Male Hypogonadism

Prohibited Substances: testosterone and human Chorionic Gonadotropin (hCG)

1. Introduction

Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (testosterone deficiency) and, in some instances, normal number of spermatozoa (infertility) due to pathological disruption (structural, genetic) of one or more levels of the hypothalamic-pituitary-testicular axis. The two distinct yet interdependent testicular functions, steroidogenesis (testosterone production) and spermatogenesis can fail independently. Organic hypogonadism with testosterone deficiency is the focus of this document. Low circulating testosterone without a clear pathological cause, in this context, is not considered to be hypogonadism.

TUEs for androgen (testosterone) deficiency should not be approved in women. For transgender athletes, please see the TUE Physician Guidelines for Transgender Athletes.

2. Diagnosis

a. Medical history

Hypogonadism may be primary, due to a problem with the testes, or secondary, due to a problem with the hypothalamus or pituitary gland or combined primary and secondary. The etiology of testosterone deficiency may be organic, in which there is a pathological structural or genetic defect within the hypothalamic-pituitary-testicular axis. Low circulating testosterone may be functional where there is no observable pathological change in the structures within the hypothalamic-pituitary-testicular axis. Organic hypogonadism is usually long-lasting or permanent while functional reductions in circulating testosterone are potentially reversible.

TUE should only be approved for hypogonadism i.e., from an organic etiology. TUE should not be approved for low testosterone due to functional states.

1. Primary hypogonadism may be due to:

   a. Genetic abnormalities
   b. Developmental abnormalities
   c. Bilateral testicular trauma
   d. Bilateral testicular torsion
   e. Orchitis
1. Bilateral orchiectomy
2. Unilateral orchiectomy where the remaining testicle has sustained organic damage (i.e., radiation or chemotherapy)
3. Radiation treatment or chemotherapy

2. Secondary hypogonadism may be due to:
   a. Genetic abnormalities of pituitary and hypothalamus
   b. Pituitary or hypothalamic tumors
   c. Other anatomical (structural), destructive and infiltrative disorders of the pituitary or hypothalamus.

3. Organic defects in androgen action or production (Disorders of Sex Development (46, XY DSD):
   a. 46, XY DSD due to androgen receptor defects that range from males with complete androgen insensitivity (CAIS, formerly known as testicular feminization) who have a near-normal female phenotype to males with mild androgen insensitivity (MAIS) who have near-normal male phenotype. Partial Androgen Insensitivity Syndrome (PAIS) have an intermediate level of androgen sensitivity and clinical phenotype.
   b. 46, XY DSD due to 5α-reductase Type 2 deficiency (5ARD2) or 17 B hydroxysteroid dehydrogenase type 3 (17HSD3) in genetic males who have ambiguous genitalia at birth.

4. Constitutional delayed puberty is viewed as a special category since TUE may be approved for treatment with testosterone even if the etiology may be temporary and reversible (see Section 8 and Appendix A).

**Functional causes of low circulating testosterone**

This list is representative of the more commonly observed conditions and not necessarily complete.

N.B.: TUEs should not be approved for low testosterone due to a functional state.

1. Functional low testosterone may be due to:
   a. Severe psychological/emotional stress
   b. Obesity (WHO grade III or IV – BMI>30)
   c. Aging
   d. Untreated obstructive sleep apnea
   e. Overtraining, malnutrition/nutritional deficiency eating disorders, Relative Energy Deficiency in Sport (RED-S)
   f. Medication such as opioids, androgens, natural or synthetic androgens including steroidal and non-steroidal (SARM) androgens, GnRH analogues, glucocorticoids, progestins, estrogens, medication-induced hyperprolactinemia
   g. Chronic systemic illness (kidney, liver, lung, heart failure, diabetes mellitus, malignancy, inflammatory joint disease, HIV infection, Crohn's disease, inherited metabolic storage diseases)
   h. Alcohol excess
2. **Varicocele** is not a cause of organic hypogonadism and not an acceptable diagnosis for a TUE for testosterone treatment.

3. **Andropause/Late Onset Hypogonadism (LOH)** is not an acceptable diagnosis for a TUE for hypogonadism.

**b. Diagnosis criteria**

A complete medical evaluation is necessary for a TUE application; nevertheless, a TUE will only be granted if a clear picture of hypogonadism with testosterone deficiency (i.e., organic etiology) is demonstrated. In this context, a low circulating testosterone without a clear pathological cause will not justify a TUE for testosterone.

The TUE application submitted to the appropriate Anti-Doping Organization (ADO) must include information such as dates of evaluation (including history and physical examination), copies of laboratory values (with reference ranges) and testing results. If testosterone 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. This information must be submitted in a letter from the treating physician (preferably a specialist in endocrinology or andrology). The evaluation for hypogonadism, unless otherwise stated, must include:

1. **Required history:**
   a. Pubertal onset and progression - incomplete or delayed sexual development
   b. Libido and frequency of sexual activity – duration and severity of any problems
   c. Erections and/or ejaculations
   d. Hot flushes, sweats
   e. Testicular disorders – cryptorchidism, testicular torsion, testicular injuries
   f. Significant head injuries
   g. Orchitis
   h. Family history of delayed puberty or infertility
   i. Non-specific symptoms – decreased energy, depressed mood, dysthymia, poor concentration, sleep disturbance or sleepiness, mild anemia, reduced muscle bulk & strength, increased body fat and BMI
   j. Medications e.g., anti-acne drugs)

2. **Physical exam features must be addressed:**
   a. Acne (especially truncal)
   b. Gynecomastia
   c. Hair pattern (facial, axillary & pubic), absence of temporal recession
   d. Testicular volume by orchidometer or ultrasound (abnormal is <15 ml)
   e. Height and weight – BMI
   f. Muscular development and tone

3. **Testing/Laboratory evaluation to demonstrate consistent testosterone concentrations** should be provided with the TUE application including:
Required Testing:

To be drawn before 10 AM with serum total testosterone and serum luteinizing hormone (LH) drawn on two occasions within a 4-week period at least a week apart

1. Serum total testosterone – assay using an accurate and reliable method
2. Serum LH
3. Serum follicle stimulating hormone (FSH)
4. Serum sex hormone-binding globulin (SHBG)

Testing, when indicated:

1. Semen analysis including sperm count, sperm motility and sperm morphology if fertility is an issue. There should be at least two semen analyses which should be performed and analyzed according to WHO Semen Analysis Manual.
2. DEXA scan if appropriate
3. Inhibin B when considering Congenital (Isolated) Hypogonadotropic Hypogonadism or Constitutional Delayed Puberty

Free testosterone

Free testosterone measured by equilibrium dialysis with a well-established reference range may be submitted. Note that calculation of free testosterone based on other variables (serum testosterone, SHBG) is not a valid or acceptable analytical variable. Direct analog-based free T assays are not acceptable. TUE will not be granted as a result of low free testosterone only.

Athletes who are already taking testosterone supplementation prior to compiling an application for a TUE may need to stop the medication for a sufficient time-period to properly evaluate their need for testosterone due to an organic cause of hypogonadism. It is expected that endogenous testosterone levels will be transiently low in the period immediately following cessation of exogenous supplementation. The washout schedule, which is in Appendix B, is to be followed prior to re-testing in order to reset the hypothalamic-pituitary-gonadal (HPG) axis.

Drug screening during evaluation for hypogonadism

1. Urine or serum drug screens may be requested and organized by the ADO.

For diagnosis of Congenital (Isolated) Hypogonadotropic-Hypogonadism:

1. MRI of pituitary with and without contrast
2. Pituitary function tests to exclude hypopituitarism where indicated, e.g., morning cortisol, ACTH stimulation test, serum TSH, T4, prolactin, IGF-1
3. Other appropriate diagnostics to identify an organic etiology for hypogonadism (e.g., karyotype, olfactory testing, iron studies (serum transferring, % saturation) and genetic testing for hereditary hemochromatosis)
4. Documentation ruling out any potential functional causes of low circulating testosterone and gonadotrophins
3. Treatment

a. Name of prohibited substances

Testosterone or human Chorionic Gonadotropin (hCG).

b. Route of administration

Treatment with approved testosterone formulations or hCG (if athlete has secondary hypogonadism documented and desires fertility). Only products and dosage regimens approved by drug regulatory agencies are allowed.

1. Testosterone may be administered by regular intramuscular injection. The treatment must be recorded by a health professional and a written record kept available for review at any time. The administration of injectable testosterone enanthate or cypionate or mixed testosterone esters (intramuscular or subcutaneous) is typically a 100 mg injection every week or 150-250 mg every two weeks. If the medication prescribed is injectable testosterone undecanoate ester (intramuscular), the standard dosage is 750 mg every 10 weeks (USA) or 1000 mg every 12 weeks (rest of the world), with the dosing intervals to be modified according to individual dose optimization. Optimal titration of the inter-injection interval is acceptable according to clinical response and trough testosterone concentration (together with serum LH and FSH levels in primary hypogonadism) but testosterone undecanoate injection intervals should be no more frequently than 8 or 12 weeks, respectively. More frequent injections should be justified by evidence of inadequacy of standard injection schedule and individual dose optimization from trough circulating testosterone with corresponding symptomatic (run-off) effects.

2. Testosterone may also be administered by transdermal patch, cream, gel or lotion. The testosterone patches, creams, gels or lotions have a daily dosing regimen. A buccal testosterone tablet and nasal spray administered twice daily are also available.

3. Testosterone may be administered by oral preparation testosterone undecanoate in oil filled capsules, usually twice or thrice daily with meals. 17α-methyl testosterone is hepatotoxic and should not be used.

4. Human Chorionic Gonadotropin (hCG) may be used for induction of sperm production for infertile men with gonadotrophin deficiency (secondary hypogonadism) using doses of 1000-2000 IU IM (urinary-derived hCG) 2-3 times per week or 250 µg (recombinant hCG) per month in divided weekly doses for those individuals requesting fertility. Higher doses may be needed in some men to maintain physiological testosterone levels and induction of spermatogenesis and fertility. FSH, if required, is not a prohibited substance.
c. Dosage and frequency

The injectable testosterone product, dosage, and timing of the previous treatment and a record of dispensed prescriptions and dosage changes must be recorded and submitted to the ADO.

The dosage and frequency are to be determined by the prescribing endocrinologist utilizing standard replacement dosage regimens. For injectable testosterone, dosage can be monitored at trough (at the time of next scheduled injection) serum testosterone levels.

Transdermal testosterone patches, gels, creams, or solutions 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 and dispensed prescriptions with hCG must be recorded and submitted for annual review or for dosage changes, if required.

Any change in product, dosage, or treatment schedule of testosterone or hCG should be approved by the ADO.

Testosterone or hCG use beyond the therapeutic dosage would result in the TUE no longer being valid and the athlete could therefore be subject to an ADRV.

d. Duration of treatment

The duration of treatment may be lifelong but regular follow-up showing evidence of well-controlled therapy must be submitted. The evidence submitted must include medication logs, injection logs and pharmacy records, dosage, and timing of treatments as well as results of serum testosterone levels by the treating physician.

4. Non-prohibited alternative treatments

If the diagnosis is confirmed, there is no non-prohibited substance alternative treatment.

5. Consequences to health if treatment is withheld

Underdeveloped genitals (if before puberty), muscle weakness, osteoporosis, diminished libido, sexual dysfunction (impotence or erectile dysfunction), infertility.

6. Treatment monitoring

Regular physician visits with documentation that testosterone treatment improved clinical manifestations of testosterone deficiency in medical records are required. The athlete is responsible for maintaining a complete record of testosterone prescriptions of oral, transdermal (patches, gels, creams, solutions) or buccal testosterone products and date, dosage (pharmacy records) and name of medical personnel administering injections of testosterone or hCG. Unannounced urine testing (at least 1-2 times per year) should be conducted by the ADO.
Furthermore, regular serum testing as ordered by the athlete’s endocrinologist and or prescribing physician (at least 1-2 times per year) is required and the relation to injection timing (trough levels preferred) or gel application should be clearly noted.

7. **TUE duration**

The duration of approval should be limited to 4 years. In all cases, the 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.

In the case of a young athlete with delayed puberty, the opinions of a pediatrician and an endocrinologist must confirm the diagnosis and a need for temporary testosterone treatment of a pre-determined fixed duration and subject to repeat after review of progress and ongoing need for testosterone treatment. This should be accompanied by the report of a relevant clinical examination including Tanner stage. The approval must always be for a period of no more than one year.

8. **Appropriate precautionary matters**

Given the potential controversy and scrutiny associated with the approval of a TUE for testosterone in sport, the opinion of an independent endocrinologist with expertise in andrology or male reproductive endocrinology is strongly suggested.

Testosterone may be prescribed to a transgender (female-to-male) athlete using the same standard doses as described herein. See also TUE Physicians Guidelines for [Transgender Athletes](#).
References


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13. WHO laboratory manual for the examination and processing of human semen [WWW Document], n.d. 

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Appendix A

Hypogonadism

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

**Primary hypogonadism may be due to:**

1. Genetic abnormalities
   a. Klinefelter’s Syndrome and variants (i.e. 47,XYY/46,XY)
   b. Dysgenetic testes
   c. Myotonic dystrophy
2. Developmental abnormalities
   a. Cryptorchidism
   b. Congenital anorchia
3. Direct testicular trauma, bilateral orchiectomy, testicular torsion
4. Orchitis – severe bilateral with subsequent testicular atrophy due to mumps or other infections
5. Radiation treatment or chemotherapy
6. 46,XY DSD due to defects in testosterone biosynthesis
7. LH/hCG receptor defects.

**Secondary hypogonadism may be due to:**

1. Genetic abnormalities of pituitary and hypothalamus
   a. Congenital (isolated) hypogonadotropic hypogonadism (IHH), including Kallmann Syndrome
   b. Congenital isolated LH deficiency
   c. Congenital pituitary defects causing multiple pituitary hormone deficiency (MPHD) complex congenital syndromes.
2. Pituitary or hypothalamic tumours
   a. Pituitary adenomas including prolactinoma
   b. Craniopharyngioma.
3. Iron Overload Syndromes
   a. Genetic or transfusional hemochromatosis
   b. Hemoglobinopathies
      i. β-Thalassemia
      ii. Sickle cell disease

4. Structural, destructive, and infiltrative disorders of the pituitary or hypothalamus
   a. Surgery or radiotherapy for pituitary tumours
   b. CNS developmental abnormalities, infection
   c. Granulomatous diseases
   d. Lymphocytic hypophysitis

5. Anatomical problems of the pituitary or hypothalamus
   a. Pituitary stalk section
   b. Hypophysectomy
   c. Pituitary-hypothalamic disease
   d. Severe or repeated traumatic brain injury causing pituitary dysfunction

6. Hypogonadotrophic Hypogonadism combined with adrenal insufficiency (X-linked adrenal hypoplasia (AHC)).

Organic defects in androgen action or production (Disorders of Sex Development (46,XY DSD))

1. 46,XY DSD due to androgen receptor defects that range from males with complete androgen insensitivity (CAIS, formerly known as testicular feminization) who have a near-normal female phenotype to males with mild androgen insensitivity (MAIS) who have near-normal male phenotype. PAIS may have intermediate androgen insensitivity and a clinical phenotype. Serum testosterone levels may be normal and LH levels may be elevated.

2. 46,XY DSD due to 5α-reductase Type 2 deficiency (5ARD2), 17β hydroxysteroid dehydrogenase type 3 (17BHSD3) or mixed gonadal dysgenesis in males who have ambiguous genitalia at birth and may be raised as female, but who at puberty, develop near-normal male somatic phenotype with normal male range testosterone levels.

Constitutional delayed puberty is a special category. Constitutional delayed puberty is not a permanent condition, although it may have a genetic component. TUEs should be allowed for this condition as prescribed by the treating endocrinologist or pediatrician but treatment should never extend past the initiation of puberty.

Female-to-male transgender individuals are another special category and can be granted a TUE for treatment with testosterone (but not hCG) doses as above. See also TUE Physicians Guidelines for Transgender Athletes.
Comment on Idiopathic Hypogonadotropic Hypogonadism

Idiopathic Hypogonadotropic Hypogonadism has sometimes been confused with Isolated Hypogonadotropic Hypogonadism. Isolated HH is an old term that distinguished a series of genetic disorders that led to gonadotropin deficiency and pubertal failure from panhypopituitarism. It is now referred to as Congenital Hypogonadotropic Hypogonadism due to organic disorders and therefore can justify the granting of a TUE.

Idiopathic Hypogonadotropic Hypogonadism is a term that has been used frequently in recent years. It includes congenital (isolated) HH but extends as an umbrella term to include various acquired (non-genetic) functional states (e.g. obesity, cardiovascular disease, depression, opiate or exogenous androgen use, overtraining, etc.) which are associated with a low circulating testosterone. Idiopathic Hypogonadotropic Hypogonadism is not an acceptable diagnosis for TUE application.
Appendix B

Washout table

Those athletes who have been taking testosterone for hypogonadism due to organic causes prior to their application for a TUE, may need to stop the medication for a certain time period to evaluate if there still is a need for supplementation. This washout table is to help determine the time-period before the HPG axis would recover after exogenous testosterone use. 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.

<table>
<thead>
<tr>
<th>Product with route of administration</th>
<th>Washout period¹</th>
<th>Urine test (anti-doping)</th>
<th>Blood tests LH, FSH, Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal testosterone (testosterone patch, gel, cream or lotion)</td>
<td>2 weeks</td>
<td>At beginning of wash-out (week 0)</td>
<td>End of wash-out (week 2) and again between weeks 3-4</td>
</tr>
<tr>
<td>Oral (testosterone undecanoate) or buccal testosterone</td>
<td>2 weeks</td>
<td>At beginning of washout period (week 0)</td>
<td>End of wash-out (week 2) and again between weeks 3-4</td>
</tr>
<tr>
<td>Intermediate acting testosterone by IM injection (testosterone enanthate, testosterone cypionate or mixed esters)</td>
<td>8 weeks</td>
<td>At week 0 plus 1 random between weeks 3-7</td>
<td>1 test at week 8 and then another within the next 4 weeks, at least one week apart</td>
</tr>
<tr>
<td>Long-acting testosterone by IM injection (testosterone undecanoate)</td>
<td>26 weeks</td>
<td>At week 0 plus 2 random tests between weeks 3-25</td>
<td>1 test at week 26 and then another within the next 4 weeks, at least one week apart</td>
</tr>
<tr>
<td>Subcutaneous testosterone pellets</td>
<td>40 weeks</td>
<td>Week 0 plus 2 or 3 random tests during weeks 8-38</td>
<td>1 test at week 40 and then another within the next 4 weeks, at least one week apart</td>
</tr>
</tbody>
</table>

¹ During washout period, drug testing to prevent the continued use of testosterone products or analogs is critical to insure adherence to medication abstinence.