

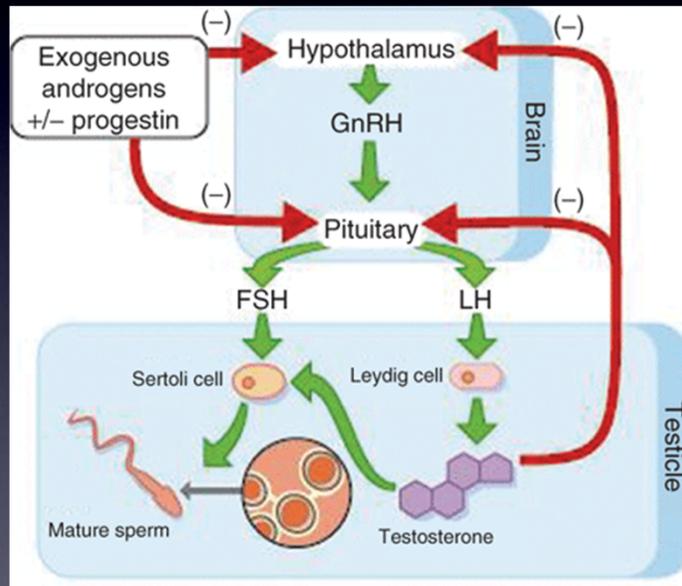
Hypogonadism and TRT in Athletes

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Definition

- Clinical syndrome that results from failure of testis to produce physiological levels of testosterone and normal number of spermatozoa due to disruption of one or more levels of hypothalamic-pituitary-testicular axis.

Hypothalamic-Pituitary-Testicular axis



Causes of Hypogonadism

- **Primary: Testicular failure.**
- **Secondary: Central defects of Hypothalamus or Pituitary.**
- **Combined: Testis + Pituitary.**

Organic Causes of Primary Hypogonadism

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

Source: WADA

Organic Causes of Secondary Hypogonadism

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 Secondary Hypogonadism

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), glucocorticosteroids, progestins, estrogens, medication-induced hyperprolactinemia

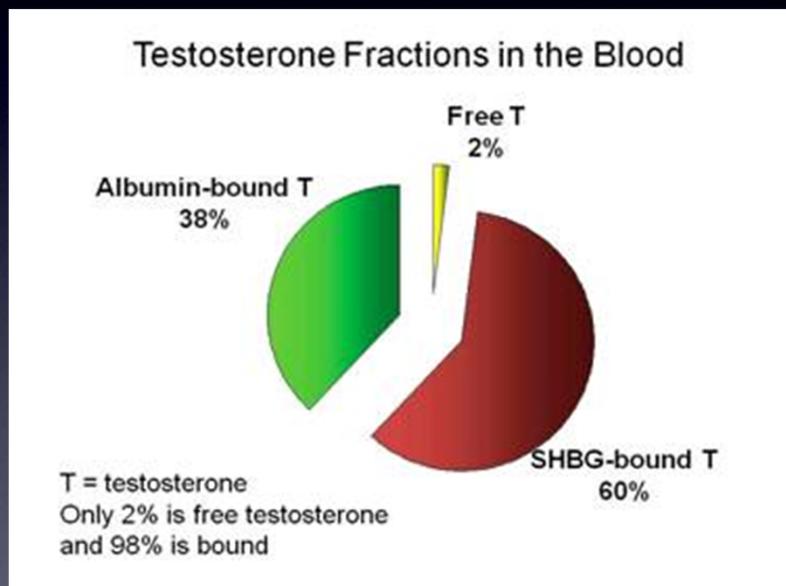
Functional Causes of Secondary Hypogonadism

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

Workup and Diagnosis

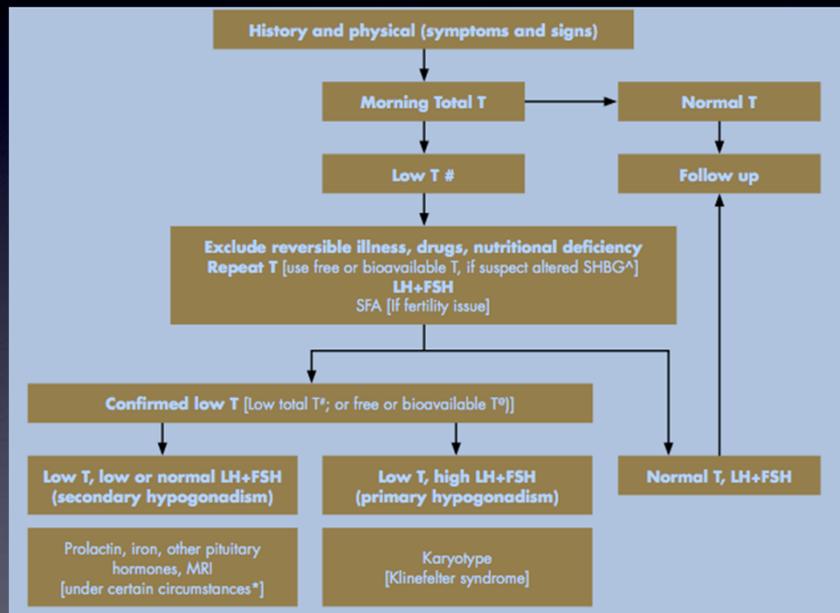
- Diagnosis only in men with consistent symptoms and signs + unequivocally low serum testosterone level
- Morning total testosterone level.
- Confirm diagnosis by repeating level:
Circadian rhythm: 30% NL on repeat, 15% healthy male below normal in 24 hr period.

Bio-Available Testosterone



- **Evaluation should not be made during acute or subacute illness.**
- **Free T level: equilibrium dialysis or calculated from Total T, SHBG and albumin.**
- **Use lower limit of normal range for lab:**
Total 280 to 300 ng/dl, Free :EDM 5-9 pg/ml

Workup



Source: Endocrine Society Guidelines 2010

Conditions associated with decrease in SHBG

- Decreased SHBG concentrations
- Obesity, Nephrotic syndrome, Hypothyroidism, Diabetes Mellitus, Acromegaly.
- Use of glucocorticoids, progestins, and androgenic steroids.

Conditions associated with Increase in SHBG

- Aging*
- Hepatic cirrhosis and hepatitis*
- Hyperthyroidism
- Use of anticonvulsants*
- Use of estrogens
- HIV disease

Could an Athlete Fein Hypogonadism

- HPT axis affected by several factors: Overtraining, exogenous androgens, opiates, glucocorticoids.
- 15% healthy below normal in 24 hr period.
- Diurnal rhythm.

Treatment Considerations

Table 5

Contraindications to testosterone replacement therapy

Very high risk of serious adverse outcomes

Prostatic carcinoma

Breast cancer

Prostate nodules or indurations

Unexplained prostate-specific antigen (PSA) elevation

Erythrocytosis (hematocrit > 50%)

Severe lower urinary tract symptoms with benign prostatic hyperplasia with an International Prostate Symptom Score (IPSS) >19

Unstable congestive heart failure (class III or IV)

Severe untreated sleep apnea

Testosterone Regimens

- IM - 75-100 mg weekly or 150-200 mg every 2 week.
- Patch - 5 to 10 mg daily.
- 1% Gel - 5 to 10 gm daily.

Treatment Goals

- Testosterone level in mid normal range.
- Intramuscular: levels vary during dosing interval: goal 350 to 700 ng / dl 1 week after injection. If more than 700, adjust dose or frequency.
- Patch: assess 3-12 hr after application.
- Gel: anytime after at least 1 week Rx.

Monitoring

- Hematocrit - 0, 3 and 6 month and annually.
- Stop therapy if Hct > 54%: evaluate for hypoxia, sleep apnea.
- Reinitiate at reduced dose after Hct decreased to safe level.
- Dexa - after 1-2 yr Rx :in patients with osteoporosis or low trauma fracture.

Monitoring Prostate

- PSA, DRE 0, 3-6 months and annually.
- Urology consult if:
 - Increase in PSA > 1.4 ng/ml within 12 month period.
 - PSA Velocity of > 0.4 ng/ml-yr.
 - Prostatic abnormality on DRE: AUA /IPSS prostate symptom score > 19 .

Formulation specific ADR

- **Injectable:** ask about fluctuation in mood / libido, rarely cough after injection.
- **Patch:** Check for skin reaction at application site.
- **Gel:** Advise to cover application site with shirt and to wash with soap and water before skin to skin contact to avoid transfer to woman or child.

Performance enhancing Effects of Testosterone

- Supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass, muscle size, and strength (1).
- Might enhance recovery from exercise and improve explosive power.
- Level of testosterone appears to be positively associated with "aggression" (2).

1) The Effects of Supraphysiologic Doses of Testosterone on Muscle Size and Strength in Normal Men: Shalender Bhasin, M.D., Thomas W. Storer, Ph.D., Nancy Berman, Ph.D., Carlos Callegari, M.D., Brenda Clevenger, B.A., Jeffrey Phillips, M.D., Thomas J. Bunnell, B.A., Ray Tricker, Ph.D., Aida Shirazi, R.Ph., and Richard Casaburi, Ph.D. *M.D.N Engl J Med* 1996; 335:1-7 [doi:10.1056/NEJM199601043350101](#). 2) Uzych L. Anabolic-androgenic steroids and psychiatric-related effects: a review. *Can J Psychiatry*. 1992;37:23-28

How can TRT be regulated in Sports?

- Based on WADA for TUE for TRT.
- TUE for androgen deficiency be should be approved only for organic etiology.
- TUE should not be approved for functional etiology.
- Etiology of Hypogonadism must be clearly identified.

- Total and Free Testosterone, SHBG, FSH, LH: must be drawn early morning, on at least 2 occasions, at least a week apart in four week period.
- If Hypogonadotropic Hypogonadism: MRI pituitary, pituitary functions, other appropriate diagnostics to identify organic etiology.

- Treatment with approved Testosterone formulations.
- Dosage and frequency to be determined by prescribing endocrinologist utilizing standard dosing regimens.
- For Injectables: Monitor peak and trough levels, For Gel: levels anytime after 1 week.

- Any change in product, dosage or treatment schedule must be approved.
- Regular physician visit with documentation that treatment improved clinical symptoms.
- Athlete responsible for maintaining complete record of prescription, date, dosage and name of medical personnel administering injections.

- Frequent testing of testosterone level including unannounced blood and urine test at least 1-2 times per year and related to injection timing or gel application.
- Treatment should return testosterone to mid normal levels.

Case Study

- MMA fighter, D.H
- Age: 41
- Presents to primary care doctor in Jan. 2007 with low energy and low libido.
- Morning blood work: Total testosterone level = 242 ng/dL.
- Post-injection level = 680 ng/dL (unknown when post-injection level drawn relative to injection).
- Goal (according to primary care doctor) = 400-800 ng/dL

- Tx: 200-300 mg every 2 weeks
- Post-injection level = 680 ng/dL
(unknown when post-injection level drawn relative to injection).
- Goal (according to primary care doctor)
= 400-800 ng/dL.

Questions

- Was the diagnosis made properly ?
- Does he really have low testosterone ?
- Was the treatment regimen appropriate ?
- Was there proper monitoring of treatment ?
- Could he have gotten unfair advantage over his competitors ?

Thank You