GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Testosterone Testing Protocol

Effective Date: June 1, 2011

Scope

This protocol reviews serum testosterone testing in adult males and females (aged ≥ 19).

Diagnosis/Investigation

General screening for testosterone deficiency (hypoandrogenism) in men is not recommended but should be guided by medical history and clinical examination.

Erectile dysfunction *by itself* is not an indication for testosterone testing. Jack and Zeitlin[1] report "The overall prevalence of clinically relevant hypogonadism in patients with erectile dysfunction is very low, probably less than 5%, and closer to 1% to 2%." In the presence of erectile dysfunction with decreased libido and/or testicular atrophy, serum testosterone testing is indicated.[1]

Testosterone testing is not indicated for the investigation of hypoandrogenism in women, including low libido in women.

Normal ranges for serum total testosterone and calculated bioavailable testosterone (cBAT) show method and age dependence and are determined by each laboratory independently.

Testosterone Deficiency in Males

a) Signs and Symptoms

In the presence of a clinical indication, serum testosterone measurement is appropriate. Hypoandrogenism is suggested by the following symptoms and signs.

Table 1: Signs of Hypoandrogenism in Males

- Incomplete or delayed sexual development, eunuchoidism.
- Reduced sexual desire (libido) and activity.
- Decreased spontaneous erections.
- Breast discomfort, gynecomastia.
- Loss of body (axillary and pubic) hair, reduced shaving.
- Very small (especially < 5 ml) or shrinking testes.
- Inability to father children, low or zero sperm count.
- Height loss, fragility fracture, low bone mineral density.
- Hot flushes, sweats.

Adapted from Bhasin et al. 2010.[2]

b) Testing

Specimens should be collected in the early morning[3] (preferably before 10 am). Testing of serum total testosterone should be done when patients are clinically stable; avoid testing during acute or subacute illness.

Serum total testosterone is the initial test of choice. If the level is below the lower limit of normal (approximately 10 nmol/L),[2] ***and a diagnostic question remains,*** cBAT can be used to confirm hypoandrogenism.

c) Diagnosis

The diagnosis of hypoandrogenism is a probabilistic process based on medical history and physical findings, followed by investigational tests, guided by the clinical findings. Further investigation to determine the etiology of hypoandrogenism in men is beyond the scope of this protocol.

d) Monitoring of Treatment

The monitoring of testosterone therapy in men is primarily clinical. The usefulness of serum testosterone testing while on treatment is controversial.[2]

Testosterone Excess in Females

a) Signs and Symptoms

A range of symptoms and signs from hypertrichosis, hirsuitism, to virilization may occur.

b) Testing

Serum total testosterone is frequently normal in women with mild clinical hyperandrogenism (due to androgen suppression of sex hormone binding globulin (SHBG) production); cBAT testing has a better diagnostic yield for testosterone excess in women.[4] Repeat serum testosterone testing is *not indicated* if cBAT is normal. A serum total testosterone level of less than 7 nmol/L will rule out almost all of the testosterone-secreting neoplasms.[5]
Other hormonal testing is dependent on clinical findings and is beyond the scope of this protocol.

c) Diagnosis

The diagnosis of testosterone excess is based on medical history and physical findings, followed by investigational tests. Virilization that appears over a short period of time should arouse suspicion of adrenal or ovarian tumors and urgent specialist referral is advised. Further investigation to determine the etiology of androgen excess in females is beyond the scope of this protocol.

d) Monitoring of Treatment

Response to treatment of hyperandrogenism in women is clinical. Therefore, testing of serum total testosterone and cBAT in patients treated for hyperandrogenism is not recommended.

Rationale

In men 40 years and over, the symptoms that suggest hypoandrogenism are relatively nonspecific and potentially attributable to a host of other conditions, including aging itself.[6] Late-onset hypoandrogenism can be 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 total testosterone and/or a low cBAT.[7] The documentation of low total testosterone levels in symptomatic elderly men does not invariably imply that a low total testosterone level is the only or foremost cause of their symptoms. A comprehensive general assessment is required to exclude potential alternative explanations.[7]

Currently, there is no defined syndrome of hypoandrogenism in women. Testosterone testing methods that are currently available have inadequate analytical performance to diagnose hypoandrogenism in females; therefore, serum testosterone should not be measured for this purpose.

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. Analog methods of free testosterone measurement are inaccurate and are not recommended.[2] Bioavailable testosterone measures free testosterone and albumin bound testosterone. cBAT is an estimate of the bioavailable testosterone calculated from the total testosterone, SHBG and albumin concentrations, and their association constants.

Serum testosterone levels can vary significantly for the following reasons:

- age (decline in serum testosterone levels with aging in men is 1% to 2% per year)
- circadian rhythms (peak levels between 8 am and 11 am)
- episodic secretion: 30% of men with mildly hypogonadal serum testosterone levels will have a normal level on retesting
- exercise - excessive exercise reduces serum testosterone
- comorbid illness with changes in SHBG concentrations (see Table 2)
- illness acuity (avoid diagnosis of hypoandrogenism when patient is ill)
- eating disorders
- medications (see Tables 3 and 4)
- laboratory variations in testosterone testing (lack of a gold standard)

Table 2: Conditions Associated with Alterations in SHBG Concentrations

Decreased SHBG concentrations	Increased SHBG concentrations
• Diabetes mellitus[α] • Moderate obesity[α] • Nephrotic syndrome[α] • Use of glucocorticoids, progestins, and androgenic steroids[α] • Hypothyroidism • Acromegaly • Hyperthyroidism	• Aging[α] • Hepatic cirrhosis and hepatitis[α] • Use of anticonvulsants[α] • Use of estrogens • HIV infection • Hyperthyroidism

Adapted from Bhasin et al. 2010[2]
[α] particularly common conditions associated with alterations in SHBG levels

Table 3*: Medications Which May Alter Testosterone Levels in Males [8,9,10]

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

** does not represent an exhaustive list*

Table 4*: Medications Which May Increase Testosterone Levels in Females [8,9,10]

- barbiturates
- clomiphene
- estrogens
- valproic acid

** does not represent an exhaustive list*

List of Abbreviations

cBAT – calculated bioavailable testosterone
SHBG – sex hormone binding globulin

References

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6. T'Sjoen G, Feyen E, De Kuyper P, et al. Self-referred patients in an aging male clinic: much more than androgen deficiency alone. Aging Male. 2003;6:157-165.
7. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123-135.
8. Wilson, DD. McGraw-Hill's manual of laboratory & diagnostic tests. New York: McGraw-Hill Professional; 2008. p. 535-536.
9. Young DS. Effects of drugs on clinical laboratory tests. 5th ed. Washington: American Association for Clinical Chemistry; 1990. p. (3)737-(3)742.
10. A complete list of references is available by contacting hlth.guidelines@gov.bc.ca

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

A mobile version of this and other guidelines is also available at www.BCGuidelines.ca

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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

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