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TESTOSTERONE REPLACEMENT THERAPY IN THE AGING MALE

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Abstract:

There is growing attention towards the hormonal deficiencies that develop in aging men. As a result, many convenient but costly methods to replace testosterone have emerged in efforts to improve health and wellbeing. Unlike females, the decline in male gonadal function seen with aging is not marked by clear clinical measurable symptoms (e.g., menopausal amenorrhea, hot flashes), making androgen deficiency in the aging male a challenging diagnosis to confirm. Before testosterone replacement therapy can be considered, the clinician must demonstrate biochemical evidence of low serum testosterone, and rule out both reversible causes of hypogonadism and contraindications to therapy. A discussion with the patient of the potential benefits and harms should also take place. There is mounting concern regarding the association between testosterone replacement therapy and cardiovascular risk among men over the age of 65 especially in those with pre-existing heart disease. Therefore, close clinical monitoring for the development of side effects and contraindications to continued therapy is required, especially during the first year of therapy. This area of clinical care will continue to evolve as data emerges from long-term safety studies of testosterone therapy in aging men.

Les déficits hormonaux qui peuvent survenir chez les hommes âgés reçoivent une attention croissante. En conséquence, de nombreuses méthodes pratiques mais coûteuses de remplacement de la testostérone ont été proposées afin d'améliorer la santé et le bien-être. Contrairement aux femmes, le déclin de la fonction gonadique masculine avec le vieillissement ne se manifeste pas toujours par des symptômes cliniques identifiables et clairs (comme par exemple, l'aménorrhée consécutive à la ménopause et les bouffées de chaleur), ce qui rend difficile le diagnostic de la déficience androgénique chez l'homme âgé. Avant de débuter le remplacement de la testostérone, il faut documenter de faibles taux de sérique et exclure les causes réversibles d''hypogonadisme ainsi que les contre-indications au traitement. Une discussion avec le patient des avantages et des inconvénients potentiels du traitement devrait aussi avoir lieu. L'association entre le traitement de remplacement de la testostérone et le risque cardiovasculaire chez les hommes âgés de plus de 65 ans suscite de l'inquiétude, particulièrement chez ceux ayant de antécédents de maladie cardiaque. Ainsi, une surveillance clinique étroite des effets secondaires et des contre-indications à poursuivre les traitements est nécessaire, particulièrement au cours de la première année de traitement. Ce champ clinique continuera à se développer surtout avec la publication de

données émanant d'études d'innocuité à long terme de la testostérone chez les hommes âgés.

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Introduction

While menopause in women is well recognized by identifiable changes in menstruation, vasomotor symptoms and hormonal measurements, androgen deficiency in the aging male (also known as andropause, low T or late-onset hypogonadism) is less clearly characterized. The slow insidious onset of gonadal decline in men, along with a concurrent rise in medical comorbidities poses a challenge to recognizing the potential clinical consequences of low testosterone to their health and wellbeing. The estimated decline in serum free and total testosterone is 1-2% per year after age 40.[1-3] For some older men, however, the serum testosterone levels may remain within the "normal" range despite a relative reduction. The prevalence of low testosterone levels in men over the age of 60 ranges widely among studies from 4-50%[2,4,5] due in part to differences in testosterone assays employed and disagreement regarding what the true threshold value is in the diagnosis of low serum testosterone.

With increased public awareness and diagnosis of androgen deficiency in the aging male, the availability and use of various testosterone replacement methods in Canada has rapidly expanded. In Ontario, one in 90 men over the age of 65 were being treated with testosterone in 2012, yet only 6.3% of these men had a documented diagnosis of hypogonadism.[6] The potential overuse of testosterone replacement has prompted Choosing Wisely Canada to put forth recommendations on therapy for testosterone deficiency (www.choosingwiselycanada.org/recommendations/endocrinology-and-metabolism/). Commonly prescribed testosterone preparations are the topical gels, which can cost greater than $3 per day and nearly $1,500 per year for each patient in Ontario.[7] Given the challenges in diagnosing androgen deficiency, its rising public awareness and the high costs of therapy, this review aims to help clinicians identify appropriate patients for therapy and guide management decisions.

Diagnosis

The diagnosis of androgen deficiency is more challenging in older men, compared to their younger counterparts. In the younger man with androgen deficiency, the etiology can be classified as primary (testicular), secondary (pituitary or hypothalamic) or occasionally a combination of both mechanisms (mixed hypogonadism) due to diseases such as hemochromatosis, sickle cell disease and alcoholism.[8] Cross-sectional studies have found that low testosterone in the aging male can be due to mixed hypogonadism without any obvious underlying disease[1,2,9] (http://press.endocrine.org/doi/pdf/10.1210/jcem.87.2.8201). Furthermore, age-related increases in sex-hormone binding globulin (SHBG) and alterations in binding characteristics can lead to a reduction in free or bioavailable testosterone.[8,10]

The clinical features of hypogonadism are often less clear in the older man. While some symptoms quoted as having high specificity such as decreased libido, decreased spontaneous erections, fragility fractures or reduced bone density may occur, other less specific symptoms often dominate the clinical presentation (Table 1).[8, 10] These less specific signs and symptoms, however, can also be seen with aging and comorbid illness and may occur independently of a decline in serum testosterone levels. It is recommended that

screening for low testosterone only be performed in symptomatic men. Questionnaires such as the ADAMq and AMS[11,12] are sometimes used to quantify the severity of symptoms associated with low testosterone. Although these questionnaires generally have good sensitivity, their specificity is poor. It is advised that physicians not use such questionnaires in their waiting rooms as this can lead to unnecessary screening of otherwise asymptomatic men.[11,13] The recommended method and interpretation of serum testosterone levels varies between guidelines and medical societies (Endocrine Society Guideline: http://press.endocrine.org/doi/pdf/10.1210/jc.2009-2354; Canadian Urological Association Guideline: www.ncbi.nlm.nih.gov/pmc/articles/PMC2910774/.[8, 10,14] A Canadian working group has advised the use of the lower limit of the reference range for young healthy men established in their local laboratory due to variations in reagents and normal values.[14] At present, there is a lack of testosterone measurement standardization between labs in North America. In the United States, the Centers for Disease Control and Prevention has created the Hormone Standardization Project (HoST) in attempts to improve upon this,[15] but similar initiatives have not yet occurred in Canada. Total testosterone should be measured in the morning (between the hours of 7:00 am and 11:00 am, and ideally as close to 8:00 am as possible) as levels peak during this time period due to circadian rhythms.[16] Low testosterone levels should be confirmed by a second measurement (ideally at the same laboratory) due to large variability in day-to-day testosterone measurements.[17] Testing should not be performed during an acute illness due to alterations in the hypothalamic-pituitary-testicular axis.[18]

Table 1. Proposed signs and symptoms of hypogonadism in the male

More specific signs and symptoms	**Less specific signs and symptoms**
▪ Reduced sexual desire (libido) and activity ▪ Decreased spontaneous erections ▪ Erectile dysfunction ▪ Breast discomfort, gynecomastia ▪ Loss of body hair (axillary, pubic), reduced shaving ▪ Very small (<5 mL) or shrinking testes ▪ Infertility, low or zero sperm count ▪ Incomplete or delayed sexual development, eunuchoidism ▪ Height loss, low trauma fracture, low bone density ▪ Hot flushes, sweats	▪ Decreased energy, motivation, initiative, and self-confidence ▪ Delayed ejaculation ▪ Feeling sad or blue, depressed mood, dysthymia, irritability ▪ Poor concentration and memory ▪ Sleep disturbance, increased sleepiness ▪ Mild anemia (normochromic, normocytic, in the female range) ▪ Reduced muscle bulk and strength ▪ Increased body fat, body mass index, visceral obesity ▪ Diminished physical or work performance
Adapted from the Endocrine Society Clinical Practice Guidelines[8] (http://press.endocrine.org/doi/pdf/10.1210/jc.2009-2354) and International Society for Sexual Medicine Standard Operating Procedures[10]	

For patients with a low or low-normal total testosterone, additional measurement of SHBG can be performed to calculate the free or bioavailable testosterone level.[8,10,14] Free testosterone refers to unbound testosterone, while bioavailable testosterone includes both free testosterone and testosterone loosely bound to albumin. While the gold standard is to directly measure the bioavailable testosterone level by the ammonium sulfate precipitation method, access to this reliable test is limited and may not be reimbursed by government health plans (therefore requiring patient payment).[14] Similarly, free testosterone is most accurately measured by equilibrium dialysis or ultrafiltration, neither of which is widely available in Canada (Table 2).[10] Given these limitations in access to accurate assay methods, clinicians should become familiar with the assays used at their local laboratories and their test characteristics (precision and accuracy). Total testosterone measurements can be primarily used in diagnosis unless abnormalities in SHBG are suspected (Table 3), in which case accurate free or bioavailable testosterone measurements or calculations should be considered.[8,19]

Table 2. Comparison of assays for total, free and bioavailable testosterone

ASSAY	PROS	CONS
TOTAL TESTOSTERONE		
Liquid chromatography or mass spectrometry	(IDEAL) ▪ Increased accuracy (especially for low values)	▪ Limited availability ▪ Costly
Radio-immuno-assay (RAI), chemilunescence	▪ Widely available ▪ Less expensive	▪ Less accuracy (particularly in low range)
FREE TESTOSTERONE		
Equilibrium dialysis	(IDEAL, gold standard) ▪ Increased accuracy	▪ Limited availability ▪ Manually performed, time consuming ▪ Costly
Ultrafiltration	▪ Increased accuracy	▪ Limited availability ▪ Manually performed, time consuming ▪ Costly
Calculated	▪ Widely available ▪ Modest accuracy, good correlation to equilibrium dialysis method ▪ Provides SHBG level ▪ Free calculator available at www.issam.ch/freetesto.htm	▪ Reliance on quality of total testosterone and SHBG assays, which are variable in accuracy and not consistent between laboratories
Analog method	▪ Widely available ▪ Low cost	▪ Highly inaccurate
Free androgen index	▪ Should not be used	▪ Unreliable ▪ Calculates ratio of total testosterone and SHBG
BIOAVAILABLE TESTOSTERONE		
Ammonium sulfate	(IDEAL) ▪ Increased accuracy	▪ Limited availability
Calculated	▪ Widely available ▪ Free calculator available at www.issam.ch/freetesto.htm	▪ Reliance on quality of total testosterone and SHBG assays ▪ Formulas are variable in accuracy

SHBG = Sex hormone binding globulin
Adapted from the International Society for Sexual Medicine Standard Operating Procedures[10]

Table 3. Conditions associated with alterations in SHBG (sex hormone binding globulin) concentrations

Decreased SHBG (leading to increased BT and FT)	Increased SHBG (leading to decreased BT and FT)
▪ Moderate obesity ▪ Nephrotic syndrome ▪ Hypothyroidism ▪ Use of progestins, androgenic steroids ▪ Acromegaly ▪ Diabetes mellitus (type 2), insulin resistant states ▪ Cachexia, malnutrition ▪ Hypercortisolism, use of glucocorticoids	▪ Aging ▪ Hepatic cirrhosis and hepatitis ▪ Hyperthyroidism ▪ Use of anticonvulsants (particularly phenobarbital, carbamazepine, phenytoin) ▪ Use of estrogens, tamoxifen ▪ HIV disease
BT = bioavailable testosterone; FT = free testosterone Adapted from Endocrine Society Clinical Practice Guidelines[8] (http://press.endocrine.org/doi/pdf/10.1210/jc.2009-2354) and the International Society for Sexual Medicine Standard Operating Procedures[10]	

Once testosterone deficiency is confirmed, further investigations to distinguish between primary or secondary hypogonadism should be performed through measurement of LH and FSH, if not already completed. If these values are low or inappropriately normal, secondary hypogonadism is suspected and evaluation for pituitary or hypothalamic lesions is recommended with assessment of other pituitary hormones (prolactin, free T4, TSH, 8 am cortisol) along with an iron saturation level for hemochromatosis[8,19]. If any further abnormalities are detected, a referral to an endocrinologist is warranted. Pituitary MRI is the preferred imaging modality for assessment of pituitary structure. It is recommended that this test be performed in cases where there is high suspicion of pituitary disease[20] or in cases of secondary hypogonadism where the total testosterone levels are <5.2 mmol/L.[21] The hypothalamic-pituitary axis can also be suppressed secondary to medications such as long-acting opiates, and medical conditions including obesity, eating disorders and excessive exercise [8,22], and thus screening for these conditions should be considered.

If LH and FSH levels are elevated, primary hypogonadism is likely and may result from testicular trauma, infarction, increased testicular temperature from varicocele or panniculus, genetic conditions like Klinefelter's Syndrome, medications such as ketoconazole or toxin exposure including chemotherapeutic agents.[19] A testicular ultrasound should be performed if an anatomic abnormality is suspected; otherwise no further workup is necessary in the older male unless fertility is sought. Klinefelter's Syndrome is an underdiagnosed cause of primary hypogonadism, with an estimated prevalence of one in 660 men.[23] A Danish registry of 696 men with Klinefelter's Syndrome found that 74 (10.6%) of men were diagnosed with this condition after the age of 60.[23] Thus, men with biochemical evidence of primary hypogonadism and small testes on physical exam should have a karyotype performed in order to diagnosis this relatively common condition.

Treatment

If a reversible cause of hypogonadism is diagnosed, treatment should be aimed at the underlying etiology, such as cessation of possible culprit medications, medical treatment of a prolactinoma or resection of a compressive pituitary adenoma or sellar mass. In obese individuals, lifestyle interventions that promote weight loss should be endorsed, as this may be an effective method of raising testosterone levels.[24] Otherwise the decision to initiate testosterone therapy requires the consideration of many patient-related factors: the severity of symptoms, the potential benefits and harms of therapy and existing comorbidities that would prohibit the use of testosterone therapy. Table 4 outlines circumstances in which it would be appropriate and inappropriate to prescribe testosterone replacement therapy.

Table 4. When and when not to prescribe testosterone replacement therapy

When to prescribe	When NOT to prescribe

▪ Symptomatic hypogonadism and biochemical confirmation with either:
  ○ low morning total testosterone on two occasions
  ○ low morning free testosterone (not by analog measurement) on two occasions
  ○ low morning bioavailable testosterone (ammonium sulphate assay or calculated preferred) on two occasions
▪ No reversible cause of hypogonadism identified (no prolactinoma, nonfunctioning adenoma, culprit medication)
▪ Absence of contraindications (listed in right column)
	▪ Normal testosterone levels
	▪ Absence of symptoms
	▪ History of breast or prostate cancer
	▪ Palpable prostate nodule/induration or PSA >4 (until further urological evaluation is completed)
	▪ PSA >4 in high-risk patients such as African American, first degree relative with prostate cancer (online risk calculator available at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp)
	▪ Hematocrit >50%
	▪ Untreated severe obstructive sleep apnea*
	▪ Severe obstructive lower urinary tract symptoms**
	▪ Poorly controlled heart failure
	▪ Desire for fertility (exogenous testosterone causes reduced spermatogenesis)

Adapted from the Endocrine Society Clinical Practice Guidelines[8] (http://press.endocrine.org/doi/pdf/10.1210/jc.2009-2354) and the International Society for Sexual Medicine Standard Operating Procedures[10] *Severe obstructive sleep apnea is defined as apnea-hypopnea index (AHI) >30 events/hour or O2sat <90% for ≥20% of night. Moderate sleep apnea in the opinion of the authors is a relative contraindication to treatment with testosterone. **Severe obstructive lower urinary tract symptoms include incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining and nocturia occurring half the time or more in one month.	

Before a shared decision is made by the patient and physician to initiate testosterone therapy, patients should be advised of the potential harms and benefits (Table 5). The most concerning potential harm is increased cardiovascular risk and death, especially among men over the age of 65 and those with pre-existing heart disease or documented coronary artery disease.[25,26] At present, there are no large randomized trials that definitively demonstrate benefit or harm of testosterone therapy on cardiac health. Health Canada is currently working with testosterone product manufacturers to update product labels to warn of possible cardiovascular risks, including heart attack, stroke, blood clots in the lungs or legs and irregular heart rate.[27] Since the quality of this data is limited by the retrospective nature of many of the studies, testosterone therapy at present is not contraindicated in men with heart disease; however, from a medico-legal perspective, it remains prudent for physicians to discuss this potential risk with their patients prior to prescribing if there is pre-existing cardiovascular disease and to document this discussion.

Table 5. The potential benefits and harms associated with testosterone replacement therapy. It should be noted that the degree of potential benefit and risk is highly variable between studies.

Potential benefits	Potential harms
▪ Improved strength ▪ Enhanced sexual desire ▪ Improved erectile function ▪ Improved energy, emotional well-being ▪ Improved cognition ▪ Increased bone mineral density ▪ Reduced body fat	▪ Increase in hematocrit ▪ Acne, oily skin ▪ Breast tenderness/gynecomastia ▪ Growth of metastatic prostate cancer ▪ Benign prostatic hyperplasia development ▪ Growth of breast cancer ▪ Reduced sperm production and fertility

Potential benefits	Potential harms
▪ Resolution of anemia	▪ Induction or worsening of obstructive sleep apnea ▪ Male pattern balding (familial) ▪ Possible increased cardiovascular risk (particularly with pre-existing heart disease, men over age 65)
Adapted from the Endocrine Society Clinical Practice Guidelines[8] (http://press.endocrine.org/doi/pdf/10.1210/jc.2009-2354)	

Testosterone replacement therapy in Canada is available in several formulations: injectable, oral and transdermal. Physicians should gain familiarity with the availability, safety, tolerability, costs and provincial coverage of the various preparations to help guide treatment selection (Table 6). While oral administration is convenient and relatively less expensive, its effectiveness is limited by poor absorption. Ingesting the medication with a fatty meal improves absorption, but several doses per day may still be required to achieve an adequate serum level of testosterone.[28] Cost is an important consideration when choosing a testosterone therapy as the convenient topical formulations are only covered by some provinces if biochemical hypogonadism is confirmed, and alternatively may not be covered at all by other provincial drug plans.[29] Clinical monitoring with symptom inquiry, physical exam and laboratory investigations should occur at 3-6 month intervals during the first year of testosterone therapy, and if stable, yearly thereafter[10] (Table 7). Symptom improvement may occur in the first months of therapy with increased libido, increased energy and improved erectile function; many other potential benefits such as improved strength, bone mineral density, cognition and reduced fat may require longer to achieve clinical significance.[14] In some studies, testosterone therapy in the aging male has been associated with improved libido,[30] improved mood[31] and possibly muscle strength,[32,33] although effect sizes are not consistently large across studies. Erectile function in the aging male is not consistently improved with testosterone replacement due to contribution from vascular factors and other underlying comorbidities including diabetes mellitus, hypertension, obesity, obstructive sleep apnea and smoking.[10, 34,35] Combined therapy with a PDE5 inhibitor (phosphodiesterase type V-inhibitor) such as sildenafil, vardenafil or tadalafil may provide additional benefit.[10] A lack of response in other domains to testosterone therapy may indicate nonadherence, drug malabsorption, insufficient dose or alternative diagnosis (symptoms unrelated to testosterone deficiency). If symptoms persist despite a dose increase or change in testosterone preparation, testosterone therapy should be discontinued and re-evaluation of the symptoms should ensue.

Table 6. Comparison of testosterone replacement therapy formulations available in Canada

Name (trade name)	Dosage	Advantages	Disadvantages	Serum testosterone measurement	Cost ($ per month)*
INJECTABLE					
Testosterone cypionate (Depo-testosterone)	Initial: 200 mg every 2 weeks or 100 mg weekly Max: 400 mg every 2 weeks	Not expensive; Long acting	▪ Fluctuations in testosterone levels (supraphysiologic early after injection, lower levels at end of cycle) ▪ Increased erythrocytosis ▪ Requires injection (by health	Midway in treatment cycle	30.17
Testosterone enanthate (Delatestryl)					53.44

Name (trade name)	Dosage	Advantages	Disadvantages	Serum testosterone measurement	Cost ($ per month)*
			professional or trained family member)		
ORAL MEDICATION					
Testosterone undecanoate (Andriol, PMS- and Tara-testosterone)	Initial: 80-160 mg daily (in two divided doses)	Easy to administer	▪ Variable absorption (best taken with high fat meal) ▪ Potential GI intolerance ▪ May require multiple daily doses	3-5 hours after ingestion of dose	28.20-56.40
TRANSDERMAL					
Testosterone patch (Androderm)	Initial: 2.5 mg daily Max: 5 mg daily	Uniform drug delivery and testosterone levels	▪ Visible skin patch ▪ Reduced adherence of patch with sweating ▪ Skin reactions more common with patch than gel	6-10 hours after application of patch	62.79
Testosterone gels (Androgel, Testim)	Initial: 5 g per day Max: 10 g per day	Can self-administer	▪ Minor skin reactions ▪ Risk of transfer of gel on skin (prevented by washing hands and skin prior to contact with women or children)	2-8 hours after application (>2 weeks after initiation of therapy)	108.09-118.35
Axillary testosterone gel (Axiron)	Initial: 60 mg per day Max: 120 mg per day	Less transfer of gel with underarm application	▪ Minor skin reactions	2-8 hours after application (>2 weeks after start of therapy)	141.35

Adapted from the Endocrine Society Clinical Practice Guidelines[8] (http://press.endocrine.org/doi/pdf/10.1210/jc.2009-2354), the International Society for Sexual Medicine Standard Operating Procedures[10] and the Canadian Urological Association Guidelines[14] www.ncbi.nlm.nih.gov/pmc/articles/PMC2910774/

*Approximate costs sourced from the Ontario Drug Benefit Formulary for initial dosing regimens[7]

Table 7. Clinical and laboratory parameters to follow on testosterone therapy. All of the following should be completed at baseline, 3 months, 6 months and 12 months after therapy is initiated. Prostate health should be assessed at 6 and 12 months following testosterone initiation. If no abnormalities are detected, follow-up can occur yearly thereafter.

Parameter	Details
Clinical history	Sexual desire, morning erections, energy, body composition, physical performance Symptoms of bladder outlet obstruction Symptoms of obstructive sleep apnea (daytime sleepiness, morning headaches, nocturnal gasping or choking) Symptoms of fluid retention (orthopnea, peripheral edema)
General physical exam	Weight, waist circumference Blood pressure Chest examination for new or worsening gynecomastia Digital rectal exam of prostate gland
Testosterone level	Total testosterone – performed in early morning at optimal time within cycle (see Table 6) [Target testosterone in low-normal range]
CBC	Hemoglobin and hematocrit to assess for erythrocytosis [Target normal hemoglobin range for men, hematocrit <50%]
Prostate health	PSA (should not be tested immediately after digital rectal exam) Digital rectal exam of prostate gland
Bone mineral density	If long-standing testosterone deficiency suspected Repeat every two years if reduced bone density or osteoporosis is detected, or if a fragility fracture occurs
Adapted from the International Society for Sexual Medicine Standard Operating Procedures[10]	

Testosterone in postmenopausal women

A meta-analysis of 35 randomized controlled trials found that testosterone administration with and without ovarian hormone replacement therapy in postmenopausal women was associated with a statistically significant improvement in sexual function and decrease in personal distress.[36] However, many of these trials did not use specific or accepted diagnostic criteria for identifying androgen deficiency, nor was there sufficient power to determine an ideal testosterone dose or target level when using therapy. As a result, there is limited data available to guide the appropriate prescribing of testosterone in women. More importantly, a number of potential harms were identified including an increase in LDL cholesterol, acne, hirsutism and possibly other unknown effects as long-term safety data is lacking.[36] In light of the above facts, the authors of this paper do not endorse the use of testosterone in this patient population.

Conclusions

There is rapidly growing attention from the public and medical community regarding declines in testosterone levels seen with aging. The syndrome of androgen deficiency in the aging male should be considered only after identification and correction of possible reversible pathologies. Given the potential harms associated with testosterone therapy, physicians must ensure that reliable biochemical testing is performed to confirm the diagnosis. Additionally, physicians must ensure a favourable benefit to risk ratio exists for their patient before consideration of testosterone replacement. While we await the results of ongoing trials assessing the long-term safety of testosterone, prescribers should engage in continued clinical and laboratory assessment of their older male patients already on testosterone therapy to ensure their benefit to risk ratio remains clinically advantageous.

5 key points

1) The clinical features of testosterone deficiency are less specific in the aging male as compared to their younger counterparts.
2) Testosterone levels should be drawn in the early morning and confirmed with repeat measurement. Total testosterone is acceptable, but consideration of free or bioavailable testosterone measurement/calculation should be done if sex hormone binding globulin (SHBG) abnormalities are suspected.
3) Analog free testosterone measurements are widely available in laboratories across Canada. Use of this assay in the diagnosis of testosterone deficiency is strongly discouraged due to inaccuracy.
4) The true effects of testosterone therapy on cardiac outcomes at present are unclear and remain controversial. Physicians should discuss this potential risk with their patients prior to prescribing, especially in patients with pre-existing cardiovascular disease and should document that discussion.
5) Testosterone administration in postmenopausal women is not recommended at present.

REFERENCES:

1. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 2002;87:589-98.

2. Harman SM, Metter EJ, Tobin JD et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31.

3. Nahoul K, Roger M. Age-related decline of plasma bioavailable testosterone in adult men. J Steroid Biochem 1990; 35: 293-99.

4. Wu FCW, Tajar A, Beynon J et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; 363: 123-35.

5. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. International Journal of Clinical Practice 2006; 60: 762-769.

6. Piszczek J, Mamdani M, Antoniou T, Juulink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. PLoS ONE 9(7): e90003.

7. Ontario Drug Benefit Formularly/Comparitive Drug Index; c2011. [updated 2014 December 14, cited 2015 January 15]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary.

8. Bhasin S, Cunningham GR, Hayes FJ et al. Testosterone therapy in men with androgen deficiency syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(6):2536-59.

9. Wu FC, Tajar A, Pye SR et al. Hypothalatmic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiaible risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008; 93: 2737-2745.

10. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: Systematic review and standard operating procedures for diagnosis and treatment. J Sex Med 2013; 10: 245-284.

11. Morley JE, Charlton E, Patrick P et al. Validation of a Screening Questionnaire for Androgen Deficiency in Aging Males. Metabolism 2000; 49 (9): 1239-1242.

12. Heinemann LA, Saad F, Zimmermann T et al. A new "Aging Males' Symptoms" (AMS) rating scale. The Aging Male 1999; 2: 105-14.

13. Zengerling F, Schrader AJ, Cronauer MV et al. The "Aging Males' Symptoms" Scale (AMS): predictive value for lowered circulating androgens. Aging Male 2012; 15 (4): 253-7.

14. Morales A, Bella A, Chun S et al. A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians. Can Urol Assoc J 2010; 4 (4): 269-75.

15. Vesper HW, Botelho JC. Standardization of testosterone measurements in humans. J Steroid Biochem Mol Biol 2010; 121 (3-5): 513-9.

16. Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol (Oxf) 2003; 58: 710-717.

17. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf) 2007; 67: 853-862.

18. Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985; 60: 444-450.

19. Pantalone KM, Faiman C. Male hypogonadism: more than just a low testosterone. Cleveland Clinic Journal of Medicine 2012; 79 (10): 717-725.

20. Rogers A, Karavitaki N, Wass JAH. Diagnosis and management of prolactinomas and non-functioning pituitary adenomas. BMJ 2014; 349: 1-5.

21. Citron JT, Ettinger B, Rubinoff H et al. Prevalence of hypothalamic-pituitary imaging abnormalities in impotent men with secondary hypogonadism. J Urol 1996; 155: 529-533.

22. Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. J Pain 2006; 7: 200-210.

23. Bojesen A, Juul S, Gravhold CH. Prenatal and postnatal prevelance of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 2003; 88: 622-626.

24. Corona G, Rastrelli G, Monami M et al. Body weight loss reverts obesity-assocaited hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol 2013; 168 (6): 829-843.

25. Finkle WD, Greenland S, Ridgeway GK et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014; 9 (1): e85805.

26. Vigen R, O'Donnell CI, Baron AE et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310 (7): 1829-36.

27. Health Canada 2014. Summary Safety Review – Testosterone Replacement Products – Cardiovascular Risk; c2014. [updated 2014 July 15, cited 2015 January 15]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/testosterone-eng.php.

28. Seftel A. Testosterone replacement therapy for male hypogonadism: Part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. Int J Impot Res 2007; 19 (1): 2-24.

29. Ontario Drug Policy Research Network. Testosterone Replacement Therapy: Environmental Scan and Local/Historical Context. September 2014 (Draft Report). http://odprn.ca/wp-content/uploads/2014/12/111-TRT-Environmental-scan-final-dec-01.pdf

30. Allan CA, Forbes EA, Strauss BJ, McLachlan RI. Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. Int J Impot Res 2008; 20: 396-401.

31. Wang C, Alexander G, Berman N et al. Testosterone replacement therapy, improves mood in hypogonadal men: A clinical research center study. J Clin Endocrinol Metab 1996; 81: 3578-83.

32. Ferrando AA, Sheffield-Moore M, Yeckel CW et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab 2002; 282 (3): E601-7.

33. Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ, Acha AA, Ostir GV. Androgen treatment and muscle strength in elderly men: A meta-analysis. J Am Geriatr Soc 2006; 54 (11): 1666-73.

34. Isidori AM, Gianetta E, Gianfrilli D et al. Effects of testosterone on sexual function in men: Results of a meta-analysis. Clin Endocrinol (Oxf) 2005; 63: 381-94.

35. Bolona ER, Uraga MV, Haddad RM et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007; 82: 20-8.

36. Elraiyah T, Sonbol MB, Wang Z et al. The benefits and harms of systematic testosterone therapy in postmenopausal women in normal adrenal function: a systematic review and meta-analysis. J Clin Endocrinol Metab 2014; 99: 3543-3550.