Hypogonadism and Testosterone Replacement in Males

Problem Statement
There is currently a great deal of interest related to direct-to-consumer marketing of new androgen replacement products including testosterone. This marketing-driven rise in interest prompts the desire for maintenance of youthfulness, strength and virility. The clinical and laboratory diagnosis of hypogonadism may not be straightforward and multiple tests may be needed. Before starting androgen replacement, the cause of hypogonadism needs to be explored and the risks need to be considered.

Recommendation
Screening:
The most common symptom prompting a laboratory test for androgens is decline in libido. Non-specific symptoms include weakness, decline in energy or endurance or mood, anemia, loss of androgen-dependent body hair and unexplained male osteoporosis. Note that erectile dysfunction rarely is a result of male hypogonadism unless there is also loss of libido. Hypogonadism may be recognized because of subnormal sperm count and infertility.

Laboratory Tests:
The simplest screening test is an early morning free testosterone level. (Do not use the total testosterone assay.) If the result is well within normal range, there is usually no need to evaluate further. Testosterone secretion is episodic and diurnal variation does occur. Therefore, borderline or low values require confirmation on 2 or 3 subsequent tests, preferably drawn as close to 8:00 a.m. as possible. If repeat testing is needed also do a sex hormone binding globulin with the second free testosterone.

Confirmatory Tests:
• Especially in obese men, a mildly low total testosterone level may not reflect hypogonadism. This is because obesity is associated with lowering of sex hormone binding globulin levels (SHBG) resulting in low total SHBG levels but normal free testosterone levels. In these men, a free testosterone level may be useful. MRI of the sella is not needed in older men with testosterone values over 150 ng/dl or younger men with values over 200 ng/dl. (these are total testosterone level measured from the Free testosterone assay)

Physical Exam Features:
• loss of androgen-dependent body hair (indicates long-standing hypogonadism)
• testicular atrophy
• gynecomastia and other phenotypic features suggestive of Klinefelters Syndrome

Differential Diagnosis:
• Luteinizing hormone (LH) and follicular stimulating hormone (FSH) are used to differentiate primary (i.e., gonadal failure) from secondary (i.e., pituitary or hypothalamic) causes of hypogonadism.
• High LH demonstrates primary or hypergonadotrophic hypogonadism (e.g., from mumps or Klinefelters Syndrome).
• Normal or low LH demonstrates secondary or hypgonadotrophic hypogonadism which may have a variety of causes some of which are critically important to recognize.
• OPMG Endocrinology recommends pituitary magnetic resonance imaging (MRI) in patients with unequivocally low testosterone levels to rule out a pituitary tumor. Unless there is laboratory evidence of other pituitary hormone abnormalities (e.g., elevated prolactin) or signs suggestive of a mass (e.g., headaches or visual field changes), MRI of the sella is not needed in older men with testosterone values over 150 ng/dl or younger men with values over 200 ng/dl.

Causes of Hypogonadism:
I. Primary
   • mumps orchitis
• Klinefelters Syndrome
• cancer chemotherapy or radiation therapy
• testicular trauma or torsion

II Secondary
• pituitary tumors (e.g., prolactinoma, nonfunctioning macroadenoma, craniopharyngioma)
• hemochromatosis
• Cushings Syndrome
• Kallmans Syndrome (anosmia with hypogonadotrophic hypogonadism – recommend to inquire about patient’s sense of smell)
• untreated sleep apnea
• chronic narcotic use
• idiopathic

Indications for Treatment:
Treatment should only be given with Unequivocal laboratory diagnosis of hypogonadism in the presence of compatible symptoms or osteoporosis.

Potential Benefits and Risks of Treatment:
I. Benefits (note that these benefits are not observed in all patients receiving androgen replacement who do not have well characterized biochemical hypogonadism)
• improvement in libido
• improvement in bone density
• improvement in lean body mass and muscle strength
• improvement in mood

II. Risks
• erythrocytosis (commonly observed)
• bladder outlet obstruction aggravation
• unrecognized prostate cancer growth acceleration
• sleep apnea aggravation
• testicular atrophy
• spermatogenesis suppression resulting in worsening infertility
• male pattern baldness and acne

III. Contraindications
• Prostate Cancer
• Breast Cancer

IV. Relative Contraindications:
• Prostate nodule
• Elevated PSA
• Erythrocytosis
• Elevated lft’s

Treatment & Monitoring:
I. Treatment with Testosterone Replacement
• intramuscular (IM) testosterone administration of a long-acting or depot testosterone injection at 200mg IM q2weeks or 400mg IM q4weeks is preferred. Contraindications to IM testosterone injection therapy include excessive bruising and bleeding (e.g., anticoagulated patients) or excessive cycling of the androgenic effect.
testosterone ointment 2%
transdermal testosterone patches

While the newer preparations have kinetic properties that more closely match native androgen levels, this may not be clinically important in most men. It is therefore not clear that the greatly increased costs of the newer, more heavily marketed androgen replacement products are justified by a meaningful clinical advantage.

II. Therapeutic Monitoring Efficacy:
Monitoring for therapeutic efficacy and adjustment of testosterone dose or frequency is often based on patient reports of symptom control. Total testosterone levels (peak or nadir) are generally not necessary. However, total testosterone levels are occasionally useful in men with poor symptomatic response to replacement therapy. In men treated with transdermal preparations, a total testosterone level can be useful to avoid unnecessary over medicating and also to guide the provider in dosing adjustments for those men who do not have symptom response to treatment.

Safety:

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<tr>
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<th>Prostate Specific Antigen (PSA)</th>
<th>Digital Rectal Exam (DRE)</th>
<th>Complete Blood Count (CBC)</th>
<th>Liver Profile (ALT, AST, alk phos, total bilirubin)</th>
<th>Serum testosterone*</th>
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<td>Baseline</td>
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*The timing of the blood draw is based upon the testosterone replacement type. Recommended timing for patients receiving injectable testosterone replacement is midpoint during the interval (i.e., 1 week after a q2week injection or 2 weeks after a q4week injection), anytime for patients receiving ointment or gel testosterone replacement, and 4 to 8 hours following placement of the testosterone patch.

V. Discontinuation of Treatment
If discontinuation of therapy is warranted, testosterone replacement may be discontinued without tapering the dose. Re-evaluation of serum testosterone levels is recommended 3 months following discontinuation.

References:
Hypogonadism and Testosterone Replacement in Males*

**Physical symptoms include:**
1) declining libido
2) weakness
3) declining energy or endurance
4) anemia
5) loss of androgen-dependent body hair
6) unexplained male osteoporosis

**Physical exam features:**
1) loss of androgen-dependent body hair
2) testicular atrophy
3) gynecomastia & other features associated with Klinefelter's Syndrome

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**Testosterone level** (drawn as close to 8:00 a.m. as possible)

**Testosterone level normal?**

**Secondary causes ruled out and treated?**
1) high luteinizing hormone (LH) indicates gonadal failure
2) normal or low LH indicates pituitary or hypothalamic failure

**Testosterone replacement therapy recommended**

**Formulary Preferred:**
1) IM testosterone cypionate (generic Depo-Testosterone)

**Formulary Alternatives:**
2) Topical testosterone ointment 2%
3) Testosterone patch (Androderm 2.5mg & 5mg)

(see online Ohio Region Formulary at http://online.lexi.com/crlonline for further prescribing information)

**Safety & Therapeutic Monitoring:**
1) prostate specific antigen at baseline, 3 months & annually
2) digital rectal exam at baseline, 3 months & annually
3) complete blood count at baseline, 3 months & annually
4) liver profile at baseline, 3 months & annually
5) serum testosterone at baseline, 3 months & annually
6) symptom control at 3 months & annually

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*Kaiser Permanente Ohio Region 9/2004
Please refer to the complete Hypogonadism & Testosterone Replacement in Males Guidelines for further information