Testosterone Replacement Therapy

Treatment of Male Hypogonadism

a report by
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Physiology
Androgens are responsible for the development and maintenance of secondary sexual characteristics, fertility, and anabolic effects of somatic tissues (lean body mass) in men.1,2 The primary androgen in circulation is testosterone. Production and secretion of testosterone is under the tonic control of leutinizing hormone (LH). LH and follicle-stimulating hormone (FSH) are secreted by the anterior pituitary and regulated by the pulsatile action of gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus. FSH, with the effects of testosterone, is responsible for spermatogenesis. Testosterone secretion is episodic and follows a distinct diurnal rhythm,12 with testosterone levels maximal in the morning and minimal in the evening.

Hypogonadism
Hypogonadism refers to deficiency of testosterone and spermatogenesis. Primary testicular failure is referred to as hypergonadotrophic hypogonadism, where the testosterone levels are low and gonadotropins are appropriately elevated. Secondary or tertiary (hypogonadotropic) hypogonadism results from reduced secretion of gonadotropins (GnRH deficiency), and the LH and FSH levels are inappropriately low or normal with low testosterone levels. Differential diagnoses for hypogonadism are listed (see Tables 1 and 2). The clinical characteristics of testosterone deficiency are summarized in Table 3.14

Diagnostic Evaluation
Measurement of 08:00h serum total testosterone levels21 is an initial test used to diagnose hypogonadism. The measurement of total testosterone can be altered in conditions that affect the levels of sex-hormone-binding globulin (SHBG): obesity, nephrotic syndrome, glucocorticoids, aging, cirrhosis, anti-convulsant use, and others.1 In these conditions measurement of free or bioavailable testosterone may be helpful. Testosterone levels are affected by illness, and a diagnosis should not be made during acute illness.1 FSH and LH levels help to distinguish between primary and secondary hypogonadism. Further work to elucidate the causes of primary and secondary hypogonadism should be pursued (karyotype, prolactin levels, iron profile, other pituitary hormones, and magnetic resonance imaging (MRI) of the pituitary if indicated).

Goals of Treatment
Testosterone replacement should be given in doses sufficient to approach normal physiological serum concentrations of testosterone and its active metabolites and to avoid adverse effects on the prostate, serum lipids, cardiovascular system, liver, and lung function.1

Indications for Treatment
• Low serum testosterone concentration, plus signs and symptoms of hypogonadism.
• Low bone mineral density with hypogonadism.
• Indications may also include increasing lean body mass and decreasing fat mass and improving energy and mood.

Evidence of Beneficial Effects of Testosterone Replacement Therapy
• Improved libido and erectile function: Testosterone replacement has been shown to improve libido, frequency of sexual activity, and erectile dysfunction.1
• Improved mood: It has also been associated with improved mood, energy, and verbal fluency.7,8
• Changes in body composition: Testosterone replacement therapy has been associated with increased lean body mass, decreased body fat,9 increase in muscle mass,10 increased fat free mass, and decreased fat mass.11,10
• Increase in muscle strength: Bhasin et al.12 found that T supplementation for 16 weeks in 61 hypogonadal, HIV-infected men aged 18–50 years resulted in increases in muscle volume and strength, whether accompanied by resistance training or not. However, a recent study suggested that replacing testosterone, dehydroepiandrosterone (DHEA),
Treatment of Male Hypogonadism

**Table 1: Hypergonadotropic Hypogonadism**

<table>
<thead>
<tr>
<th>CONGENITAL</th>
<th>ACQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelter’s syndrome</td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>47, XXY syndrome</td>
<td>Crypto-orchidism</td>
</tr>
<tr>
<td>Dysgenetic testes</td>
<td>Vanishing testes syndrome</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td>Trauma</td>
</tr>
<tr>
<td>Testicular hypoplasia</td>
<td>Mumps orchitis</td>
</tr>
<tr>
<td>Testicular hypoplasia</td>
<td>Radiation</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Sertoli cell syndrome</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>HIV</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Testicular aplasia</td>
<td>Opiates</td>
</tr>
</tbody>
</table>

**Table 2: Hypogonadotropic Hypogonadism**

<table>
<thead>
<tr>
<th>CONGENITAL</th>
<th>ACQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic hypogonadotropic hypogonad</td>
<td>Structural</td>
</tr>
<tr>
<td>including Kallmann’s syndrome</td>
<td>Tumors: craniopharynoma, pituitary</td>
</tr>
<tr>
<td></td>
<td>adenomas</td>
</tr>
<tr>
<td>Genetic defects of gonadotropin sub-units</td>
<td>Infiltrative disorders such as</td>
</tr>
<tr>
<td></td>
<td>sarcoidosis, hemochromatosis</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>Head trauma</td>
</tr>
<tr>
<td>Laurence-Moon-Biedl syndrome</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Pituitary apoplexy</td>
</tr>
<tr>
<td></td>
<td>Primary hypothyroidism</td>
</tr>
</tbody>
</table>

**Testosterone Replacement**

Daily output of testosterone is about 4–7mg, with the concentrations being higher in the morning and lower in the evening.22 (see Table 4). There are a variety of formulations on the market, listed below.

**Oral Preparations**

The first orally active, synthesized derivative of T was 17-α-methyl-T. Blood levels peak at 1.5–2 hours and serum half-life is about 150 minutes, indicating the need for several daily doses to maintain therapeutic levels. Side effects include cholestasis, peliosis, elevation of liver enzymes, and reduction of high-density lipoprotein-cholesterol.23 Fluoxymesterone is a 17α-methyl testosterone steroid with fluorne in the 9-position and is longer acting than its parent steroid, but is limited by hepatotoxicity.24 Mesterolone is derived from 5-alpha-dihydrotestosterone with a methyl group in the 1-position. It is not hepatotoxic, but relatively large doses must be taken several times a day and dosing is difficult to monitor.

**Intramuscular Preparations**

Two widely used formulations of testosterone esters are testosterone cypionate and enanthate. Testosterone esters lengthen the retention and duration of activity of the drug. Commonly used regimens are administration of 200mg of testosterone enanthate or cypionate once every two weeks intramuscular (IM) or 100mg weekly. Serum testosterone concentrations are supranormal initially and decline to the lower range of normal by the end of two weeks. The advantages of this formulation are that they are inexpensive (if self-administered) and allow flexibility of dosing. The disadvantages are that it is an IM injection and symptoms of energy and libido may vary depending on the serum levels of testosterone. A testosterone undecanoate injection, when given in doses of 1000mg IM, maintains normal testosterone levels in the majority of patients.25 It requires infrequent administration but a large volume (4ml) in each injection.

**Transdermal Preparations**

Scrotal patches deliver approximately 4–6 mg of testosterone daily.26 Normal androgen concentrations were achieved in 80% of hypogonadal men.27 Dihydrotestosterone (DHT) levels are elevated and scrotal shaving is necessary for optimal adherence of the patch.
Testosterone Replacement Therapy

### Table 3: Clinical Characteristics

| Decreased lean body mass | Increased fat mass | Decreased muscle mass and strength | Decreased bone mineral density | Decreased libido and erections | Decreased energy | Decreased cognitive function | Decreased sleep quality | Decreased spontaneous erections | Loss of axillary/pubic hair | Decreased frequency of shaving | Hot flushes, sweats | Infertility |

### Table 4: Formulations for Testosterone Replacement

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/α-methyl T</td>
<td>10–40mg/day</td>
<td>Oral administration</td>
<td>Hepatotoxic, low HDL</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
<td>5–20mg/day</td>
<td>Long-acting Oral administration</td>
<td>Hepatotoxic</td>
</tr>
<tr>
<td>Mesterone</td>
<td>25–150mg/day in divided doses</td>
<td>Oral administration</td>
<td>Large doses needed, dosing difficult to monitor</td>
</tr>
<tr>
<td>T undecanoate</td>
<td>120–160mg/day in divided doses</td>
<td>Oral administration</td>
<td>Varying testosterone levels, not available in the US</td>
</tr>
<tr>
<td><strong>INTRAMUSCULAR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cypionate or enanthate</td>
<td>1000mg weekly or 200mg every two weeks</td>
<td>Inexpensive, Flexibility of dosing</td>
<td>IM injection, Fluctuating symptoms</td>
</tr>
<tr>
<td>T undecanoate</td>
<td>Two loading injections of 1mg each, six weeks apart. After this, 1gm every 12 weeks</td>
<td>Prolonged action, Potential as a male contraceptive</td>
<td>Deep and slow intragluteal injection of large volume (4ml)</td>
</tr>
<tr>
<td><strong>TRANSDERMAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androderm®</td>
<td>5mg per day starting dose</td>
<td>Ease of application, Less rise of Hb</td>
<td>Contact dermatitis, Hypothyroidism</td>
</tr>
<tr>
<td>Scrotal patch</td>
<td>One patch delivers 4–6 mg of T</td>
<td>Physiological concentration of T, DHT supraphysiological</td>
<td>Scrotal shaving is required</td>
</tr>
<tr>
<td>Androgel®/Testim®</td>
<td>5gm gel (containing 50mg of T)</td>
<td>Ease of application, Physiologic concentration of T</td>
<td>No skin irritation, Potential for partner transfer</td>
</tr>
<tr>
<td><strong>BUCCAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striant®</td>
<td>30mg CR BID</td>
<td>Physiological concentration of T</td>
<td>Gum irritation</td>
</tr>
</tbody>
</table>

### Non-scrotal Testosterone

The available formulation is Androderm®. One to two patches a day deliver approximately 5–10mg of testosterone and restore physiological ranges of testosterone, DHT, and estradiol. Advantages are ease of application and lesser rise of hemoglobin than injectable esters. Chronic contact dermatitis (mainly from the alcohol component) occurs in about 10% of hypogonadal men after several weeks of use of Androderm®. Two drops of 0.1% triamcinolone acetonide cream applied to the skin under the central drug reservoir reduces contact dermatitis and itching without significantly affecting testosterone delivery or adrenal function.

### Testosterone Gel

Available formulations are Androgel® and Testim®. Packets weighing 5, 7.5, or 10gm contain 50mg, 75mg, or 100mg of testosterone (with systemic absorption of 5mg, 7.5mg, or 10mg, respectively). On average, about 10% of the applied dose is absorbed across the skin, producing physiological ranges of testosterone in blood. Steady-state levels are achieved by the second or third day of dosing. Estradiol concentrations are maintained in the physiological range, but the DHT levels are higher than normal range.

The advantages are ease of administration and good skin tolerability. However, there is potential for transfer of testosterone to partner by direct skin–skin contact. This can be avoided by using a barrier, such as a shirt, to cover the application site.

### Buccal Preparation

The available formulation is Striant®, which provides 30mg controlled-release used twice daily. It is applied to the depression in the gum above the upper incisors and releases testosterone into the peripheral circulation. T and DHT are normalized. Gum-related adverse effects occur in 16.3% of treated men.

### Induction of Fertility by using Human Chorionic Gonadotropin

In men with hypogonadotropic hypogonadism desiring fertility, human chorionic gonadotropin (hCG) alone or in combination with human menopausal gonatotropins (hMG) can be used to induce spermatogenesis and fertility. Since hMG is expensive, hCG is the initial therapy. hCG can be given IM 1,000–2,000 units two to three times per week. Testosterone levels and sperm counts can be monitored to reach normal levels. Sperm counts lower than normal can be sufficient to induce fertility in such circumstances. If spermatogenesis/induction of fertility have not occurred after 6–12 months, hMG can be added to the regimen at doses of 75 international units (IU) IM three times a week. This can be increased to 150 IU three times a week in six months, if desired results have not occurred.

### Side Effects

- Erythrocytosis: This has been associated with testosterone replacement therapy, but transdermal preparations tend to have fewer cases of polycythemia compared with testosterone enanthate injections. Erythrocytosis is correlated with elevated bioavailable testosterone and estradiol levels.
- Acne and oily skin.
- Growth of undiagnosed prostate cancer.
- Azoospermia: When used as a means of male contraception, exogenous testosterone induces azoospermia within 10 weeks of therapy. Fertility after cessation of therapy has also been reported.
- Changes in lipid profile: A recent meta-analysis showed that there were insignificant changes in low-density lipoprotein and thyroglobulin (Tg) levels after replacement of testosterone in men with low to low-normal testosterone.
- Gynecomastia.
Worsening of benign prostatic hyperplasia or hypertrophy (BPH) symptoms: A recent study of men with BPH treated with dutasteride (5 α-reductase inhibitor) suggested that BPH can occur in men considered to be hypogonadal as high levels of 5-reductase and dihydrotestosterone in the prostate allow the development and progression of prostatic hyperplasia, even at low circulating testosterone levels.27

Monitoring

- Periodic symptomatic evaluation: Three months after beginning treatment and then annually.
- Serum testosterone levels: These can be taken 3–12 hrs after applications of patch, at least a week after being on testosterone gel, and midway between injectable preparations. The goal is to maintain testosterone in the mid-normal range.
- Hemotocrit (HCT) should be checked at baseline, three months, and then annually. A patient with an HCT >55% should be evaluated for hypoxia, sleep apnea, or reduction of testosterone dosage.
- Bone mineral density measurement by dual X-ray absorptiometry should be considered one-to-two years after initiating treatment in patients with low bone mineral density.
- Digital rectal exams (DREs) and PSA level at baseline, three months, and then annually; an abnormal DRE, PSA level >4 ng/ml, or increase of >1.4 ng/ml warrants urological evaluation.
- Evaluated side effects related to different preparations, as detailed in the side effects section.
- Lipid profile: There are no specific recommendations for monitoring the lipid profile, but it may be considered annually, as there are some reports of significant reduction of high-density lipoprotein associated with physiological replacement of testosterone.28

Contraindications

- Prostate cancer.
- Breast cancer.
- Undiagnosed prostate nodule.
- Unexplained prostate-specific antigen (PSA) elevation.
- Erythrocytosis.
- Unstable severe congestive heart failure (class III or IV).


growth of breast cancer.
- New onset or worsening of obstructive sleep apnea.
- Hepatotoxicity (oral preparations).
- Fluctuation of hypogonadal symptoms (IM preparations).
- Dermatitis (transdermal preparations).
- Potential partner testosterone transfer (gels).
- Gum irritation (buccal preparation).

24. AACE Hypogonadism Guidelines, Endocr Pract, 2002;8(No. 4).

US ENDOCRINE DISEASE 2007

91