CUA Guideline:
Testosterone Deficiency in Men – *Evidence-Based Q&A*

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Originally published in *Can Urol Assoc J 2021;15(5):E234-43..*
http://dx.doi.org/10.5489/cuaj.7252

Disclosures

Dr. Grober has received research and educational support from Boston Scientific; is an investor in MHB Labs; and has been a speaker and consultant for Paladin Labs.

Dr. Karkowsky has been a consultant for Felix and Paladin Labs; a speaker for Pfizer; and has received research support from Boston Scientific.

Dr. Khera has been a consultant for AbbVie, Acerus, Boston Scientific, Clarus, and Metuchen.

Dr. Holmes has been a consultant for Dian Diagnostics; has received research support from SCIEX; and has received honoraria from the American Association for Clinical Chemistry and MSACL.org.

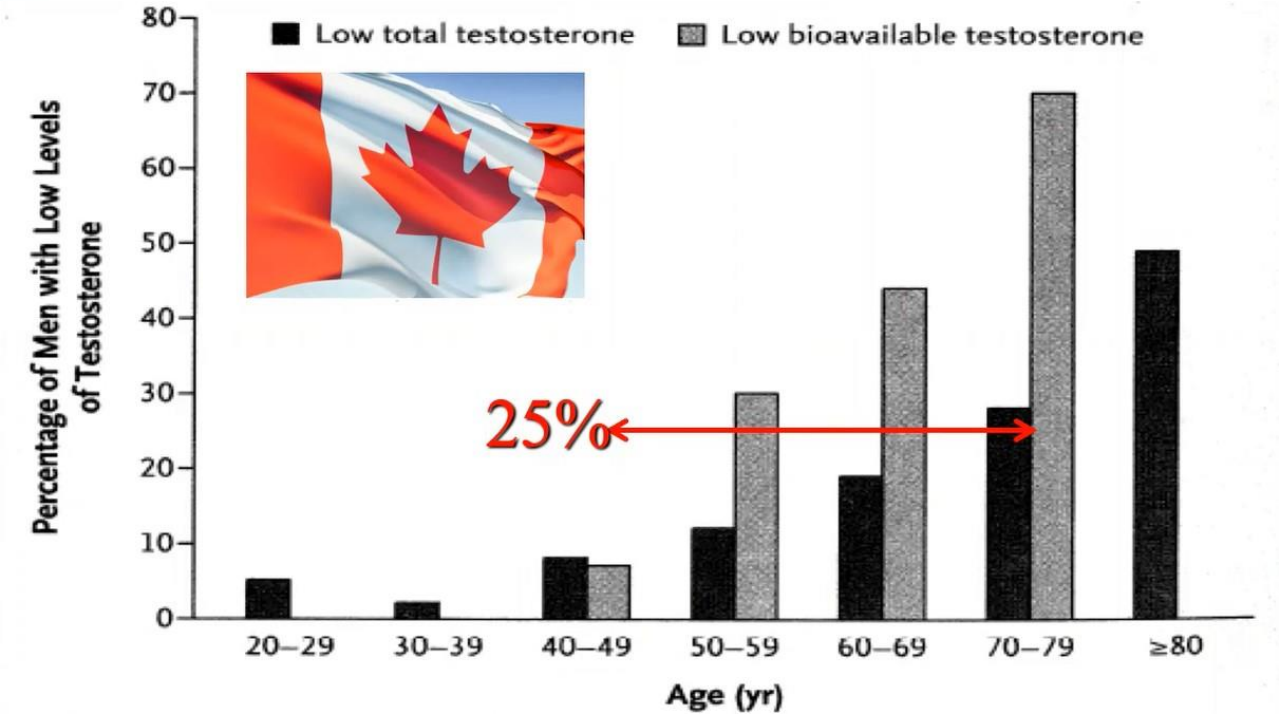
Dr. Lee has been a speaker for Acerus, Astellas, Paladin, and Pfizer; and an advi-sory board member for Acerus and Paladin.

Dr. Patel has been a consultant for Boston Scientific and Nestle Health; has received honoraria from Boston Scientific, and Paladin; and has received an investigator-initiated grant from Coloplast.

Dr. Carrier has been an advisory board member for Paladin; a speaker for Acerus, Coloplast, Endo, and Paladin; has received research grants from and participated in clinical trials supported by SMSNA/Boston Scientific and Urotronic; and has been a proctor for Red Leaf Canada.

Dr. Morgentaler has been a consultant for Acerus and Marius; has received speaker honoraria from Bayer; and has received research support from Endo.

Prevalence in Canada



Testosterone Molecule

Estrogen Molecule

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Testosterone	Different Hormone	Estrogen
Male	Different Sex	Females
Not universal. Very gradual decrease in the signaling and production of testosterone	Different Physiology	Universal, permanent and rapid decrease in ovarian production of Estrogen

Questions addressed in the 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?

Questions addressed in the guideline cont'd

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?

Questions addressed in the guideline cont'd

Treatment risks:

21. Does testosterone replacement therapy increase the risk of prostate cancer?
22. Does testosterone replacement therapy increase the risk of benign prostate 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?

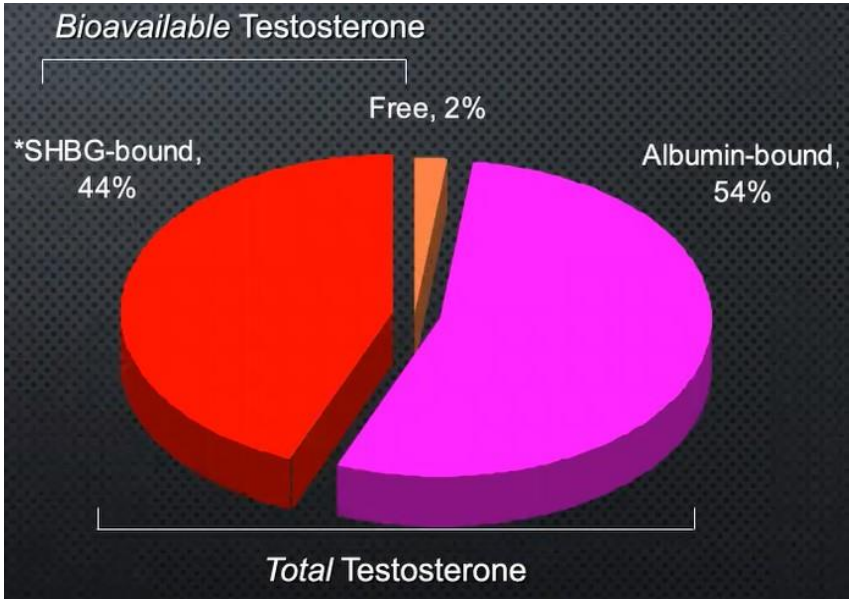
Monitoring:

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?

Focus on:

- What lab test to diagnose TD?
- What biochemical “cut off” to diagnose TD?
- Approach to the symptomatic patient with “normal” T?
- T and prostate health?
- T and cardiac health?
- Recommendations for monitoring T therapy?

What is the recommended lab test to diagnose testosterone deficiency?



What is the recommended lab test to diagnose testosterone deficiency?

Recommendation:

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

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Strict cut-off <300 ng/dl cut off to establish the diagnosis of TD (<10.4 nmol/l)

What is the recommended 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).*

Does testosterone replacement 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 and 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 replacement 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 trial 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 replacement therapy increase the risk of BPH progression 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 replacement therapy increase the risk of cardiovascular disease?

Low endogenous (natural) levels of testosterone are associated with increased cardiovascular risk: obesity, diabetes, dyslipidemia, metabolic syndrome, and cardiovascular death

Impact of testosterone therapy?

Prior to 2010: Cardiovascular benefit
After 2010: Cardiovascular concern

Does testosterone replacement 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 trial of testosterone therapy.* An individualized risk-benefit assessment is prudent *(LE-low weak recommendation).*

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 effects.

	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*)

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 of testosterone therapy.*

*From Rendon RA, et al. Canadian Urological Association guideline on prostate cancer screening and early diagnosis of prostate cancer. *Can Urol Assoc J* 2017;11(10):298-309. http://dx.doi.org/10.5489/cuaj.4888