Canadian Urological Association
The Voice of Urology in Canada

Association des Urologues du Canada
La voix de l'urologie au Canada

Testosterone Deficiency & Therapy

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cua.org

Speaker Disclosures | Ethan Grober

Relationships with financial sponsors:

- Advisory Board: Paladin (advisor)
- Grant/Honorarium: Boston Scientific (education & research support), Paladin (speaker)
- Investments: Pfizer (stock ownership)

Disclosure of Financial Support

Potential for conflict(s) of interest:

- Members of the SPC committee (Alan Bell, Peter Lin, and Arthur Kushner) received honorarium from the Canadian Urological Association.
- Ethan Grober received honorarium from the Canadian Urological Association at the start of the program.

Mitigating Potential Bias

The scientific planning committee of this program have complete control over the content of this program.

There has been no influence from the sponsors on the content.

Disclosures

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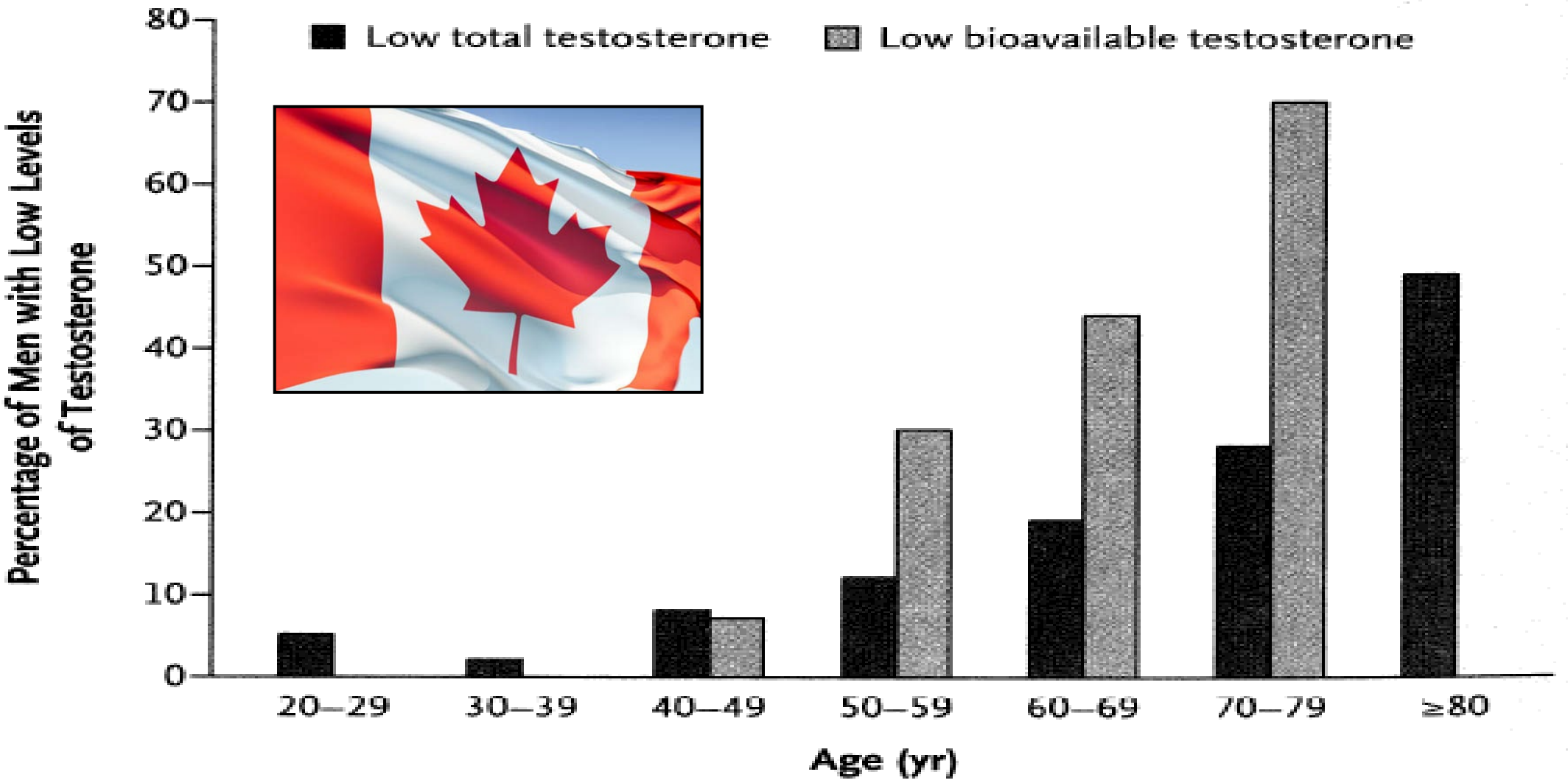
Learning Objectives

Upon completion of this program, participants will be able to:

- cite the definition, prevalence and etiology of testosterone deficiency
- highlight fundamental aspects of the diagnosis of testosterone deficiency
- summarize current treatment options available to Canadian physicians
- outline a monitoring strategy for patients receiving testosterone therapy
- resolve controversies related to testosterone therapy

What is the Prevalence of Testosterone Deficiency ?



Physicians Have Questions & Concerns

25% of Canadian GPs expresses confusion regarding the diagnosis & treatment of testosterone deficiency.

Testosterone Replacement vs. Estrogen Replacement

Testosterone Molecule

≠

Estrogen Molecule

Testosterone

Male

Not universal. Very gradual decrease in the signaling and production of testosterone

Different Hormone

Different Sex

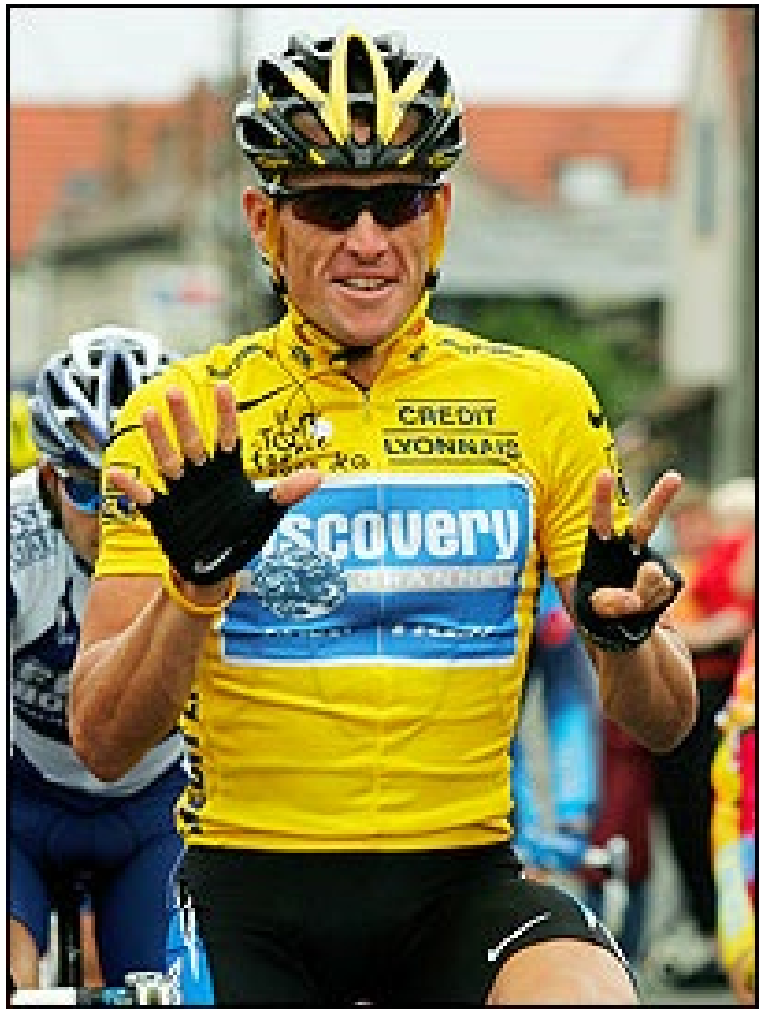
Different Physiology

Estrogen

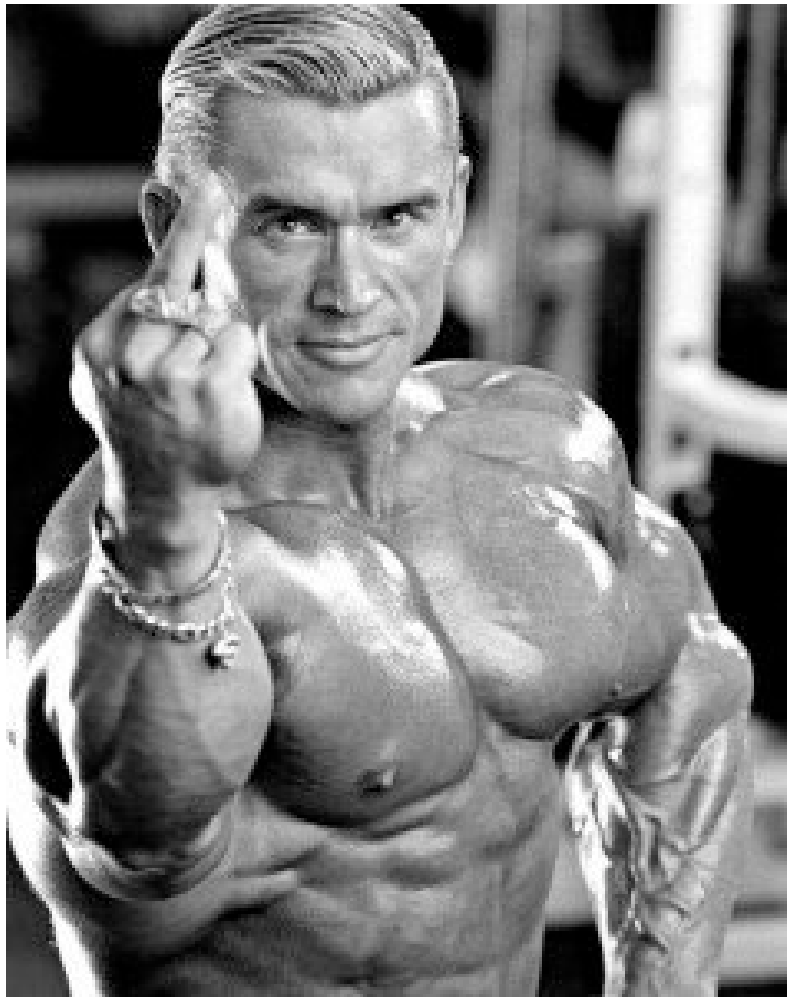
Females

Universal, permanent and rapid decrease in ovarian production of Estrogen

Testosterone (Steroid) Abuse



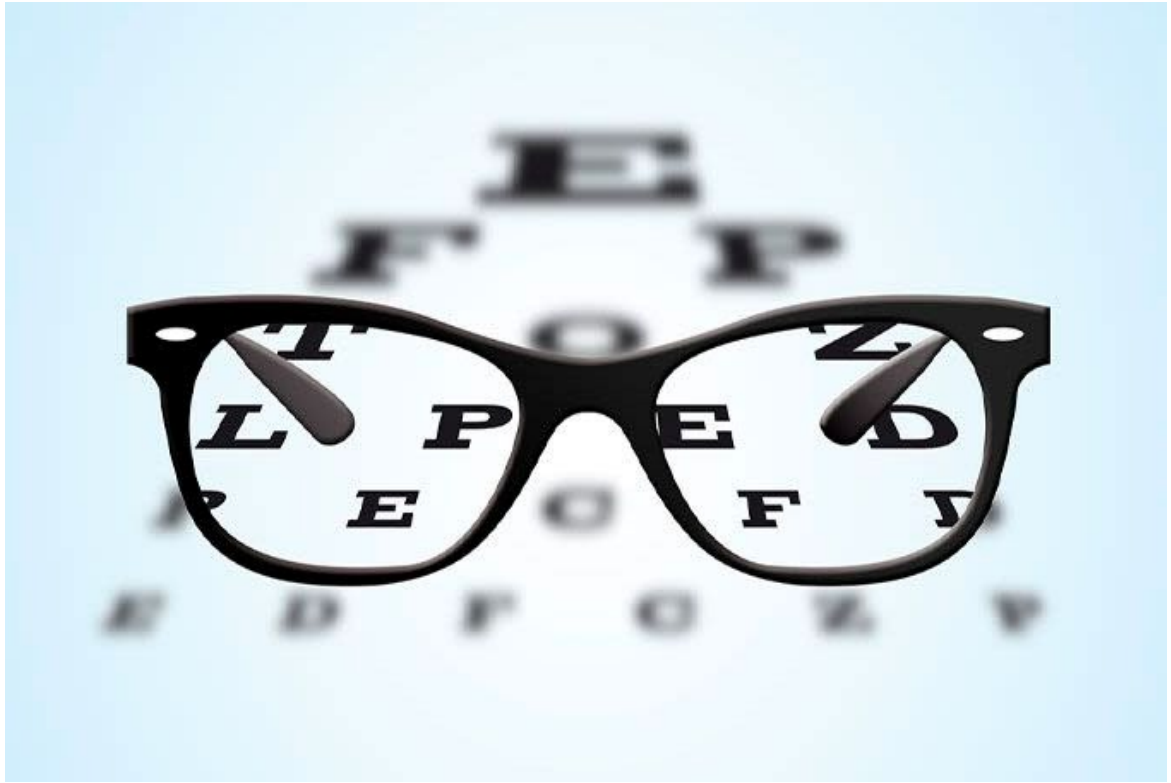
Enhanced Athletic Performance



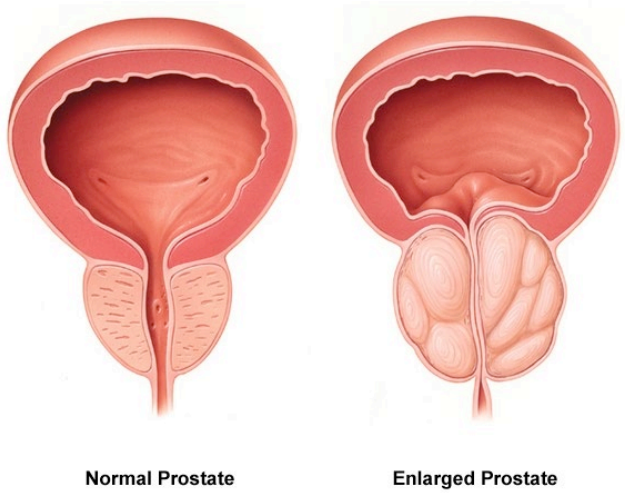
Roid Rage

Is Low T Simply Not the Normal Process of Aging?

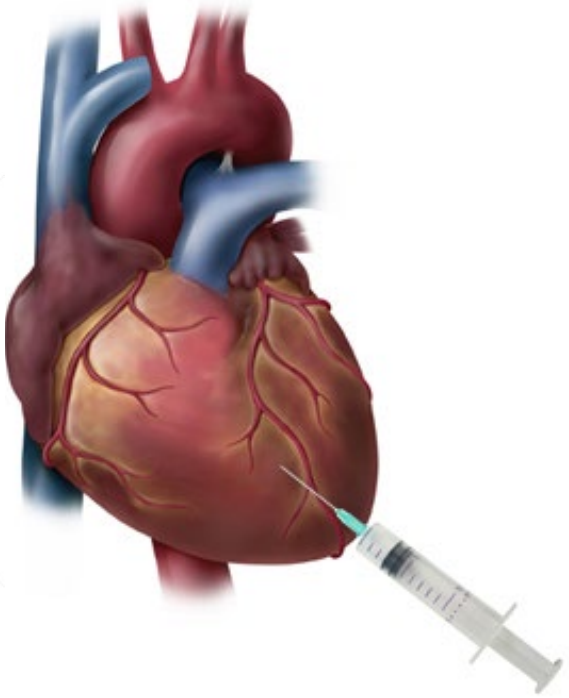
Other Conditions of Aging…



Urological Conditions of Aging…



Concerns About Cardiac & Prostate Health



2021 New CUA Guideline

CUA GUIDELINE

Canadian Urological Association guideline on testosterone deficiency in men: Evidence-based Q&A

Ethan D. Grober, MD[1]; Yonah Krakowsky, MD[2]; Mohit Khera, MD[3]; Daniel T. Holmes, MD[4]; Jay C. Lee, MD[5]; John E. Grantmyre, MD[6]; Premal Patel, MD[7]; Richard A. Bebb, MD[8]; Ryan Fitzpatrick, MD[9]; Jeffrey D. Campbell, MD[10]; Serge Carrier, MD[11]; Abraham Morgentaler, MD[12]

2021 New CUA Guideline

QUESTIONS

Q&A

ANSWERS

Evidence-Based

Practical

User-Friendly

Canadian Specific

2021 New CUA Guideline

Practical Overview:

1.What is the definition of testosterone deficiency?
2.What is the prevalence of testosterone deficiency among Canadian men?
3.What are the common signs and symptoms of testosterone deficiency?
4.Why does testosterone deficiency occur?

Diagnosis:

5.How best to establish the diagnosis of testosterone deficiency with history & physical examination?
6.Are there valid screening questionnaires for testosterone deficiency? Are they helpful in establishing the diagnosis?
7.What is the recommended laboratory test to diagnose testosterone deficiency?
8.What is the biochemical level or cut off to diagnose testosterone deficiency?
9.Besides measuring testosterone, what adjunctive laboratory testing is indicated?
10.What are potentially reversible causes of testosterone deficiency that physicians should consider?
11.What are the common co-morbid conditions associated with testosterone deficiency?

Treatment:

12.What are the goals and benefits of testosterone therapy?
13.What are the current treatment options for testosterone deficiency in Canada?
14.What is the recommended approach to treating a patient with characteristic symptoms of testosterone deficiency with a "normal" testosterone level?
15.What is the recommended approach to treating a patient with *NO* symptoms of testosterone deficiency but a "low" testosterone level?
16.What is the likelihood that my patient will respond/benefit from treatment?
17.What is the best treatment approach to a patient with testosterone deficiency who is interested in fertility preservation?
18.What is the suggested level of testosterone to achieve while on treatment?
19.What is the evidence for herbal or natural testosterone "boosters" in treating testosterone deficiency?
20. Aside from testosterone, are there other treatments that can be used to treat testosterone deficiency?

Treatment Risks:

21.Does testosterone replacement therapy increase the risk of prostate cancer?
22.Does testosterone replacement therapy increase the risk of benign prostatic hyperplasia (BPH) progression and lower urinary tract symptom (LUTS)?
23.Does testosterone replacement therapy increase the risk of cardiovascular disease?
24.What are the contraindications to testosterone therapy?

Monitoring:

25.What monitoring is required for a patient receiving testosterone therapy?
26.What is a reasonable timeline to begin to observe improvements in the signs and symptoms of testosterone deficiency?
27.How and when should testosterone therapy be discontinued?

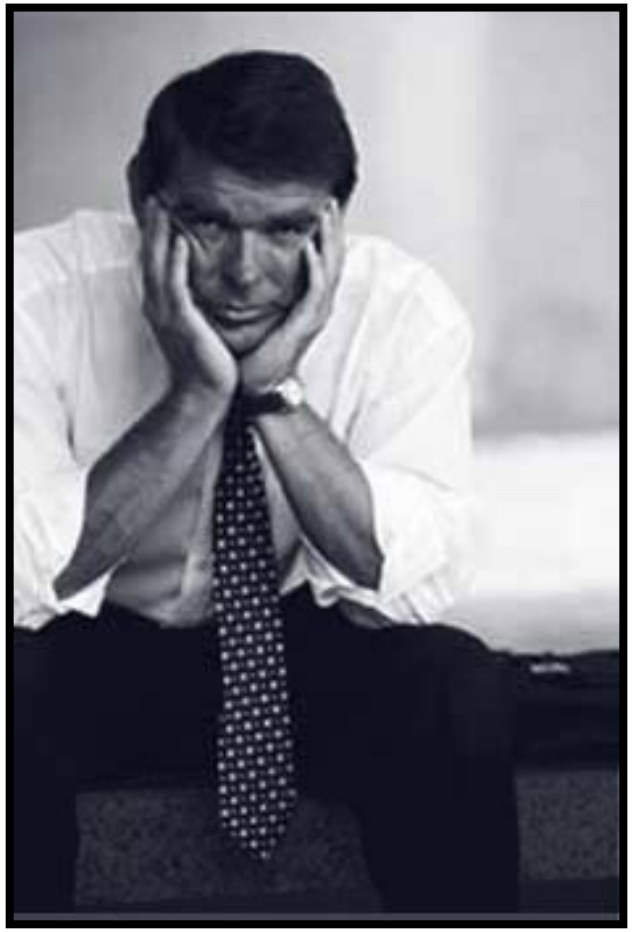
What is the Definition of Testosterone Deficiency?

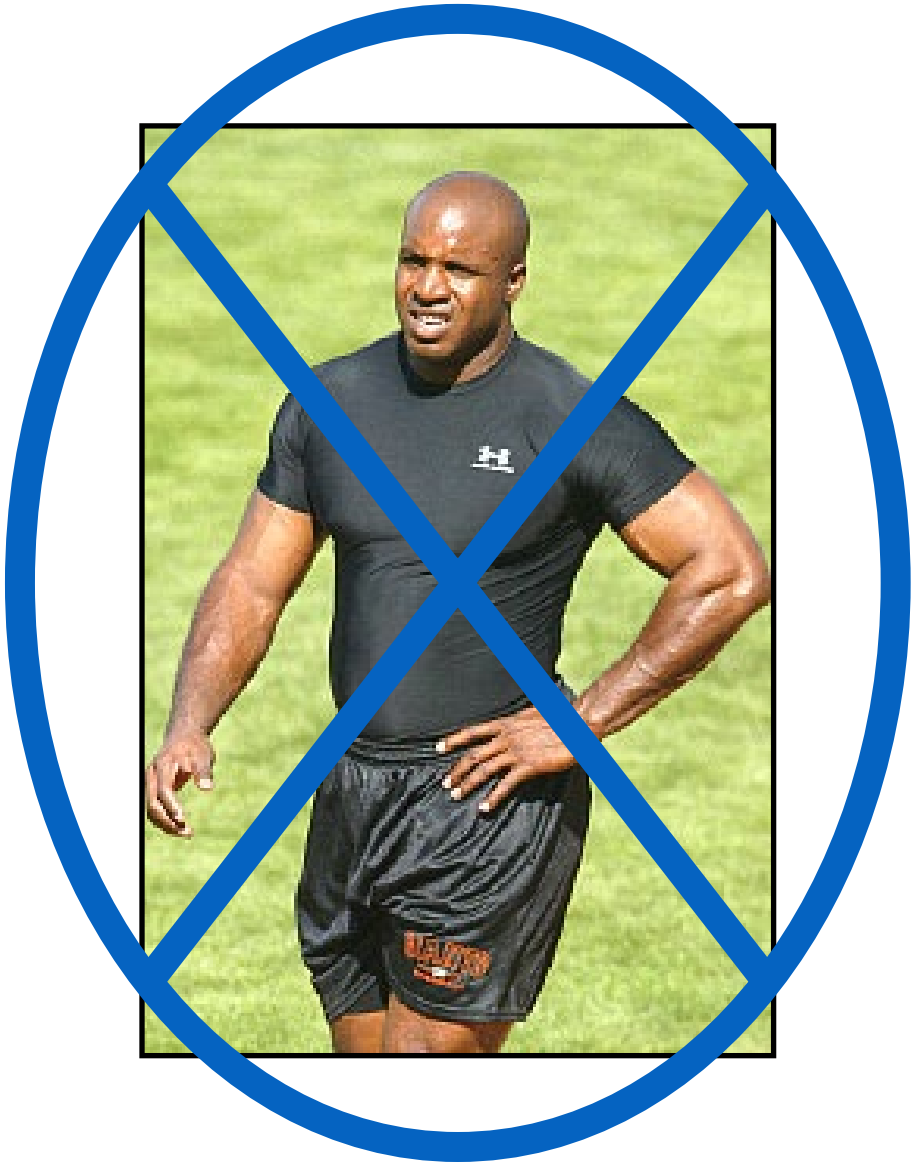
- Testosterone deficiency is a clinical and biochemical syndrome that may occur in men in association with advancing age, however younger men with certain conditions may also be affected.

- The condition is characterized by *deficient testicular production of testosterone*, with or without changes in *receptor sensitivity* to androgens.

- It may affect multiple organ systems and can result in significant health consequences and a negative impact on quality of life.

Who Are We Talking About?





Clinical Manifestations of Testosterone Deficiency?

	Clinical manifestation
Sexual	Decreased libido Delayed ejaculation Reduced ejaculate volume Decreased intensity of orgasm Erectile dysfunction Loss of morning erections Infertility
Cognitive/Psychological	Fatigue Changes in mood Depression Insomnia Poor concentration /memory Irritable
Physical/Structural	Decreased vitality/energy Anemia Gynecomastia Hot flushes Decrease in muscle mass and strength Increased visceral body fat Decreased bone mineral density/osteopenia Testicular atrophy Loss of facial, axillary and pubic hair

Why Does Testosterone Deficiency Occur?

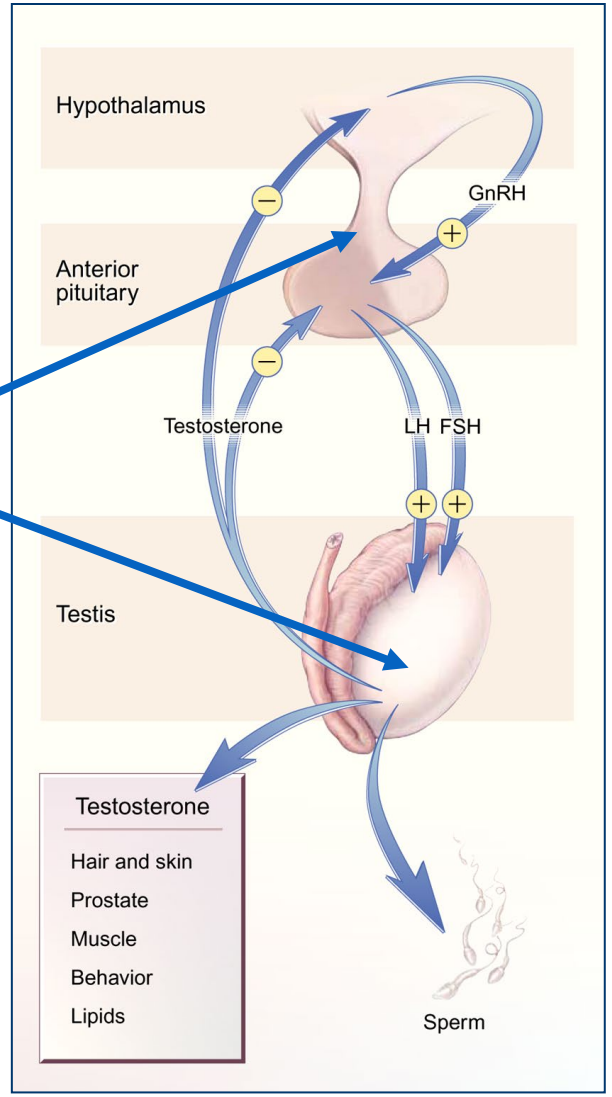
After the age of 50, mean T levels decrease by 1%/year

1) Loss of Leydig cells > progressive loss of T production with age (primary failure)

2) Decreased GnRH pulse amplitude results in decreased T production (secondary failure)

3) Increased SHBG > less free and bioavailable testosterone

4) Diminished receptor sensitivity to T



Why Does Testosterone Deficiency Occur?

Medications or substance use		Opioids Glucocorticoids (prednisone) Chemotherapy Anticonvulsants Androgen deprivation therapy Exogenous estrogen Exogenous testosterone abuse Marijuana Alcohol abuse
Associated conditions	Acquired	Diabetes mellitus Metabolic syndrome HIV Hyperprolactinemia End-stage renal disease Liver disease Hemochromatosis COPD Sleep Apnea Orchitis (mumps) Sarcoidosis Pituitary tumor / adenoma Primary hypothyroidism
	Genetic	Kallman's syndrome Klinefelter syndrome Congenital defect – anorchia, myotonic dystrophy, cryptorchidism
	Iatrogenic	Radiation Trauma Nutritional deficiency Excessive exercise

What is the Recommended Laboratory Test to Diagnose Testosterone Deficiency?

What is the Recommended Laboratory Test to Diagnose Testosterone Deficiency?

Recommendation:

- *Total testosterone* (morning draw: 7am-11am) remains the best initial screening test to diagnose T

- *Calculated free or bioavailable* testosterone based total testosterone, sex hormone binding globulin (SHBG) and albumin concentrations can be determined to resolve equivocal total testosterone measures in symptomatic men. (LE-moderate, strong recommendation)

What is the Biochemical Level or Cut Off to Diagnose Testosterone Deficiency?

- Establishing an absolute biochemical cut-off diagnostic for TD is challenging:
- Lab variability, different reference ranges
- lack of age-related reference standards
- unknown baseline testosterone levels in individual patients
- variable target organ receptor sensitivity to circulating testosterone concentrations

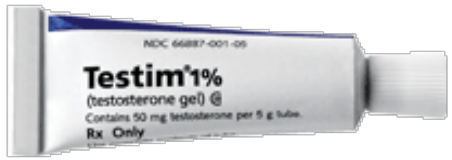
What is the Biochemical Level or Cut Off to Diagnose Testosterone Deficiency?

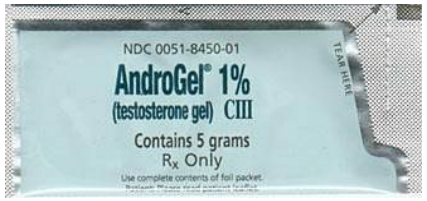
Recommendation:

- Most clinician experts and previously published guidelines would suggest that a total testosterone ***< 10 nmol/L*** represents a reasonable diagnostic threshold consistent for TD, while appreciating that some patients may manifest symptoms of TD at higher levels.

- ***Testosterone measures can be used as a complimentary tool (as opposed to an absolute or diagnostic one)***, to support the diagnosis of TD in the context of characteristic signs and symptoms identified by way of a detailed clinical evaluation (LE-low, weak recommendation).

What are the Current Treatment Options for Testosterone Deficiency in Canada?





What are the Current Treatment Options for Testosterone Deficiency in Canada?

Generic Name	Trade Name	Dosage	Comments
Injectables **Testosterone Enanthate** **Testosterone Cypionate**	Delatestryl Depo-testosterone	100-200 mg every 1-4 weeks 200 mg every 2 weeks or 100mg weekly	Cost effective Typically delivered intramuscularly (IM) into large muscle including the thigh or gluteal. May require regular clinic visits Wide fluctuations in testosterone levels requires mid-cycle testosterone monitoring Higher risk for polycythemia
Oral Medication **Testosterone Undecanoate**	Andriol	40 mg capsules Initial dose of 120-160 mg per day in 2 divided doses	Absorption enhanced with fat rich diet Short half-life requires multiple daily dosing Clinical & biochemical variability
Transdermal **Testosterone Patch** **Testosterone Gels**	Androderm Androgel Testim	2.5 or 5 mg per day 5-10 g per day	Rash/skin irritation common (patch) Transfer of medication to intimate contact (gel) Variable absorption
Tans-nasal Gel	Natesto 4.5%	5.5 mg (1 pump from the actuator device) applied to each nostril (11 mg total), two times daily, at least 6 hours apart. Total daily dose of 22mg.	Approved by Health Canada but currently unavailable due to a manufacturing modification Potentially less suppression of spermatogenesis

What are the Current Treatment Options for Testosterone Deficiency in Canada?

Compounded testosterone products are available at many compounding and online pharmacies within Canada, however published data has demonstrated significant variability of testosterone concentrations within such products leading to concerns regarding efficacy and safety.

Approach to Treating a Patient with Characteristic Symptoms of Testosterone Deficiency with a *"Normal" Testosterone* Level?

Rule out conditions with an overlapping symptom complex (i.e. depression, hypothyroidism, sleep disorders)

Recommendation:
Recognizing the limitations of T measurement, a *supervised trial of testosterone therapy (3-months)* with close monitoring of both the symptomatic and biochemical response to treatment is recommended. (LE-low, weak recommendation)

What is the Suggested Level of Testosterone to Achieve While on Treatment?

- Treating physicians should aim to prescribe the minimal required dosing to improve serum testosterone and hypogonadal symptoms.

- Recognizing the variations in normal ranges among the various laboratories throughout Canada, the current recommendations are to target correction of serum levels to the ***mid-normal reference range (total testosterone 14-17 nmol/L, LE-low, weak*** *recommendation*)

- Patients without significant symptomatic improvement and serum testosterone levels measured below the mid-normal range can be considered for dose escalation to improve clinical efficacy.

- Patients with satisfactory resolution of their symptoms, but serum testosterone below the recommended target range typically do not require dose adjustment.

- Dose reductions should be prescribed in patients with serum testosterone concentrations consistently measuring above the normal range while on treatment.

Does Testosterone Therapy Increase the Risk of Prostate Cancer?

60 year old male
T = 8
ED, declining libido & vitality
PSA = 2.0, normal DRE

- Despite historical teachings about the relationship between testosterone on prostate cancer biology & risk, consistent evidence suggests *that testosterone therapy does not increase a man's risk for developing prostate cancer.*

- *No clinically significant increase in PSA*

Does Testosterone Therapy Increase the Risk of Prostate Cancer?

- 62 year old male
- T = 7
- ED, declining libido & vitality
- Gleason 7 prostate cancer
- PSA <0.0001 following radical prostatectomy

Recommendation:

Symptomatic men with TD who have been diagnosed with *localized prostate cancer and treated (surgery, radiation) or followed with active surveillance without evidence of active disease* can be considered for a medically supervised trail of testosterone therapy (LE-low, weak recommendation).

Consultation with a urologic specialist is recommended.

Patients with *metastatic or high-risk prostate cancer* who are likely to require androgen depravation therapy should not be offered testosterone therapy.
(LE-moderate, strong recommendation)

Does Testosterone Therapy Increase the Risk of Benign Prostatic Hyperplasia (BPH) and Lower Urinary Tract Symptom (LUTS)?

- 60 year old male
- T = 8, ED, declining libido & vitality
- PSA = 2.5, 75 cc benign prostate
- Increasing LUTS - started on 5ARI

Testosterone therapy does not worsen urinary symptoms/LUTS due to BPH or have a negative impact (often positive) on prostate volume, peak flow rates, volumes voided.

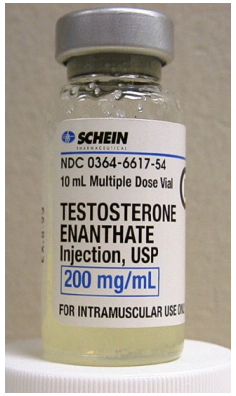
Recommendation:

Testosterone therapy can safely be administered to men with BPH and lower urinary tract symptoms (LE-moderate, weak recommendation).

Does Testosterone Therapy Increase the Risk of Cardiovascular Disease?

<u>*Low endogenous*</u> (natural) levels of testosterone are associated with increased cardiovascular risk:

- obesity, diabetes, dyslipidemia, metabolic syndrome & cardiovascular death



? Impact of Testosterone Therapy

Prior to 2010: Cardiovascular benefit
After 2010: Cardiovascular concern

Does Testosterone Therapy Increase the Risk of Cardiovascular Disease?

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By MICHELLE CASTILLO / CBS NEWS / February 25, 2014, 5:58 PM

Group asks FDA for black box warning on testosterone products due to heart risks

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'Low-T?' Testosterone therapy may boost serious risks in men with heart troubles

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Testosterone Supplements Tied to Heart Attacks, Strokes, Early Death

By ABC News Nov 5, 2013 4:00pm

Does Testosterone Therapy Increase the Risk of Cardiovascular Disease?

To date, there are no large, long-term placebo-controlled trials to help make definitive statements on testosterone therapy and cardiovascular risk.

The available literature suggests that *untreated* testosterone deficient men are at increased risk of heart disease, cardiovascular events and death.

Recommendation:

Based on the best available evidence, *symptomatic hypogonadal men with stable cardiovascular disease remain candidates for a medically supervised trail of testosterone therapy.* An individualized risk-benefit assessment is prudent (LE-low, weak recommendation).

What are the Contraindications to Testosterone Therapy?

- Allergy or hypersensitivity to prescribed treatment
- Known or suspected male breast cancer
- Patients who desire fertility preservation
- Patients with metastatic or high-risk prostate cancer who are likely to require androgen deprivation therapy
- Patients with unstable cardiovascular disease

What Monitoring is Required for a Patient Receiving Testosterone Therapy?

After initiating testosterone therapy, patients should have regular monitoring for response to treatment and adverse events.

	BASELINE	3 MONTHS	6 MONTHS	YEARLY
Symptom Evaluation	X	X	X	X
Adverse Event Monitoring		X	X	X
Serum Testosterone	X	X	X	X
Hematocrit	X	X	X	X
Prostate Specific Antigen (PSA)	X	X	X	X
Digital Rectal Examination (DRE)	X			X

What Monitoring is Required for a Patient Receiving Testosterone Therapy?

Prostate specific antigen (PSA) testing and digital rectal examination should be performed to monitor prostate health in accordance with the evidence-based guidelines for prostate cancer screening *(LE-low, weak recommendation)*.

> The Canadian Urological Association guideline on prostate cancer screening and early diagnosis of prostate cancer

While discontinuation of testosterone therapy may be considered while investigating a PSA elevation, *significant increases in PSA while on testosterone therapy should not be attributed to the use of testosterone alone and should be investigated irrespective of the use or discontinuation testosterone therapy*.

How and When Should Testosterone Therapy be Discontinued?

- For most men, the initiation of testosterone therapy is discretionary and is based on the nature of their signs and symptoms, their degree of disability and impact on quality of life.

- Testosterone therapy should be discontinued if significant adverse events or contraindications to treatment arise or if there is no clinical improvement despite normalization of serum testosterone levels after an adequate therapeutic trial (approximately 3 months).[5]

- There is no need for tapered dose titration when discontinuing of testosterone therapy *(LE-high, strong recommendation)*.

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