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Testosterone Testing Protocol - DRAFT

Scope

This protocol reviews the appropriate use of serum testosterone testing in men and women aged ≥ 19 years. This document is intended to direct primary care practitioners and to help constrain inappropriate test utilization, particularly as it pertains to "wellness" and "anti-aging" practices. This protocol expands on the guidance provided in the associated BC Guideline *Hormone Testing – Indications and Appropriate Use*. Testosterone testing for pediatric and transgender* patients is out of scope of this protocol.

Key Recommendations

- General screening for testosterone deficiency is not recommended in men or women.
- The decision to test must be guided by medical history and clinical examination.
- Testosterone deficiency in men usually presents with a constellation of symptoms. Erectile dysfunction in isolation is not an indication for testosterone testing.
- In men, serum total testosterone must be collected in the morning, preferably before 10AM, or within 3 hours of waking, and preferably in a fasting state.
- Men receiving stable androgen replacement can be tested annually.
- Testosterone testing is not useful for the investigation of low libido in women.

Tests

The testosterone tests available in British Columbia are:

- serum total testosterone;
- calculated bioavailable testosterone (cBAT) or equivalently, calculated free testosterone; and
- sex hormone binding globulin (SHBG).

MSP Cost of Tests[1]	
Testosterone – total	$15.81
cBAT (includes SHBG)	$29.37

Current to January 1st, 2018.

Circulating total testosterone exists in three forms: free or unbound, weakly bound to albumin, and strongly bound to SHBG. Serum total testosterone measures all three forms. Bioavailable testosterone is the sum of free testosterone and albumin bound testosterone. Calculated bioavailable testosterone (cBAT) and calculated free testosterone are estimated (rather than directly measured) quantities calculated from the total testosterone, SHBG and albumin concentrations, and their association constants. In BC, all bioavailable and free testosterone results are calculated. Reference ranges for serum total testosterone, cBAT and calculated free testosterone are method and age dependent and are determined by each laboratory independently.

Patients should use the same lab for initial and follow up testosterone tests because reference ranges are lab-dependent,[2] meaning that results from different labs may not be comparable. For more information about the different forms of testosterone in plasma and their measurement, refer to BCGuidelines.ca – *Hormone Testing Guideline Appendix A: Testosterone Testing and Measurement in BC*.

* **Note:** For information and guidance on testosterone testing for transgender people, refer to *Gender-affirming Care for Trans, Two-Spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit*, produced by Trans Care BC at the Provincial Health Services Authority.

Testosterone Deficiency in Men

Routine biochemical screening for testosterone deficiency (hypogonadism) in men is not recommended. Testosterone testing for biochemical evidence of hypogonadism is not indicated in asymptomatic men. Decision to test must be guided by medical history and clinical examination. In the case of isolated, or non-specific symptoms only, a comprehensive general assessment is required to exclude potential alternative explanations[3] and guide further investigations. In the case of follow up of a previously ordered, relatively low, testosterone measurement, refer to *Appendix A: Testosterone and SHBG Variation in Men and Women* and *Appendix B: Medications that May alter Testosterone Levels in Men and Women* for conditions and medications associated with changes in testosterone concentration.

Signs and Symptoms of Testosterone Deficiency in Men

There are many non-specific somatic and psychological symptoms associated with hypogonadism (refer to Table 1 below). Any one finding alone is insufficient grounds to order a testosterone test.

Late-onset (age ≥ 40 years) hypogonadism is most specifically defined by the presence of at least three sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual thoughts, and erectile dysfunction) associated with low testosterone and/or a low cBAT.[3] Erectile dysfunction in isolation is not an indication for testosterone testing because the prevalence of hypogonadism among patients with erectile dysfunction is low[4].

Table 1: Symptoms and signs of testosterone deficiency in men, in order of specificity[5,6]

Specific to testosterone deficiency	Supportive of testosterone deficiency	Not specific to testosterone deficiency
• Loss of body (axillary, facial, pubic) hair • Very small testes (<6 mL)	• Breast discomfort, gynecomastia • Eunuchoidal body proportions • Infertility, low sperm count • Height loss, low-trauma facture, low bone mineral density • Hot flushes, sweats • Pervasive decrease in sexual desire (libido) and activity • Erectile dysfunction • Decreased frequency of morning erections or spontaneous erections	• Fatigue or decreased energy • Depression or depressed mood • Poor concentration and memory • Sleep disturbance, increased sleepiness • Anemia • Decreased muscle bulk and strength • Increased body fat, body mass index (BMI)

Adapted from Bhasin 2010[6] *and Bhasin 2018*[5]

Some symptoms of hypogonadism in men ≥ 40 years overlap with normal effects of aging.[7] The documentation of low total testosterone in elderly men with non-specific symptoms of hypogonadism does not necessarily imply that low testosterone is the cause.

Occasionally the cause of hypogonadism is congenital/pituitary/hypothalamic in nature and if there are pre-existing risk factors (e.g. cranial irradiation, hemochromatosis), referral to endocrinology is recommended.

Testing for Testosterone Deficiency in Men

Serum total testosterone is the initial test of choice. Specimens must be collected in the morning,[8] preferably before 10AM, or within 3 hours of waking, and preferably in a fasting state[5,9]. Testing should occur when the sleep-wake pattern is stable (e.g. not during shift changes or jetlag). Testing of serum total testosterone should be performed when patients are clinically well; do not test during illness or hospitalization.

If the total testosterone level is below the lab-specific lower limit of normal (approximately 8 nmol/L in younger

men (<30 years), and 6 nmol/L in older men (> 50 years))[10–13], ***and a diagnostic question remains***, SHBG and cBAT can be used to confirm or rule out hypogonadism.

Diagnosis in Men

It has been observed that men in BC frequently receive prescriptions for testosterone replacement without first having a serum testosterone test to confirm low levels.[14] This practice is not appropriate, as biochemical confirmation of a low for age serum total testosterone (or cBAT) is necessary to confirm the clinical impression of hypogonadism. While specific investigation is beyond the scope of this protocol, it is important to establish the etiology of hypogonadism, *after* biochemical confirmation of the clinical diagnosis, and *before* initiating testosterone replacement. Refer to *Appendix C: Hypogonadism Investigation Algorithm* for guidance on initial investigation and testing.

Prior to initiating testosterone replacement, the following baseline tests are recommended: hematocrit, prostate-specific antigen (PSA), and digital rectal exam (DRE).[7]

Consider non-urgent referral if uncertain. Indications for non-urgent referral are outlined in Table 2 below.

Monitoring of Testosterone-Replacement Treatment in Men

Monitor men receiving androgen replacement by repeating the hematocrit, PSA test, and DRE at 3 and 6 months after initiation, then annually if stable.[7] Some recommend that PSA testing after one year is not necessarily obligatory.[5] Men receiving stable androgen replacement can be tested with serum total testosterone testing annually[5,7].

Blood collection timing by route of administration:[5]

- **Injectable testosterone enanthate or cypionate:** measure testosterone midway between injections
- **Transdermal gels/Intranasal:** measure T 2-8h after application
- **Transdermal patches:** 3-12 hours after application
- **Oral testosterone undecanoate:** 3-5 hours after ingestion with a fat-containing meal

Testosterone Testing in Prostate Cancer

Total testosterone testing is indicated to confirm adequacy of androgen deprivation therapy (ADT) in men with prostate carcinoma. Only tandem mass spectrometry is sufficiently sensitive to accurately measure the low total testosterone seen in men rendered chemically castrate for treatment of prostate carcinoma[15]. In BC, testosterone analysis by tandem mass spectrometry is not routinely available and should be specifically requested on the requisition. PSA should be tested 3 months after initiating ADT, and tested in the event of any increase in PSA levels.

Testosterone Analysis in Women

Testosterone testing is indicated for investigation of hyperandrogenism in women based on medical history and clinical examination. **Testosterone testing is not indicated for investigating low libido in women.**[16]

The upper limit of normal for testosterone in women is approximately 2-3 nmol/L, or slightly higher depending on menstrual phase and use of oral contraceptive medications[17]. In polycystic ovarian syndrome, total testosterone concentrations are within the normal reference interval or slightly higher. Consequently, testosterone concentrations greater than twice the upper limit of normal (ie greater than 5 nmol/L) suggest an alternate etiology, such as an androgen-secreting tumour.

Signs and Symptoms of Hyperandrogenism in Women

A range of symptoms and signs from hirsutism to virilisation may occur. The Endocrine Society recommends

testing for hyperandrogenism in women with hirsutism that is moderate or severe, of rapid onset, or accompanied by menstrual dysfunction, obesity or clitoromegaly.[18] Other indications for referral are outlined at the end of this document.

Testing for Hyperandrogenism in Women

Serum total testosterone is frequently normal in women with mild clinical hyperandrogenism (due to androgen suppression of SHBG production). cBAT testing has a better diagnostic yield for testosterone excess in women.[19] Repeat serum testosterone testing is not indicated if cBAT is normal. Testing of other androgens is dependent on clinical findings and is beyond the scope of this protocol; for more information refer to the BC Guideline *Hormone Testing - Indications and Appropriate Use*. For women who have regular menstrual cycles, collection should be performed in the morning on day 4-10.[18]

Diagnosis of the Cause of Hyperandrogenism in Women

The diagnosis of testosterone excess is based on medical history and physical findings, followed by investigational tests. The most common cause of hirsutism[20] and of excess androgen production in pre-menopausal women[18] is polycystic ovary syndrome (PCOS). It is important to rule out non-classic congenital adrenal hyperplasia, which occurs in 1.5-6.8% of women with hyperandrogenism.[21] Further investigation to determine the etiology of androgen excess in women is beyond the scope of this protocol. Indications for non-urgent referral are outlined in Table 2 below.

Monitoring Response to Treatment

Women receiving treatment for hyperandrogenism: Response to treatment of hyperandrogenism in women is clinical. Therefore, testing serum total testosterone and cBAT in patients treated for hyperandrogenism is not recommended unless a concrete cause has been identified, such as non-classical congenital adrenal hyperplasia or an androgen-secreting tumour.

Women receiving androgen therapy for low libido: Testosterone testing is not useful for monitoring women receiving androgen therapy for low libido unless overuse is suspected or unexpected virilisation has developed.

Indications for Non-Urgent Referral

Table 2: Indications for consideration of non-urgent referral to an endocrinologist, urologist, or obstetrician/gynaecologist as appropriate.

Men[5–7]	Women[21,22]
Confirmed or suspected: • Hemochromatosis • Hypothalamic/pituitary tumour • Hyperprolactinemia • Idiopathic hypogonadotropic hypogonadism • Cryptorchidism, anorchia • Genetic conditions including Kleinfelter syndrome, Kalmann syndrome, myotonic dystrophy • Male factor infertility	**Confirmed or suspected:** • Rapid virilisation/rapid hair loss (this is an indication for **urgent** referral) • Symptoms consistent androgen-secreting tumour of adrenal or ovarian origin (this is an indication for **urgent** referral) • Congenital adrenal hyperplasia (CAH) • Polycystic ovary syndrome (PCOS) • Cushing syndrome • Gestational hyperandrogenism • Acromegaly • Ovarian hyperthecosis • Exogenous androgen administration

Resources

Abbreviations

TT	total testosterone
cBAT	calculated bioavailable testosterone
SHBG	sex hormone binding globulin
PSA	prostate-specific antigen
DRE	digital rectal examination

Practitioner Resources

- **RACE: Rapid Access to Consultative Expertise Program – www.raceconnect.ca**

  A telephone consultation line for select specialty services for physicians, nurse practitioners and medical residents.

  If the relevant specialty area is available through your local RACE line, please contact them first. Contact your local RACE line for the list of available specialty areas. If your local RACE line does not cover the relevant specialty service or there is no local RACE line in your area, or to access Provincial Services, please contact the Vancouver Coastal Health Region/Providence Health Care RACE line.

  - **Vancouver Coastal Health Region/Providence Health Care:** www.raceconnect.ca
    Available Monday to Friday, 8 am to 5 pm
    ☎ 604-696-2131 (Vancouver area) or 1-877-696-2131 (toll free)
  - **Northern RACE:** ☎ 1-877-605-7223 (toll free)
  - **Kootenay Boundary RACE:** www.divisionsbc.ca/kb/race ☎ 1-844-365-7223 (toll free)
  - **Fraser Valley RACE**: www.raceapp.ca (download at Apple and Android stores)
  - **South Island RACE:** www.raceapp.ca (download at Apple and Android stores) or see www.divisionsbc.ca/south-island/RACE

- **Pathways – PathwaysBC.ca**
  An online resource that allows GPs and nurse practitioners and their office staff to quickly access current and accurate referral information, including wait times and areas of expertise, for specialists and specialty clinics. In addition, Pathways makes available hundreds of patient and physician resources that are categorized and searchable.

Patient and Caregiver Resources

- **ChoosingWisely.ca:**
  Treatment for Erection Problems: When you need testosterone treatment and when you don't

- **HealthLinkBC.ca:** Testosterone

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Appendices

- **Appendix A:** ***Testosterone and SHBG Variation in Men and Women***
- **Appendix B:** ***Medications that May Alter Testosterone Levels in Men and Women***
- **Appendix C:** ***Hypogonadism Investigation Algorithm***

This draft guideline is based on scientific evidence current as of May 2018.
The draft guideline was developed by the Guidelines and Protocols Advisory Committee.

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- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

Contact Information:

Guidelines and Protocols Advisory Committee
PO Box 9642 STN PROV GOVT
Victoria, BC V8W 9P1
Email: hlth.guidelines@gov.bc.ca
Website: www.BCGuidelines.ca

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Appendix A: Testosterone and SHBG Variation in Men and Women

Table 1: Conditions Associated with Alterations in Testosterone Concentrations
• Comorbid illness or medication use with changes in SHBG concentrations (Table 2) • Hypothyroidism • Acromegaly • Eating disorders • Exercise – excessive exercise reduces serum testosterone • Substance use (e.g. alcohol, marijuana, opioids)
Episodic secretion: 30% of men with mildly hypogonadal serum testosterone levels will have a normal level on retesting

Table 2: Conditions Associated with Alterations in SHBG Concentrations[1,2]	
Decreased SHBG concentrations:	**Increased SHBG concentrations:**
• Diabetes mellitus[α] • Obesity[α] • Nephrotic syndrome[α] • Use of glucocorticoids, some progestins, and androgenic steroids[α] • Hypothyroidism • Acromegaly	• Aging[α] • Cirrhosis and hepatitis[α] • Use of some anticonvulsants[α] • Use of estrogens • HIV infection • Hyperthyroidism
[α] Particularly common conditions associated with alterations in SHBG levels	

Adapted from Bhasin et al. 2018[1] and Bhasin et al. 2010[2].

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Appendix B: Medications that May Alter Testosterone Levels in Men and Women

Table 1*: Medications that May Alter Testosterone Levels in Men[1,2]		
Increase serum testosterone levels	**Decrease serum testosterone levels**	
• bicalutamide • cimetidine • finasteride • leuprolide • phenytoin • rifampin • tamoxifen • valproic acid	• anabolic steroids • carbamazepine • corticosteroids • cyclophosphamide • cyproterone • digoxin • estrogens • finasteride • goserelin	• ketoconazole • leuprolide • nilutamide • opioids** • spironolactone • tetracycline • thioridazine • verapamil
Notes: ** Does not represent an exhaustive list.* *** Studies indicate opioid-induced testosterone deficiency is likely linked to long term therapy with opioids.[3] Consistent with the evidence, the recommendations from the 2018 Endocrine Society Guideline suggest to only test those who are receiving long-term opioids rather than short-term.[4]*		

Table 2*: Medications that May Increase Testosterone Levels in Women[1,2]
• barbiturates • clomiphene • estrogens • valproic acid
Notes: ** Does not represent an exhaustive list.*

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Appendix C: Hypogonadism Investigation Algorithm

Adapted from Bhasin et al. *2018*[5].