ANDROGEN DEFICIENCY - MALE HYPOGONADISM

1. Medical Condition

Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and in some instances normal number of spermatozoa (infertility) due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis. The two distinct yet interdependent testicular functions, spermatogenesis and steroidogenesis (androgen production), operate and can fail independently. Androgen deficiency is the focus of this document.

2. Diagnosis

A. Etiology

Androgen deficiency may be primary, due to a problem with the testes, or secondary, due to a problem with the hypothalamic-pituitary-gonadal axis or combined primary and secondary. The etiology of androgen deficiency may be organic, in which there is a pathological physical change in the structure of an organ or within the hypothalamic-pituitary-testicular axis. Androgen deficiency may be functional in which there is no observable pathological change in the structure of an organ or within the hypothalamic-pituitary-testicular axis. Organic defects are usually long lasting or permanent while functional defects are potentially reversible.

Organic causes of androgen deficiency *

Organic primary androgen deficiency may be due to:

1. Genetic abnormalities – Klinefelter's Syndrome and variants (i.e. 47,XYY/46XY, 46,XX testicular DSD, 45,X/46,XY), dysgenetic testes, myotonic dystrophy

2. Developmental abnormalities – cryptorchidism, congenital anorchia

3. Metabolic abnormalities – hemochromatosis (usually consistent with secondary hypogonadism)

4. Direct testicular trauma, surgical bilateral orchidectomy, testicular torsion

5. Orchitis – severe bilateral with subsequent testicular atrophy due to mumps or other infections.

6. Radiation treatment or chemotherapy.

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Organic secondary androgen deficiency may be due to:

1. Genetic abnormalities – Isolated hypogonadotropic hypogonadism (IHH) and variants.

2. Pituitary disorders – hypopituitarism, tumor, infection, hemochromatosis, hyperprolactinemia due to prolactin-secreting pituitary tumor.

3. Structural and infiltrative effects of systemic diseases – CNS developmental abnormalities, infection, β-thalassemia/hemoglobinopathies, granulomatous diseases, lymphocytic hypophysitis hemochromatosis, sickle cell disease.

4. Anatomical problems - pituitary stalk section, hypophysectomy, pituitary-hypothalamic disease, traumatic brain injury.

Functional Causes of androgen deficiency*

Functional androgen deficiency may be due to:

1. Severe emotional stress.

2. Morbid Obesity, untreated obstructive sleep apnea.

3. Overtraining, malnutrition/nutritional deficiency, eating disorders.

4. Medication – opioids, androgens, selective androgen receptor modulators (SARMs), glucocorticoids, progestins, estrogens, medication-induced Hyperprolactinemia.

5. Chronic systemic illness (chronic organ failure, diabetes mellitus, malignancy, rheumatic disease, HIV infection, Crohn's disease, inherited metabolic storage diseases).

6. Constitutional delayed puberty.**

7. Aging/Late onset hypogonadism (LOH).

8. Alcohol excess.

Defects in androgen action include:

a) Androgen receptor defects of which there is a full spectrum from testicular feminization to Reifenstein's Syndrome to mild defects. Serum testosterone levels are not reduced and LH and estradiol levels may be increased.

b) 5α-reductase deficiency: May present with selective signs of partial androgen deficiency. Serum testosterone levels are not reduced.

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In general, varicocele alone is not an etiology of pathological (or organic) androgen deficiency.

TUE should only be approved for androgen deficiency that has an organic etiology. TUE should not be approved for androgen deficiency due to functional disorder. TUE for androgen deficiency should not be approved for females.

* The list is representative of observed conditions and not necessarily complete

** May be approved for limited time until puberty is attained

B. Medical Evaluation

The TUE application must include the following information submitted to the appropriate Antidoping organization (ADO). This information must be submitted in a letter from the treating physician (preferably a specialist in endocrinology). This submission must include information listed below, dates of evaluation, copies of laboratory and testing results. If androgen deficiency is iatrogenic in origin (orchiectomy, pituitary surgery or irradiation, radiotherapy or chemotherapy), details of the diagnosis and treatment including surgery reports should be submitted. The evaluation for androgen deficiency, unless otherwise stated, must include:

1. History:
   a. Pubertal progression - incomplete or delayed sexual development
   b. Reduced libido and sexual activity
   c. Decreased spontaneous erections and/or ejaculations
   d. Hot flushes, sweats
   e. Non specific symptoms – decreased energy, depressed mood, dysthmia, poor concentration, sleep disturbance, hypersomnolence, mild anemia, reduced muscle bulk & strength, increased body fat and BMI, diminished work performance
   f. Low or zero sperm count (may not be associated with low testosterone)
   g. Low bone density (loss of height or low trauma fractures)
   h. History of cryptorchidism, torsion or significant testicular injuries
   i. History of significant head injuries
   j. History of orchitis
   k. Family history of delayed puberty

2. Physical Exam:
   a. Gynecomastia
   b. Changes in hair pattern (axillary & pubic), reduced shaving, absence of temporal recession
   c. Decreased testicular volume (small testes) <15cc by orchidometry or ultrasound

3. Testing/Laboratory evaluation (blood drawn in the morning) to demonstrate consistent androgen deficiency should be provided with the TUE application including:

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a. Total testosterone – assay using an accurate and reliable method
b. Free testosterone – using an accurate and reliable method (e.g. calculated free testosterone from total testosterone and SHBG measurements or free testosterone by equilibrium dialysis), if available
c. LH and FSH
d. SHBG
e. Semen analysis including sperm count if fertility an issue
f. DEXA scan if bone density an issue
g. Urine drug screens may be requested and organized by the Anti-Doping Organization

a, b (if available) & c must be drawn on at least two occasions at least a week apart in a 4-week period.

Athletes who are already taking testosterone supplementation will need to stop the medication for a sufficient time period to properly evaluate the true levels of testosterone. It is expected that natural testosterone levels will be low in the period following cessation of exogenous supplementation. The washout schedule which is in Appendix A is to be followed prior to re-testing.

4. If hypogonadotropic hypogonadism or hypopituitarism is diagnosis:
   a. MRI of brain with pituitary (sella) cuts with and without contrast
   b. Pituitary function tests if appropriate
   c. Other appropriate diagnostics to identify an organic etiology for secondary hypogonadism (e.g. prolactin, iron studies and genetic testing for hereditary hemochromatosis)
   d. Documentation of appropriate evaluation of the etiology of hypogonadism should be provided with the TUE application.

3. Medical Treatment

A. Name of prohibited substances

Testosterone or human Chorionic Gonadotropin (hCG)

B. Route/Dosage/Frequency

Treatment with approved testosterone formulations or hCG (if athlete has secondary hypogonadism documented and desires fertility)

1. Testosterone may be administered by regular intramuscular injection. The treatment must be recorded by a health professional and kept available for control at any time. The administration of intramuscular testosterone is typically a 100 mg injection every week or 200-250 mg every two weeks to replace endogenous secretion. If testosterone undecanoate ester is the medication prescribed, the standard dosage is 1000 mg with the dosing intervals of every 12

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weeks on average.

2. Testosterone may also be administered by transdermal patch or gel. The testosterone patch or gels have a daily dosing regimen. A buccal testosterone tablet applied twice daily is also available.

3. Testosterone may be administered by oral preparation testosterone undecanoate, usually twice or thrice daily with meals. 17α-methyl testosterone is not suggested due to hepatotoxic side effects and potential liver toxicity.

4. Human Chorionic Gonadotropin (hCG) may be used in doses of 1000-2000 IU IM 2-3 times per week for those individuals requesting fertility. Higher doses may be needed in some men in order to maintain physiological testosterone levels. FSH, if required, is not a prohibited substance.

C. Monitoring dosage

The dosage and frequency are to be determined by the prescribing endocrinologist utilizing standard dosage regimens. The dosage should be monitored with trough serum testosterone levels for injectable testosterone. The testosterone product, dosage and timing of the previous treatment with injectable testosterone products must be recorded and submitted for annual review or for dosage changes. Gel testosterone can be monitored by serum testosterone levels at any time. HCG should be monitored with trough serum testosterone levels. The dosage and timing of treatments with hCG must be recorded and submitted for annual review or for dosage changes. Any change in product, dosage or treatment schedule of testosterone or hCG should be approved by ADO.

D. Duration of treatment

The duration of treatment may be lifelong but annual renewal including evidence of well-controlled therapy including dosage and timing of treatments, serum testosterone levels must be submitted for review.

4. Other non-prohibited alternative treatments?

If the diagnosis is confirmed, there is not a non-prohibited substance alternative treatment.

5. Consequences to health if treatment is withheld

Under developed genitals (if before puberty), muscle weakness, osteoporosis, diminished libido, erectile dysfunction/impotence, infertility, depression.

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6. Treatment monitoring

Regular physician visits with documentation that testosterone treatment improved clinical manifestations of androgen deficiency in medical record are required.
The athlete is responsible for maintaining a complete record of testosterone prescriptions of oral, gel or buccal testosterone products and date, dosage and name of medical personnel administering injections of testosterone or hCG. Frequent testing of serum testosterone including unannounced urine and blood testing as ordered by ADO (at least 1-2 times per year) should be required and related to injection timing or gel application. Treatment should use standard testosterone doses which should return the trough testosterone to mid-normal levels.

7. TUE validity and recommended review process

The duration of approval will be limited to 4 years in all cases at a maximum. In all cases the annual review process demonstrating testosterone level and symptom control of well adapted dose should occur every year. Copies of medical records of visits with prescribing physician, laboratory reports for serum testosterone levels (with dates and times) must be provided and accompanied by prescriptions for oral, transdermal or buccal preparations and the product, dosage, dates and names of administering medical personnel of all injectable testosterone or hCG administrations. Another independent specialist may be consulted as necessary. Documentation in medical records of the reason for changes in the dosage of testosterone and testosterone levels before and after a dosage change should be provided with a report prior to dosage change. The ADO should approve any changes in the dosage of testosterone or hCG.

8. Any appropriate cautionary matters

In the particular case of a young athlete with delayed puberty, the opinions of a pediatrician and an endocrinologist must confirm the diagnosis and a need for testosterone supplementation. This should be accompanied by the report of a relevant clinical examination. The approval must always be for a period of no more than one year.

Given the potential controversy associated with the approval of a TUE for testosterone, the opinion of an independent endocrinologist with expertise in Andrology is strongly suggested.

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Product with route of administration	**Washout period[1] [2]**	**Urine test (anti-doping)**	**Blood tests LH, FSH, Test**
Transdermal testosterone (testosterone patch, gel or cream)	2 weeks	At beginning of wash-out (wk 0)	End of wash-out (wk. 2) and again between wk 3-4
Oral (testosterone undecanoate) or buccal testosterone	2 weeks	At beginning of washout period (week 0)	End of wash-out (wk. 2) and again between wk 3-4
Intermediate acting testosterone by IM injection (testosterone enanthate, testosterone cypionate or mixed esters)	8 weeks	At week 0 plus 1 random between weeks 3-7	1 test at week 8 and then another within the next 4 weeks, at least one week apart.
Long acting testosterone by IM injection (testosterone undecanoate)	26 weeks	At week 0 plus 2 random tests between weeks 3-25	1 test at week 26 and then another within the next 4 weeks, at least one week apart.
Subcutaneous testosterone pellets	40 weeks	Wk 0 plus 2 or 3 random tests during weeks 8-38	1 test at week 40 and then another within the next 4 weeks, at least one week apart.

[1] Washout period represent the time that the exogenous testosterone would have left the system and one would likely see recovery from medication effects for men using standard testosterone doses. For those using higher than standard doses for prolonged periods, the washout period for the medication and the full reproductive axis recovery can be more prolonged.

[2] During washout period, drug testing to prevent the continued use of testosterone products or analogs is critical to insuring adherence to medication abstinence during this washout period.

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