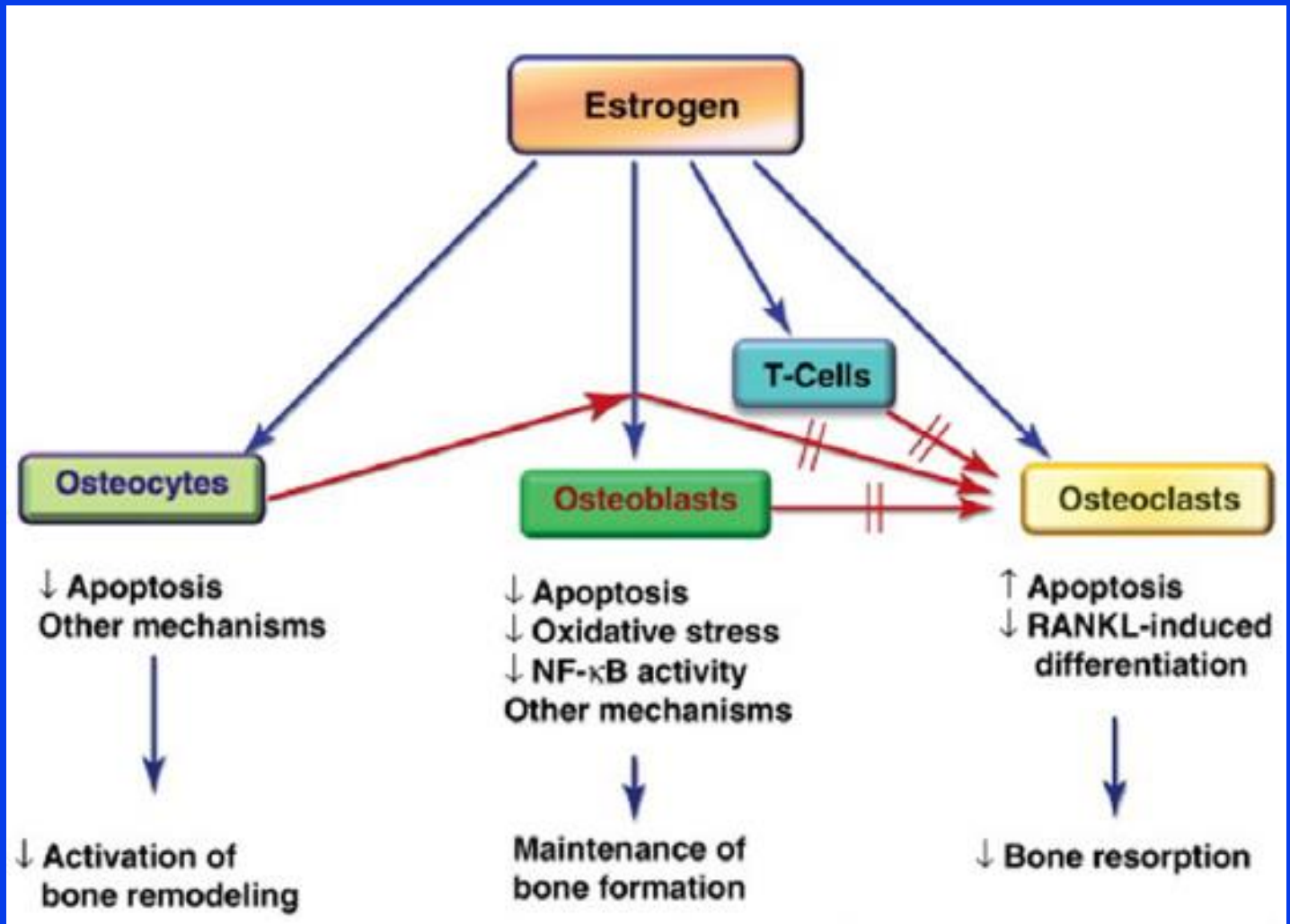
Gender-Specific Differences in Bone Structure with Aging

Seeman E. J Clin Endocrinol Metab 2001;86:4576-4584.



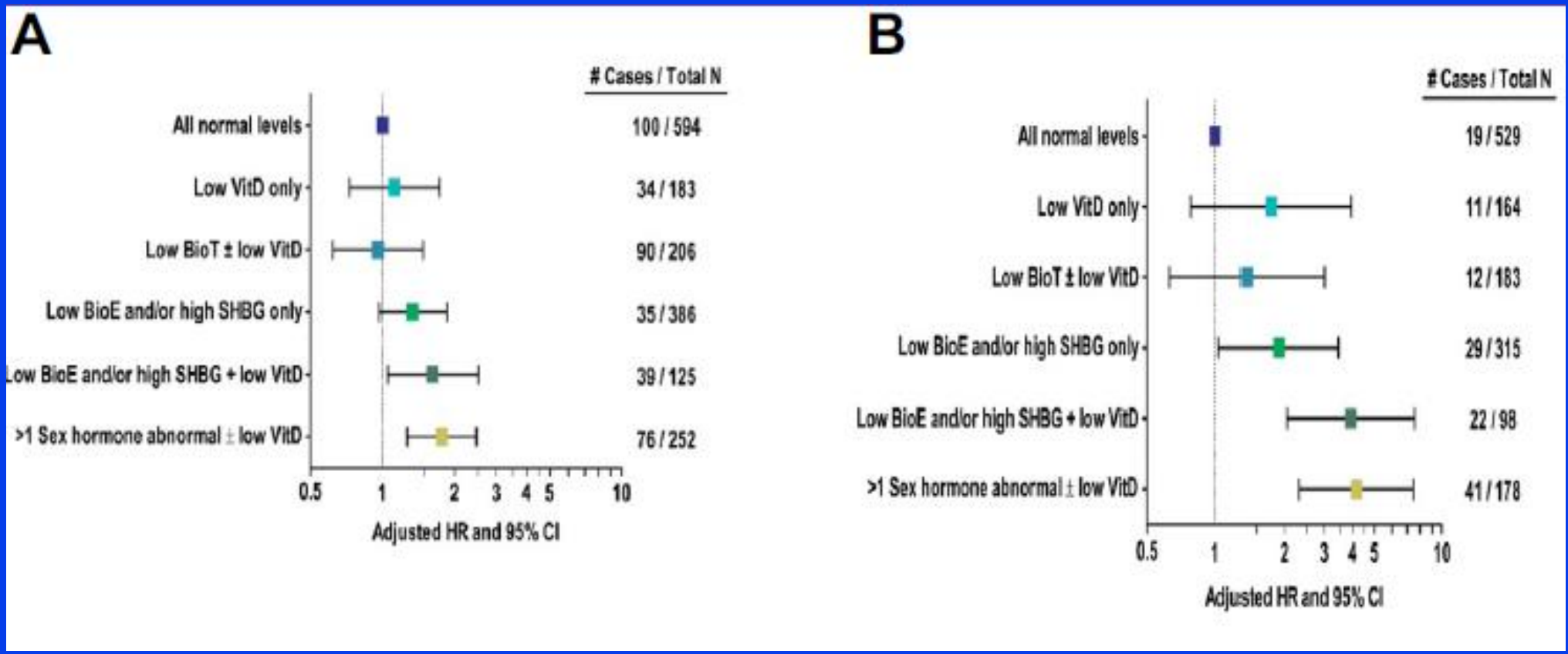
Estrogen Regulation of Bone Turnover in Men

Khosla S et al. Trends Endocrinol Metab. 2012;23:576-581.



Risk of Nonvertebral and Major Osteoporotic Fractures in Aging Men

Barrett-Connor E et al. J Bone Miner Res. 2012;27:2306-2013.



Testosterone Effects in Symptomatic Hypogonadism

Kloner RA et al. J Am Coll Cardiol. 2016;67:545-557.

TABLE 1 Testosterone's Role in Therapy of True Symptomatic Hypogonadism in Young and Older Men

Organ	Young Men	Older Men	Ref. #
Libido	++	++	33-38
Erectile function	++	++	33-38
Cardiovascular	+	+	69-71
Mood	+	+	42,43
Cognition	+	+	47,48
Energy	+	+	49,50
Bone mineral density	++	++	58-63
Fat mass	++	++	54
Hematopoiesis	++	++	69,71
Muscle mass	++	++	53-55
Muscle strength	++	++	54-56
Insulin sensitivity	+	+	67
Sperm count	– –	– –	121

++ = strong evidence of positive effect; + = weak evidence of positive effect; – – = strong evidence of negative effect; – = weak evidence of negative effect.

Testosterone Effects on Cardiovascular System

Kloner RA et al. J Am Coll Cardiol. 2016;67:545-557.

TABLE 2 Cardiovascular Effects of TRT

Cell/Tissue	Physiological Effect	Clinical Effect	Ref. #
Endothelial function	Enhanced vasodilatation	Increased peripheral and coronary blood flow	111,112
Hemodynamics	Decreased SVR Decreased LVEDP	Increased cardiac output	103,111,115
CV inflammation and atherosclerosis	No consistent data on CIMT, CRP, IL-1β, IL-6, IL-10, TNF-α	None	104
Conduction tissue	Decreased action potential duration and early after-depolarizations	Shortens QTc interval, resulting in improved antiarrhythmic substrate	116
Lipid levels	No consistent effects demonstrated	None	69-71
Myocardial protection	Activation of STAT3	Decreased reperfusion injury	115
Atheroma	No consistent effect on VCAM1	No consistent effect on atherogenesis	113
Hemostasis	Increased TXA2 platelet aggregation	Thrombosis	117

CIMT = carotid artery intima-media thickness; CRP = high-sensitivity C-reactive protein; IL = interleukin; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; QTc = QT interval corrected for heart rate; STAT3 = cardioprotective signal transducer and activator of transcription; sVCAM-1 = soluble vascular cell adhesion molecule-1; SVR = systemic vascular resistance; TNF = tumor necrosis factor; TRT = testosterone replacement therapy; TXA2 = thromboxane A2 receptor expression; VCAM1 = vascular cell adhesion molecule 1.

Testosterone Preparations for Treatment of Hypogonadism

Nieschlag E. Best Pract Res Clin Endocrinol Metab. 2015;29:77-90.

Table 1
Testosterone preparations for substitution of hypogonadism.

Route of application	Preparation	Trade name
Intramuscular	**Testosterone enanthate**	
	250 mg/2–3 weeks	Testoviron® Depot 250 Testosterone Depot®
	Testosterone undecanoate	
	1000 mg, first after 6, then every 12 weeks	Nebido®
	750 mg, every 10 weeks	Aveed®
Transdermal	**Testosterone**	
	Two systems every 48 h	Testopatch®
	125 mg in 5 g gel daily	Testotop®
	100 mg in 5 g gel daily	Tostran®
	2 × 50 mg in 5 g gel daily	Testogel®, Androgel®, Testim®, Androtop®
	60 mg in 2% solution daily	Axiron®
Oral	**Testosterone undecanoate**	
	3-4 capsules à 40 mg daily	Andriol® Testocaps
Buccal	**Testosterone**	
	2 tablets daily	Striant®

Testosterone Treatment of Hypogonadism

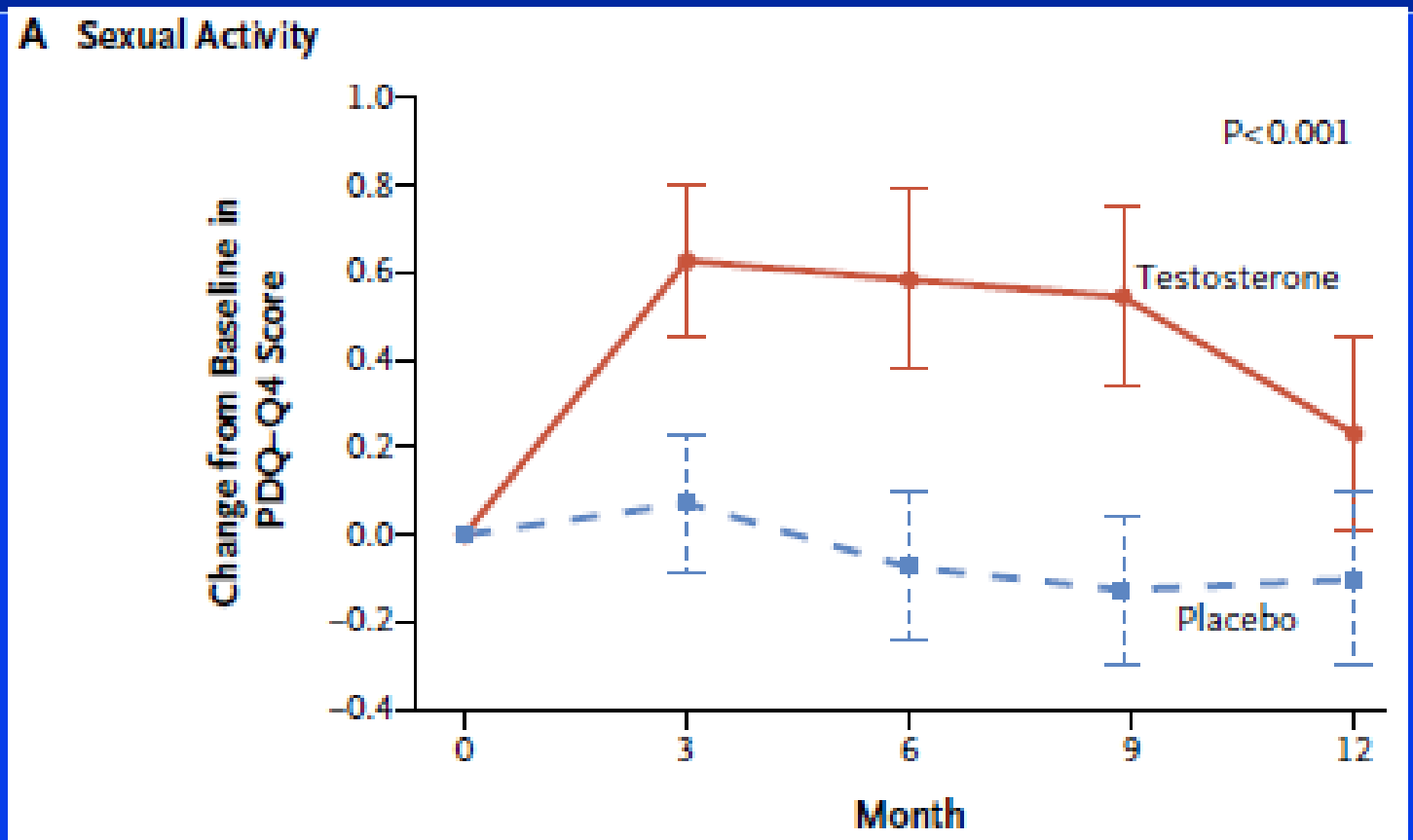
Nieschlag E. Best Pract Res Clin Endocrinol Metab. 2015;29:77-90.

Practice points

- Testosterone is the most important male hormone and not a life-style drug. Its prescription requires the proper diagnosis of hypogonadism as well as regular monitoring of therapeutic effectiveness.
- Substitution therapy should use natural testosterone and aim at physiologic serum levels in order to avoid adverse side effects.
- Testosterone does not cause prostate carcinoma, but may support its growth. Therefore a prostate carcinoma must be excluded before substitution is initiated.
- Overdosing should be avoided as it may cause polycythaemia possibly leading to thromboembolism, especially in obese and ageing hypogonadal patients.
- If erectile dysfunction in hypogonadal patients does not respond to testosterone substitution, combination with phosphodiesterase-5-inhibitors may be considered.

Primary Outcomes in Testosterone Trials 0-12 Months

Snyder PJ et al. N Engl J Med. 2016;374:611-624.



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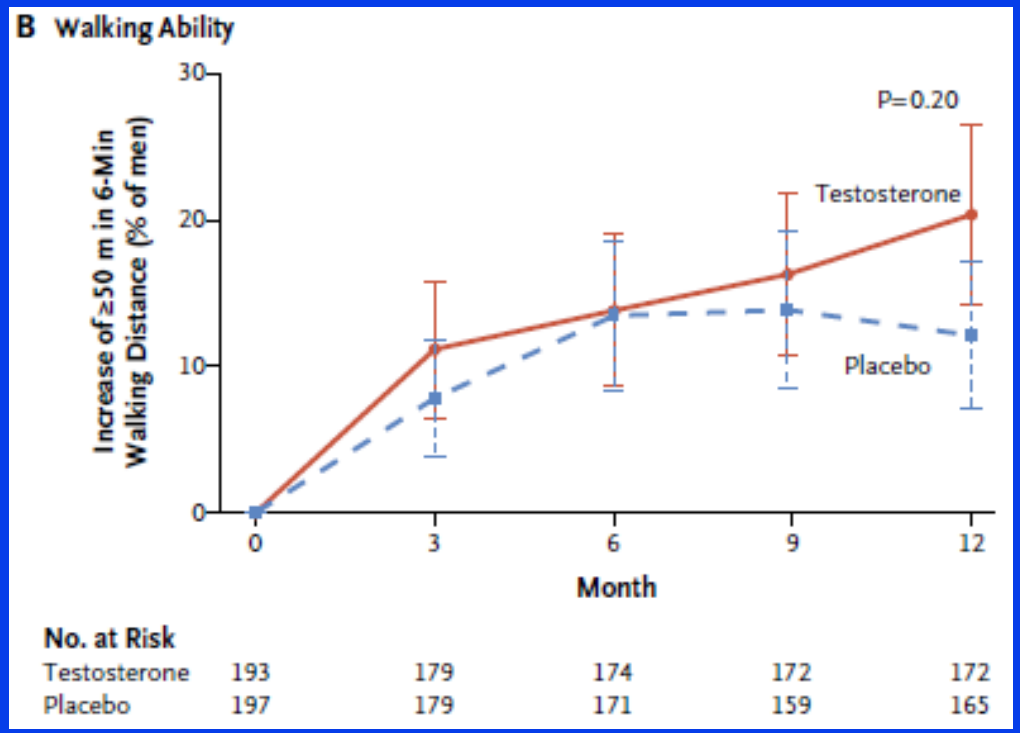
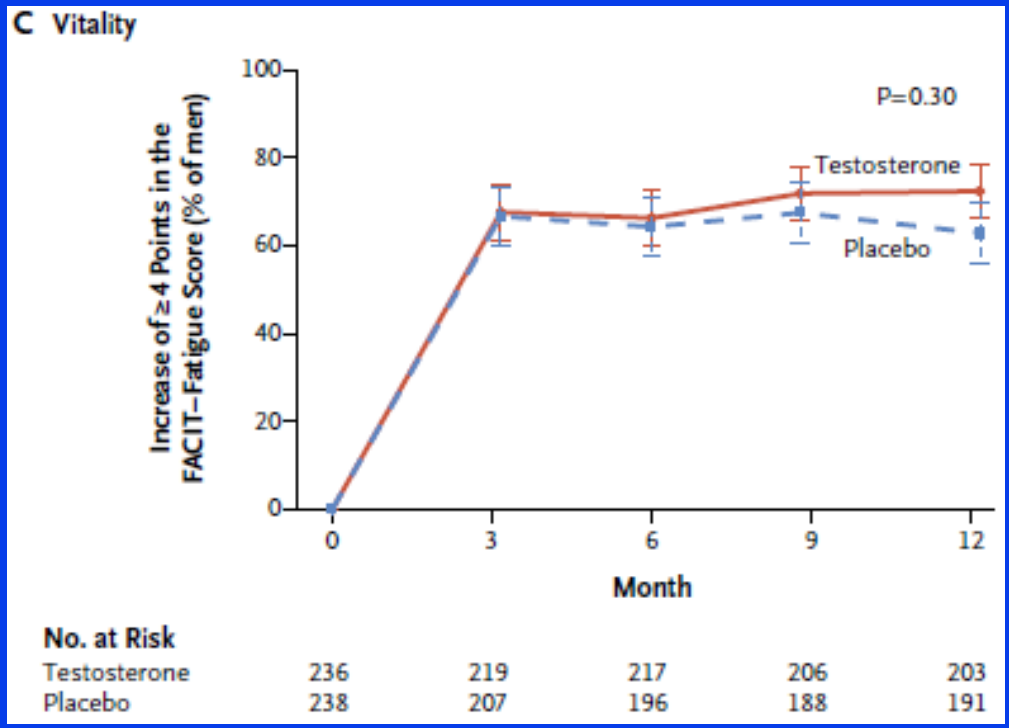




Adverse Events in Testosterone Trials 0-12 Months

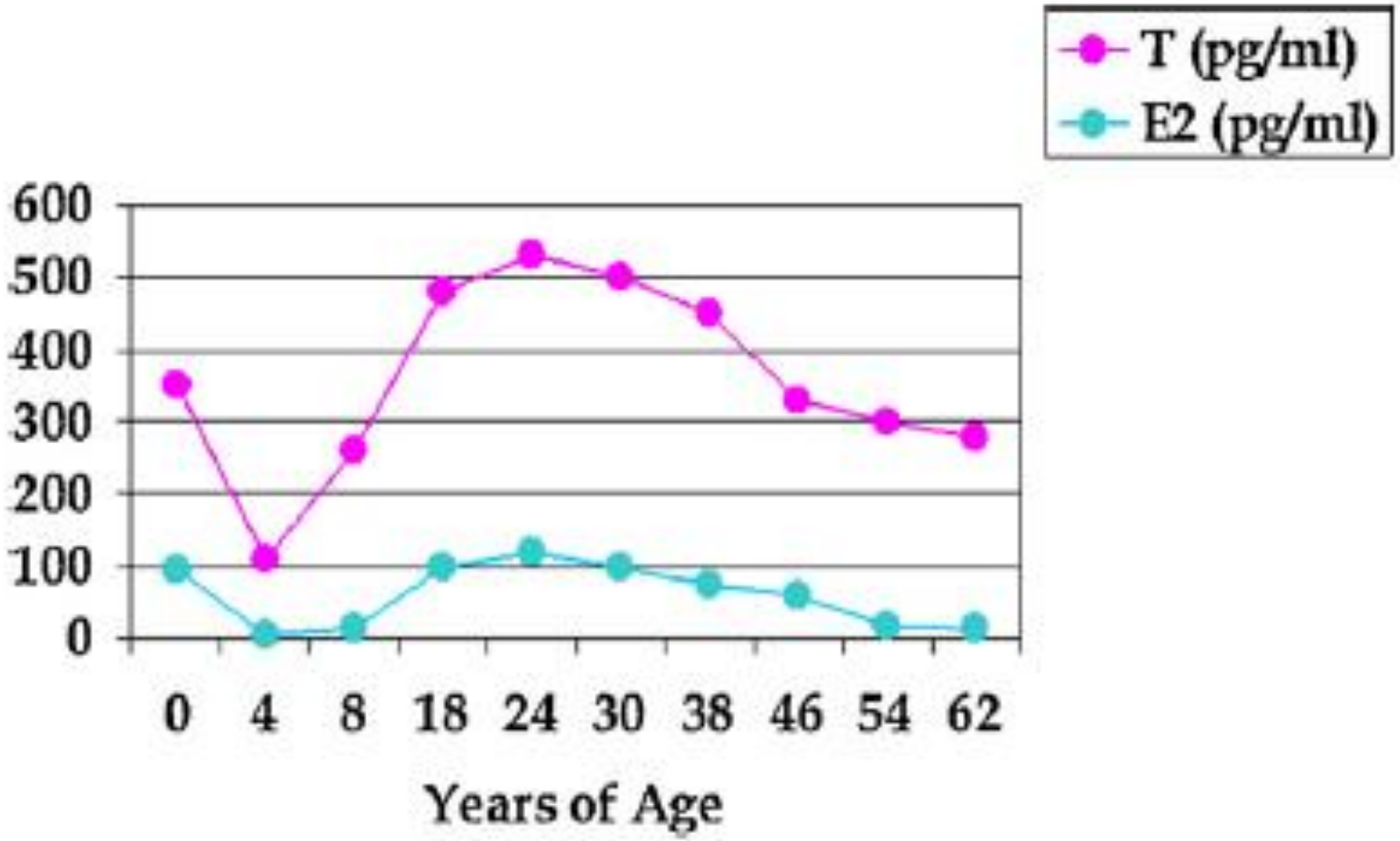
Snyder PJ et al. N Engl J Med. 2016;374:611-624.

Table 4. Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.*

Event	Placebo (N=394)	Testosterone (N=394)
	no. of participants	
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

Testosterone Across the Female Lifespan

Glaser R, Dimitrakkis C. Maturitas 2013;74:230-234.



Testosterone Therapy in Women: Myths and Misconceptions

Glaser R, Dimitrakkis C. Maturitas 2013;74:230-234.

- 1. Testosterone is a male hormone
- 2. Testosterone's only role in women is sex drive and libido
- 3. Testosterone masculinizes females
- 4. Testosterone causes hoarseness and voice changes
- 5. Testosterone causes hair loss
- 6. Testosterone has adverse effects on the heart
- 7. Testosterone causes liver damage
- 8. Testosterone causes aggression
- 9. Testosterone may increase the risk of breast cancer
- 10. The safety of testosterone use in women has not been established

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