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Androgen Replacement Therapy for Male Hypogonadism

Program No. 424-999-98-001-H01

This program furnishes 2.0 hours of credit (0.20 CEU).

Lesson Expires: March 31, 2001

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LEARNING OBJECTIVES

Upon completion of this lesson, the pharmacist should be able to:

1. Compare and contrast the clinical features of prepubertal and adult onset hypogonadism.
2. Contrast the pathophysiology between primary and secondary hypogonadism.
3. Describe the tissues that respond primarily to DHT and testosterone.
4. List the common disorders associated with hypogonadism.
5. State the goals of androgen replacement therapy.
6. Compare and contrast the pharmacokinetics of testosterone dosage forms.
7. Compare and contrast the differences in dosing androgen therapy in adolescents and previously virilized hypogonadal adults.
8. State the potential benefits and risks of androgen replacement therapy.

INTRODUCTION

Male hypogonadism with a deficiency of testosterone is a relatively common disorder in clinical practice and has significant effects on the fertility, sexual function, and general health of patients.¹⁻⁸ Some causes of this disorder are relatively common while others are rare. Klinefelter's syndrome, for example, occurs in about 1 in 500 men; it is a primary testicular disorder that results in both androgen deficiency and infertility.⁹⁻¹¹ In men with clinical symptoms of primary or secondary hypogonadism, deficiency of testosterone can be treated effectively with currently available preparations. Infertility in men with primary testicular disease of the seminiferous tubules, such as Klinefelter's syndrome, is irreversible.

OVERVIEW OF PHYSIOLOGY OF THE TESTES

Gonadotropin Releasing Hormone (GnRH) produced by the hypothalamus stimulates the release of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH).^{1,8} In the testes, Leydig cells synthesize and secrete testosterone in response to LH, which is counter-regulated by feedback influences of testosterone and its metabolites. FSH binds to receptors in the seminiferous tubule compartment, which comprises about 85% of the mass of the testes, and stimulates sperm production and maturation. Sertoli cells make inhibin which has feedback influence on FSH secretion.¹²⁻¹⁶

Testosterone and its potent 5-alpha metabolite, dihydrotestosterone (DHT), exert androgenic influences during embryogenesis, puberty, and adulthood.⁸ During fetal development, they cause normal differentiation of male internal and external genitalia^{17,18}: during puberty testosterone and DHT are required for the development and maintenance of male secondary sexual characteristics. DHT affects prostate growth and masculinization of the skin,^{8,19} while the remaining androgenic effects on muscle, bone, larynx, testes, phallus, libido, and sexual function are produced by testosterone. The testes of younger men produce an average of 5 mg of testosterone daily. In adults, testosterone and DHT are needed to maintain libido and potency,

muscle mass and strength, fat distribution, bone mass, erythropoiesis, prostate growth, male hair growth, and spermatogenesis.

Pathophysiology

Hypogonadism can be caused by disorders of the testes (primary), pituitary (secondary), or the hypothalamus (tertiary).^{1,8} (See [Table 1](#)) Testosterone deficiency may occur as a result of Leydig cell dysfunction from primary disease of the testes, or insufficient LH secretion from diseases of the pituitary, or insufficient GnRH secretion from the hypothalamus.

Pinpointing the cause of testosterone deficiency with laboratory testing ([Table 2](#)) makes it possible to tailor successful replacement therapy for men with androgen deficiency when successful fertility is improbable or not desired.

General Manifestations

Clinical Presentation—The clinical presentation of male hypogonadism depends on the stage of sexual development.^{1,8} When it occurs during fetal development from defects in androgen synthesis, metabolism, or androgen responsiveness, various manifestations of inadequate male sexual differentiation may be observed.

Prepubertal—In boys with prepubertal hypogonadism, the androgen deficit is seldom recognized before the age of onset of puberty. Failure of normal puberty is well characterized by several clinical features.

Postpubertal—Postpubertal testosterone deficiency may also be manifested by infertility. The clinical symptoms and signs may evolve slowly, may be relatively difficult to detect, and in aging men may be mistaken for symptoms of aging and thus go unrecognized. The growth of male pattern body hair usually slows, but the voice and the size of the phallus, testes, and prostate show little change. Patients with postpubertal hypogonadism may present with some or all of the these clinical

findings.

GOAL OF ANDROGEN THERAPY

When testosterone replacement therapy is indicated, a safe general principle is to mimic the normal concentrations of testosterone (350-1050 ng/dL) and its active metabolites;²⁰⁻²⁴ thus avoiding unphysiologically high testosterone serum concentrations to prevent possible side effects or low concentrations to prevent androgen deficiency. When these goals of therapy are met, physiological responses to androgen replacement therapy can be expected allowing virilization in prepuberal males and restoration or preservation of virilization in postpuberal men. The treatment should not have untoward effects on the prostate, serum lipids, or cardiovascular, liver, and lung function; should allow self-administration, be convenient, cause minimal discomfort, and be affordable. None of the currently available androgen replacement therapies achieves the ideal, but the relative merits of each is important to consider in making the best selection for each patient.

OVERVIEW OF PHARMACOLOGY OF ANDROGENS

[Tables 3](#) and [4](#) summarize the pharmacokinetics and chemical differences of androgen preparations.

Oral Testosterone Preparations

Pure Testosterone—Although unesterified pure testosterone administered orally may be well absorbed by the gut, it is largely inactivated by the liver.²⁵⁻²⁸

Methyltestosterone—17-alpha-methyltestosterone was the first synthetic derivative of testosterone. After oral administration, peak blood levels are achieved between 1.5 and 2 hours and half-life is about 2.5 to 3 hours, suggesting that several doses daily would be required to maintain a therapeutic level of the steroid.²⁹ Hepatic toxicity, including cholestasis, peliosis,

elevation of liver enzymes, and suppression of HDL-cholesterol limit its use.³⁰⁻³³ Further, most clinical laboratories are unable to monitor adequate therapy by measurement of the steroid in the blood.

Sublingual Methyltestosterone—Sublingual administration of testosterone complexed with hydroxypropyl-beta-cyclodextrin results in a rapid rise in serum testosterone, but subnormal concentrations return within about 2 hours of use. The short half-life limits its practical use for long-term replacement therapy.

Fluoxymesterone—This 9-fluoro derivative of 17-alpha-methyltestosterone has a longer half-life in serum than the parent steroid, but hepatotoxicity is a complication that limits its use.^{30,34-36}

Since cost is often an important consideration, [Table 5](#) summarizes the average wholesale cost for some androgen preparations used to treat hypogonadism.

New/Upcoming Therapy

Testosterone Cyclodextrin—A recent study in a small number of hypogonadal men for 7 days suggests that 2.5 mg or 5.0 mg TID appears to be the appropriate dose for androgen replacement. Studies in hypogonadal men (age range 22 to 60 years) demonstrate that the 5 mg dose produces peak testosterone concentrations of about 1,400 ng/dL within 60 minutes after administration, and the nadir is reached at 360 minutes on average.⁴¹ The profiles of estradiol and DHT parallel those for testosterone. When 5 mg of testosterone cyclodextrin was administered three times per day, there was a small reduction in serum HDL without adverse profiles for liver function tests, or changes in hematocrit, blood pressure, or gynecomastia, and sexual activity benefited. Serum testosterone concentrations would be expected to be subnormal during the night and within about 3 hours following administration of a dose. This preparation has not been marketed yet, but may be in the near future.

Intramuscular Testosterone Preparations

Testosterone Esters—Overview—Esterification of testosterone at position 17 with propionic or enanthic acid prolongs the intramuscular retention and duration of activity of testosterone in proportion to the length of the fatty acid. When administered intramuscularly,⁴² the androgen ester is slowly absorbed into the circulation where it is then rapidly metabolized to active unesterified testosterone.⁴³ Intrinsic potency, bioavailability, and rate of clearance from the circulation are determinants of the biological activity of androgens.

Testosterone propionate—SINGLE-DOSE

PHARMACOKINETICS: Testosterone propionate has a short release phase of only 2 to 3 days and should not be used for long-term replacement therapy.⁴⁶ Two days after the injection, concentrations are subnormal. These pharmacokinetics indicate that testosterone propionate would have to be administered every two days to maintain therapeutic concentrations of testosterone, which is impractical for routine, long-term androgen replacement therapy.

Testosterone enanthate and cypionate

comparison—Intramuscular injections of testosterone enanthate (194 mg) and cypionate (cyclopentylpropionate 200 mg) in hypogonadal men demonstrate comparable pharmacokinetics over a 10 day interval. Thus, these two preparations are interchangeable for androgen replacement therapy.^{47,48} However, both preparations result in supraphysiologic concentrations of testosterone for 1 to 4 days after injection. The pharmacokinetics of testosterone cyclohexanecarboxylate and testosterone enanthate are also similar. A satisfactory regimen is to administer 200 mg of one of these esters once every two weeks intramuscularly,^{49,50} but a more physiologic replacement therapy would be 100 mg of one of these testosterone esters IM weekly.

Transdermal Testosterone

Scrotal Testosterone Patch Therapy (Testoderm®)—A 60 cm² and 40 cm² Testoderm® patch applied to the scrotum of hypogonadal men resulted in peak concentrations of testosterone

with either dose between 3 and 5 hours, and the peak concentrations of testosterone were 12 and 17 nmol/L, respectively. Using this system, 61.5% of patients achieved normal concentrations of testosterone, and 80% had normal levels when the combined concentrations of testosterone plus DHT were measured.⁵¹ During prolonged Testoderm therapy, estradiol levels were in the normal range, and DHT concentrations were elevated ([Figure 1](#)).^{23,51-57}

Non-scrotal Testosterone Patch Therapy

(Androderm[®])—PHARMACOKINETICS: After two 2.5 mg Androderm systems were applied to non-scrotal skin at about 10PM, the serum testosterone concentration profile mimicked the normal circadian variation observed in healthy young men ([Figure 2](#)).^{21,58,59} In addition, bioavailable testosterone, DHT, and estradiol serum testosterone concentrations (BT) measured during Androderm treatment paralleled the serum testosterone profile ([Figure 2](#)) and remained within the normal reference range as summarized in [Table 6](#). The results of a study conducted to assess the bioequivalence of two Androderm 2.5 mg/day patches and a newly formulated Androderm 5 mg/day patch concluded that the new Androderm 5 mg/day patch is bioequivalent to two Androderm 2.5 mg/day patches.

CLINICAL STUDIES: In clinical studies of 2.5 mg Androderm, 93% of patients were treated with two systems daily, 6% used three systems daily, and 1% used one system daily.^{21,58,59} In those clinical trials of men between the ages of 15 and 65 years, Androderm produced mean morning serum concentrations of testosterone within the normal reference range in 92% of patients. The mean (SD) serum hormone concentrations and percentage of patients who achieved average concentrations within the normal ranges are shown in [Table 6](#).

Androderm therapy had positive effects on fatigue, mood, and sexual function as determined from questionnaires and nocturnal penile tumescence.^{21,58,59,61}

COMPARISON WITH INTRAMUSCULAR TESTERONE: In a

study of hypogonadal men previously treated with testosterone injections, 66 patients were randomized to receive either Androderm or intramuscular testosterone enanthate (200 mg every 2 weeks) treatment for 6 months.⁵⁸ The serum concentrations of testosterone, bioavailable testosterone, DHT, and estradiol that were within the normal range are summarized in [Table 6](#). Sexual function assessment and lipid profiles were comparable between the study groups.

EFFECT ON PLASMA ON PLASMA LIPIDS: In another study of 29 hypogonadal men withdrawn from androgen therapy, Androderm treatment for one year decreased cholesterol 1.2% and HDL 8% but increased the ratio of cholesterol/HDL by 9%.⁵⁸ However, these results were not statistically significantly different from the baseline hypogonadal state.

An elevated serum concentration of low-density lipoprotein cholesterol and a low concentration of high-density lipoprotein cholesterol are considered risk factors for cardiovascular disease. Although many studies have shown that androgen replacement therapy with Androderm, Testoderm or testosterone enanthate in recommended doses causes small alterations in serum lipids, dose-dependent reductions in serum high-density lipoprotein cholesterol have been reported.⁸²⁻⁸⁴ In contrast, oral methyltestosterone is known to produce substantial reductions in serum high-density lipoprotein cholesterol.⁸⁵

MANAGEMENT OF SKIN IRRITATION: As with any transdermal system, occasional mild redness or itching are common under the patch. In clinical trials, 53% of patients experienced application site reactions at sometime during Androderm treatment; 5% discontinued treatment due to chronic skin irritations and 4% due to allergic contact dermatitis. Pretreatment with triamcinolone acetonide 0.1% **cream** has been shown to reduce the severity and incidence of skin irritation with Androderm.⁶³ This glucocorticoid cream preparation does not significantly affect testosterone absorption from the patches, and the quantity of glucocorticoid applied and absorbed is insufficient to produce significant alteration of the hypothalamic-pituitary-adrenal axis. Ointment formulations

should not be used for pretreatment as they can significantly reduce testosterone absorption.

Summary of Therapy

Intramuscular injection of available testosterone esters (propionate, enanthate, cypionate, cyclohexanecarboxylate) does not achieve normal serum testosterone profiles for the treatment of male hypogonadism ([Table 7](#)). Doses and injection intervals frequently prescribed result in initial supraphysiologic testosterone values and subnormal levels before the next injection. Injections of 100 mg of testosterone enanthate or cypionate IM at weekly intervals, which may be unacceptable to many patients, would better approximate normal physiology than 200-250 mg every two to three weeks. Further, no advantage in combining short-acting testosterone esters (i.e., testosterone propionate) and longer-acting esters (i.e., testosterone enanthate) for testosterone replacement therapy has been reported.^{44,45}

Oral administration of testosterone preparations results in short-term blood levels and undesirably high interindividual and intraindividual variability of concentrations of testosterone. Derivatives of testosterone administered orally cause unwanted toxicity as well as problems in monitoring therapeutic efficacy.

The scrotal or non-scrotal testosterone patch systems produce the most favorable pharmacokinetic profile of testosterone. The scrotal system has the disadvantage of producing supraphysiologic DHT concentrations and requires shaving of the scrotum; inadequate scrotal size and adherence problems are limitations. Androderm mimics normal physiology but has the disadvantage of local skin reactions. These reactions can often be successfully managed with topical OTC hydrocortisone or antihistamine product administration. With both transdermal systems, monitoring of testosterone levels can be used to monitor efficacy.

Currently, satisfactory options for testosterone replacement therapy must be tailored for each patient, and important considerations include ease of use, physiologic replacement, side

effects, and cost. All of these should be discussed with the patient before making the selection. Although the testosterone esters, testosterone enanthate and cypionate, are effective, safe, and the least expensive androgen preparations available (particularly if self-administered), they require an injection into a large muscle ([Table 7](#)). The scrotal and non-scrotal patches can be self-administered but are more expensive than the injectable generic preparations.

Adults—In adults with hypogonadism, androgen replacement therapy may begin by self-administering Androderm 5 mg nightly, Testoderm 4 or 6 mg daily, or either testosterone enanthate or cypionate 200 mg, intramuscularly (IM), every two weeks. (The fluctuations of serum testosterone concentrations can be expected to occur after intramuscular injection of either ester at 200 mg every two weeks or 100 mg weekly.^{50,64})

The therapeutic efficacy of androgen replacement is assessed by monitoring the patient's clinical and serum testosterone responses.^{1,8} In hypogonadal men, the responses are variable and include improvement in libido, potency, sexual activity, feelings of well-being, motivation, energy level; increased aggressiveness, stamina, and hematocrit may also occur during the first few weeks to months of androgen replacement therapy. Body hair, muscle mass and strength, and bone mass increase over months to years. In sexually immature, eunuchoidal men, testosterone replacement therapy stimulates development of secondary sexual characteristics, but requires many months to years of therapy to achieve adult status and, if epiphyses are unfused, long bone growth will occur.

Prepubertal—Androgen replacement therapy in prepubertal hypogonadal boys is usually started at about 14 years of age.^{1,8} In boys with simple delayed puberty or hypogonadism, gradual replacement therapy with testosterone is indicated and is usually begun using 50 or 100 mg of testosterone enanthate or cypionate IM monthly^{1,8} or one 2.5 mg Androderm patch for 12 hours daily at night. The regimen in boys is designed to duplicate the changes in testosterone that occur with puberty in normal boys and thus, gradual virilization and progression of secondary sexual

development. This regimen should stimulate long bone growth and initiate virilization without interfering with the onset of spontaneous puberty. If simple delayed puberty or hypogonadism is diagnosed, dosage of testosterone ester is increased to 50 to 100 mg every 2 weeks or one 2.5 mg Androderm patch daily for about 6 months, and then stopped for 3 to 6 months for assessment of the spontaneous onset and progression of puberty in those suspected of delayed puberty. If spontaneous pubertal development and growth do not occur, androgen therapy is reinstated for another 6 months. This will produce further virilization in hypogonadal boys, but full virilization can be achieved over the next few years with full adult replacement doses if needed.

POTENTIAL BENEFITS OF ANDROGEN THERAPY

Testosterone Effects on Body Composition

Studies in older men treated with testosterone replacement have generally confirmed that body fat mass declines, lean body mass increases, muscle strength and bone mineral density improves. The studies had limited numbers of patients and were of inadequate length to make it possible to compare one treatment modality to another.

Testosterone Effects on Bone

In normal men, androgens affect both the peak bone mass achieved during development and the subsequent amount of bone loss. The dramatic increase in both cortical and trabecular bone density during puberty in boys^{70,71} is attributed to the pubertal rise in testosterone or one of its metabolites. During puberty, an increase in serum alkaline phosphatase heralds a rise in osteoblast activity and subsequent bone density increases. In normal boys, peak trabecular bone density is usually achieved by the age of 18 years⁷¹ and peak cortical bone density is often reached a few years later. Bone density remains relatively stable in young adult males and then declines slowly after age 35 years⁷²; the bone loss

is regulated by genetic, endocrine, mechanical, and nutritional factors. In about 55% of men with vertebral crush fractures, secondary causes of osteoporosis may be detected; the most common causes are glucocorticosteroid therapy, hypogonadism, skeletal metastases, multiple myeloma, gastric surgery, and anticonvulsant or neuroleptic treatment.⁷³⁻⁷⁶

PRECAUTIONS OF ANDROGEN THERAPY

Several complications of androgen replacement therapy have been reported and include water retention, polycythemia, hepatotoxicity, hypercalcemia, sleep apnea, prostate enlargement, and cardiovascular disease. However, with pure testosterone preparations in physiologic doses, these risks appear small.

Contraindications

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate. They should not be used in patients with known hypersensitivity to a preparation or in patients with cardiac, renal, or hepatic decompensation. Testosterone may cause fetal harm if given to pregnant women.

Warnings

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with the development of peliosis hepatis, cholestatic jaundice, and hepatic neoplasms, including hepatocellular carcinoma. Peliosis hepatis can be a life-threatening or fatal complication. Pure testosterone is not known to produce these adverse effects.

In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men. Edema, with or without congestive heart failure, may be a serious complication of androgen treatment in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required. Gynecomastia frequently develops and occasionally persists in

patients being treated for hypogonadism.

General Precautions

The physician should instruct patients to report any side effects while receiving androgens, such as frequent or persistent erections, nausea, vomiting, jaundice, ankle swelling, or virilization of female sexual partners. (Although transfer of the system to the partner is unlikely, any changes in body hair distribution, a significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.)

MONITORING THE PATIENT

In patients with male hypogonadism, reversal of hypogonadal symptoms is monitored; they may take several weeks to improve fully after adequate androgen replacement therapy is begun. In some men, impotence may not be corrected after several months of therapy despite improvement in other hypogonadal symptoms. For these men, evaluation for causes of erectile dysfunction other than hypogonadism is indicated. After one week or more of transdermal androgen replacement therapy, serum testosterone levels can be measured about 12 hours after patch application. They should be in the normal reference range if satisfactory testosterone replacement occurs. If levels are too high, a reduction in dose is indicated, and if they are too low, an increase in dose is needed. For oral methyltestosterone therapy, no assays are available to monitor therapy. After intramuscular injections of testosterone enanthate or cypionate, testosterone concentrations fluctuate considerably, but a testosterone concentration before the next dose may provide some information about adequacy of therapy.

Prostate Disease

Benign Prostate Enlargement—Progressive growth of the prostate develops in both the transition and peripheral zones of the prostate as men age.^{77,78} In both normal and hypogonadal aging men, androgen withdrawal results in a significant reduction in

prostate volume and PSA.⁷⁹ Testosterone-treated hypogonadal men and normal men showed a positive correlation with prostate volume and age, and no significant age-adjusted differences were observed between the testosterone-treated men and normal controls, suggesting that testosterone therapy does not accelerate prostate enlargement.

Prostate Cancer—Prostate cancer is an androgen-responsive cancer, but there is no evidence to indicate that testosterone therapy causes prostate cancer.^{80,81} An undiagnosed prostate cancer may grow in a hypogonadal man during testosterone therapy. Therefore, a PSA and digital rectal examination is recommended in men age 40 and over before initiation of androgen replacement therapy for hypogonadism. Further, the usual guidelines of screening for prostate cancer should be followed for both androgen-treated and untreated patients consistent with their peer group.

OTHER CONSIDERATIONS OF TREATMENT OF ANDROGEN DEFICIENCY

The main use of androgen replacement therapy is in the management of men with hypogonadism. The cause of the hypogonadism should be established to determine if it might be reversible. If so, therapy should be directed at correction of the underlying cause. For example, hyperprolactinemia from a pituitary tumor can be treated with bromocriptine, which will often correct the testosterone deficiency. Some tumors of the pituitary or hypothalamus may require surgical or irradiation therapy. Thus, in addition to secondary or tertiary hypogonadism, other deficiencies such as ACTH, growth hormone, and TSH may exist and require management. Systemic illness and glucocorticoid therapy will cause hypogonadism and, depending on the clinical situation, androgen replacement therapy may be considered in such patients. In aging men, androgen replacement therapy requires the usual monitoring for diseases incident to age but may offer benefits in bone preservation, lean body mass, mood and sexual function.

For men who desire fertility at some time in their life, hormonal therapy directed at enhancing spermatogenesis may offer them that opportunity. After fertility therapy is deemed a success or a failure, resumption of conventional testosterone therapy is then indicated.

SUMMARY OF ANDROGEN REPLACEMENT OF ANDROGEN THERAPY

Hormone replacement for management of male hypogonadism depends upon both the cause and the stage of sexual development of the patient. In prepubertal boys and men with either primary or secondary hypogonadism, androgen replacement therapy is indicated to stimulate and sustain normal secondary sexual characteristics, sexual function, and behavior. Several options for replacement therapy are available in various countries, and the availability of those preparations should be taken into consideration by the clinician before beginning therapy. The ultimate goal is to safely normalize physiology, with comfort to the patient at the lowest possible cost. Parenteral testosterone esters—testosterone enanthate or cypionate—are effective, safe, and relatively inexpensive androgen preparations, but they produce early supraphysiologic concentrations of testosterone and may be more prone to cause gynecomastia and polycythemias than transdermal testosterone systems. Transdermal testosterone delivery results in more physiologic testosterone and estradiol concentrations with a circadian variation. The transdermal systems are more expensive than testosterone ester preparations, however. Transdermal systems allow monitoring of therapeutic response through assessment of testosterone concentrations about 12 hours after application. The scrotal patch has fewer skin reactions than the non-scrotal patch, but results in supraphysiologic concentrations of DHT. Oral and sublingual preparations produce widely fluctuating testosterone concentrations. The oral derivative of testosterone results in unpredictable concentrations of testosterone and may cause hepatic toxicity and reduce HDL-cholesterol more dramatically than pre-testosterone formulations.

STUDY CASES

Case 1

Facts—A 50-year-old male presented with a 3-year history of diabetes treated with insulin complaining of impotence for two years. He had normal virilization and sexual development at puberty. His sexual function had been normal until two years previously when he began to have problems sustaining an erection for successful intercourse. His past medical history was unremarkable. He denied symptoms of hypothyroidism, adrenal insufficiency, or gynecomastia. The physical examination was within normal limits except for slightly soft testes of normal size and moderate obesity. He had no gynecomastia, thyroid enlargement, retinal abnormalities, or neuropathy. Laboratory studies revealed a morning serum testosterone concentration of 200 ng/dL (normal for age 350-1000 ng/dL). Thyroid function studies, prolactin, and cortisol were normal. An MRI of the head showed no abnormalities of the pituitary or hypothalamus. LH and FSH were within the low normal range.

Discussion—It was concluded that he had secondary or tertiary hypogonadism, possibly associated with diabetes and obesity. Androgen replacement therapy was discussed with him, and he elected to use injectable testosterone because of cost considerations. He was begun on testosterone enanthate 200 mg IM every two weeks. In follow-up 3 months later, his libido had improved and his impotence was much improved.

Case 2

Facts—A 25-year-old man presented complaining of infertility, decreased libido, and modest erectile dysfunction. Puberty was reportedly uneventful and began about age 12 years. He reported normal virilization and sexual function. On physical examination, he had Tanner stage IV gynecomastia, some increase in female fat distribution of the hips, and testes measured <2cm (normal, 4.5 cm x 2.8). Laboratory evaluation revealed azoospermia, morning serum testosterone was 250 ng/dL (normal, 400-1000 ng/dL), LH was moderately elevated, FSH was markedly elevated, and prolactin was normal. A karyotype was done and showed a 47XXY pattern.

Discussion—He was diagnosed with Klinefelter's syndrome. Various therapies were discussed with him, and he elected to use Androderm 5 mg nightly. After three months of therapy, he had some breast tenderness without further breast enlargement. His libido had improved as had sexual function. He had developed some redness and itching at the patch application sites. Pre-treatment of the patch application sites with triamcinolone acetonide, 0.1% was prescribed. Three months later, he had minimal redness and itching of the patch application sites. The breast tenderness had resolved, but he was still concerned about the appearance of his breasts. He was advised to undergo bilateral simple mastectomy to remove the breast tissue.

Questions:

Assessment Questions.

1. Male hypogonadism is associated with many disorders. Which of the following is a common cause of infertility and testosterone deficiency?

- (A) pituitary tumors
- (B) hypothyroidism
- (C) Klinefelter's syndrome
- (D) hypothalamic tumors
- (E) diabetes

2. The synthesis of testosterone occurs in which of the following cells?

- (A) Sertoli cell
- (B) Islet cell

- (C) Parietal cell
- (D) Leydig cell
- (E) Seminiferous tubule cell

3. Hypogonadism may be caused by dysfunction at three levels of control. If gonadotropin-releasing hormone is deficient, which hormonal abnormalities would be most likely?

- (A) Low testosterone, high LH and FSH
- (B) Low testosterone, high LH and low FSH
- (C) Low testosterone, low LH and high FSH
- (D) Normal testosterone, low LH and low FSH
- (E) Low testosterone, low LH and low FSH

4. Sexual maturation at the time of puberty is produced by testosterone and dihydrotestosterone (DHT). Which tissues respond primarily to DHT?

- (A) larynx
- (B) skeletal muscle
- (C) skin
- (D) brain
- (E) testes

5. The goal of an ideal formulation for treatment of testosterone deficiency would include all of the following except:

- (A) Low cost
- (B) Ease of use
- (C) Minimal discomfort
- (D) Supraphysiologic testosterone concentrations
- (E) Low hepatic toxicity

6. Several androgen replacement formulations are available in various countries. Which preparation is more likely to be associated with liver toxicity and lowering serum high-density lipoprotein cholesterol (HDL-cholesterol)?

- (A) testosterone undecanoate
- (B) 17- methyltestosterone
- (C) testosterone cyclodextrin
- (D) testosterone propionate
- (E) transdermal testosterone

7. Several preparations of testosterone esterified with fatty acids can be administered by injection and produce good blood levels of testosterone for several days. Which preparation has the shortest duration of action and should not be used for testosterone replacement therapy?

- (A) testosterone propionate
- (B) testosterone enanthate
- (C) testosterone cypionate
- (D) testosterone cyclohexanecarboxylate

8. Several testosterone esters have similar pharmacokinetics and are interchangeable when administered by injection. Which combinations are about equal?

- (A) Testosterone enanthate, cypionate and propionate
- (B) Testosterone cyclohexanecarboxylate, enanthate and propionate
- (C) Testosterone cyclohexanecarboxylate, cypionate and propionate
- (D) Testosterone cyclohexanecarboxylate, cypionate and enanthate
- (E) Testosterone cyclohexanecarboxylate, cypionate and buclilate

9. Several preparations of short and long acting testosterone esters have been produced with the rationale that they may have more physiologic pharmacokinetics. Which statement is true concerning the short and long acting combinations?

- (A) They have better delivery patterns than testosterone enanthate alone
- (B) They have worse delivery patterns than testosterone enanthate alone
- (C) They are always recommended over single preparations

- (D) They offer no advantages over single preparations
- (E) They are particularly useful for treatment of older men

10. Several preparations have been developed. Which of the following is associated with a testosterone/DHT ratio which is not physiologic?

- (A) Percutaneous DHT gel
- (B) Testoderm, the scrotal patch system
- (C) Androderm, the non-scrotal patch system
- (D) Testosterone undecenoate

11. Many preparations are available for testosterone replacement therapy. Which is associated with a normal circadian variation, normal concentrations of estradiol and DHT?

- (A) Testosterone cypionate
- (B) 17-methyltestosterone
- (C) Testoderm, the scrotal patch system
- (D) Androderm, the non-scrotal patch system
- (E) Testosterone pellets

12. Substantial reductions in serum high density lipoprotein cholesterol has been reported with the following testosterone dosage form:

- (A) Scrotal patch
- (B) Non-scrotal patch
- (C) Oral methyltestosterone
- (D) IM testosterone enanthate

13. The testes of normal men produce several mg of testosterone daily. How many mg of testosterone does the average younger man produce?

- (A) 30 mg
- (B) 15 mg
- (C) 2 mg
- (D) 5 mg
- (E) 60 mg

14. As men age testosterone concentrations begin to decline between 30-40 years of age. What percentage of men age 60 years have subnormal testosterone levels compared to younger normal men?

- (A) 5%
- (B) 50%
- (C) 30%
- (D) 1%
- (E) 20%

15. In clinical trials, the non-scrotal patch has been associated with skin irritation and itching in about 53% of men. The skin irritation can best be managed without affecting pharmacokinetics by which of the following?

- (A) Pretreatment with 0.1% triamcinolone cream
- (B) Pretreatment with 0.1% triamcinolone ointment
- (C) Pretreatment with 0.1% hydrocortisone ointment
- (D) Posttreatment with oral antihistamines
- (E) Pretreatment with antihistamine creams

16. Testosterone is used to manage boys of pubertal age but without pubertal sexual development. What guidelines would you recommend to a physician who was not accustomed to managing such patients?

- (A) Full adult doses of testosterone injections
- (B) 5 mg of the non-scrotal patch system daily
- (C) About 1/4 of the adult replacement dose
- (D) Higher than usual adult replacement doses for several months
- (E) Testosterone and estrogen preparations

17. In hypogonadal men, which of the following would not be an expected result of androgen replacement therapy?

- (A) Increase bone mass
- (B) Increase muscle mass
- (C) Increase in body fat
- (D) Improve sexual interest and function
- (E) Reduce frailty

18. Testosterone therapy would be contraindicated in men with any of the following diseases except:

- (A) prostate cancer
- (B) anemia
- (C) polycythemia
- (D) angina pectoris
- (E) breast cancer

19. In men beyond age 50, prostate disease occurs with increased frequency. Which statement is not correct concerning testosterone and prostate disease?

- (A) Testosterone causes prostate cancer
- (B) Testosterone deficiency is associated with atrophy of the prostate
- (C) Testosterone deficiency throughout life is associated with a small prostate gland
- (D) Testosterone increases at the time of normal puberty and results in normal growth and development of the prostate
- (E) The reduction of serum testosterone occurs in most older men who also develop prostate enlargement and prostate cancer

20. Since testosterone may cause growth of an unrecognized prostate cancer, it is important to screen for prostate cancer before initiation of androgen replacement therapy. Which of the following would best reflect your recommendation before androgen replacement therapy is begun in an older man?

- (A) A prostate symptom score assessment
- (B) A rectal examination
- (C) A PSA
- (D) A study to evaluate the urine flow rate
- (E) Both a PSA and digital rectal examination

Program Evaluation

21. How would you rate this educational program overall?

- (A) Excellent.
- (B) Very Good
- (C) Good.
- (D) Fair.
- (E) Poor.

22. How well did this program achieve its educational objectives?

- (A) Very well.
- (B) Well.
- (C) Somewhat.
- (D) Not at all.

23. How well did this program improve your knowledge of the subject matter?

- (A) Very well.
- (B) Well.
- (C) Somewhat.
- (D) Not at all.

24. Will this be useful and relevant in your practice?

- (A) Very useful/relevant.
- (B) Useful and relevant.
- (C) Somewhat useful/relevant.
- (D) Not at all useful/relevant.

25. Do you think this CE program furnished:

- (A) The proper amount of credit (2.0 hours).
- (B) Not enough credit.
- (C) Too much credit.

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Androgen Replacement Therapy for Male Hypogonadism

Program No. 424-999-98-001-H01

This program furnishes 2.0 hours of credit (0.20 CEU).

Lesson Expires: March 31, 2001



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Table 1

Summary of Etiology of Male Hypogonadism

A. Causes

1. Gonadal Defects

- . Genetic Defect - Klinefelter's syndrome, myotonic dystrophy, Prader-Willi syndrome
- b. Polyglandular autoimmune failure syndromes (e.g., Schmidt syndrome)
- c. Anatomic Defects
- d. Toxins - cytotoxic agents, spironolactone, alcohol
- e. Radiation
- f. Orchitis - usually due to mumps

2. Hormone Resistance

- . Androgen insensitivity
- b. Luteinizing hormone insensitivity

3. Hypopituitarism

- . Idiopathic
- b. Tumor
- c. Other causes

4. Hyperprolactinemia

- . Usually due to pituitary adenoma

- b. Idiopathic increased prolactin production
- 5. Gonadotropin Deficiency
 - . Hypogonadotropic hypogonadism
 - b. Isolated congenital idiopathic GnRH deficiency
 - i. GnRH deficiency with anosmia - Kallman syndrome
 - ii. Acquired GnRH deficiency is very uncommon
 - c. Respond to pulsatile GnRH administration
 - d. Hypothalamic insufficiency
 - e. LH or FSH deficiency
- 6. Systemic Diseases
 - . Chronic diseases
 - b. Malnutrition/Starvation
 - c. Massive obesity
 - d. AIDS/HIV

Table 2**Laboratory Testing of Hypogonadism**

Hypothalamic	Primary Hypogonadism	Seminiferous Tubule Disease	Leydig cell Failure	Pituitary Disease	Hypothalamic Disease
Testosterone	Low	Normal	Low	Low	Low
LH	High	Normal	High	Low	Low
FSH	High	High	Normal	Low	Low
Sperm Count	Low	Low	Low	Low	Low
LH and FSH Response to GnRH	Normal	Not Done	Not Done	Low	Normal

Review: Interpreting the results

1. *Testosterone low, LH and FSH elevated... primary hypogonadism; order karyotype.*
2. *Testosterone low, LH and FSH normal or low...secondary hypogonadism, obtain PRL and CT scan of head to screen for mass lesion; remaining pituitary hormones must be tested for deficiency.*
3. *Testosterone and LH normal, FSH high => abnormal seminiferous tubule compartment; order semen analysis.*
4. *Testosterone, LH and FSH high ==> androgen resistance syndrome.*

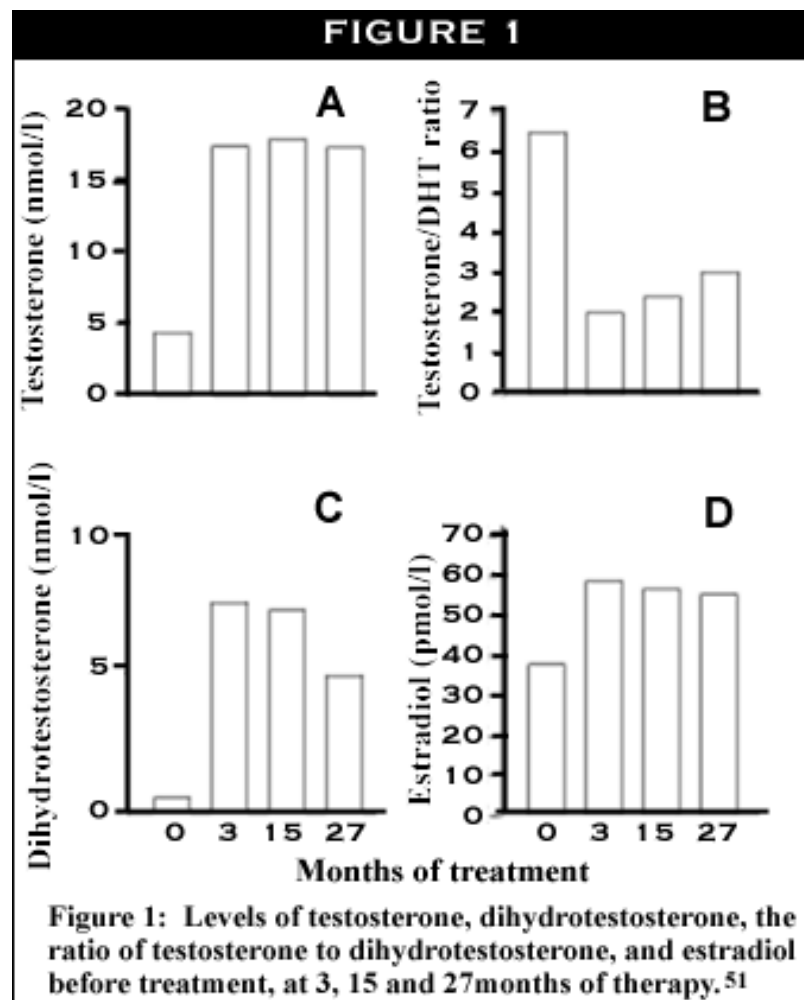
Table 3**Summary of Pharmacokinetics of Androgen Preparations**

Preparation	Peak	Trough	T monitoring	DHT	Estradiol	Liver dysfunction	HDL-Chol.	Skin irritation
T propionate	1 day	2-3 days	None	Dose dep.	Dose dep.	None	Dose dep.	None
T enanthate	1-2 days	10-14days	One week	Dose dep.	Dose dep.	None	Dose dep.	None
T cypionate	1-2 days	10-14days	One week	Dose dep.	Dose dep.	None	Dose dep.	None
T cyclo-dextrin	1 hour	6 hours	2-4 hours	Normal	Normal	None	Modest	None
MethylT	1.5-2 hours	4-5 hours	None	Low	Low	Yes	30% dec.	None
Fluoxymesterone				Low	Low	Yes		None
T Scrotal	3-5 hours	20-24 hours	12 hours	Elevated	Normal	None	Modest	Minimal
T Non-Scrotal	6-8 hours	24 hours	12 hours	Normal	Normal	None	Modest	Yes

Table 4

Generic Name	17- α	17- β (at OH)	Other Modifications
Natural Androgens			
Testosterone	H	H	
5- α -dihydrotestosterone	H	H	"4,5-ane"
Synthetic Androgens			
Testosterone cypionate	H	COCH ₂ CH ₂ -ring	
Testosterone enanthate	H	CO(CH ₂) ₅ CH ₃	
Testosterone propionate	H	COCH ₂ CH ₃ ring	
Testosterone undecenoate	H	CO ₂ (CH ₂) ₈ CH ₂ =CH ₂	
Methyltestosterone	CH ₃	H	

Fluoxymesterone	CH ₃	H	9-F; 11-OH
Anabolic Steroids			
Danazol	C≡H	H	
Nandrolone decanoate	H	CO(CH ₂) ₈ CH ₃	19-nor CH ₃
Nandrolone phenylpropionate	H	CO(CH ₂) ₂ CH-ring	19-NOR CH ₃
Oxandrolone	CH ₃	H	C2 replaced by O; 4,5-ane
Oxymetholone	CH ₃	H	2=CHOH; 4,5-ane
Stanozolol	CH ₃	H	4,5-ane;[3,2-c]pyrazole

**Table 5**

<u>Androgen</u>	<u>Product Name*</u>	<u>Typical Doses</u>	<u>Average Wholesale Price (AWP)**</u>
Testosterone Enanthate 10 cc; 100, 200 mg/cc	generics, Andro-LA, Delatestryl, Durathate-200, Andropository-200, Everone-200, Testo-LA	50-400 mg every 2-4 weeks	\$10-20 per 10 cc
Testosterone Cypionate 10cc; 100, 200 mg/cc	generics, depAndro 100/200, Depotest 100/200, Duratest-100/200 Depo- Testosterone	50-400 mg every 2-4 weeks	\$10-20 (generic) \$30-50 (brand) per 10cc
Testosteronem Propionate 10cc; 100 mg/cc	generics	25-50 mg two to three times weekly	\$10-20 per 10 cc
Testosterone Aqueous 10 cc; 25, 50, 100 mg/cc	generics, Histerone 100, Tesamone	25 - 50 mg two to three times weekly	\$10-20 per 10 cc
Methyltestosterone 10, 25 mg	generics, Android-10, Oreton Methyl, Testred, Virilon	10 - 50 mg daily	\$0.06 - 0.15 (generic) \$0.43 -1.46 (brand) per tablet
Fluoxymeterone 2, 5, 10 mg	generics, Halotestin	5 - 20 mg daily	\$0.90 - 1.20 (generic) \$0.50 - 1.80 (brand) per tablet
Transdermal Testosterone-scrotal 4, 6 mg/24 hr	Testoderm	4 - 6 mg daily	\$2.51 per patch
Transdermal Testosterone-nonscrotal daily 2.5, 5mg/24hr	Androderm	5 mg daily	\$3.40 per patch
*Source: 1998 Drug Facts and Comparison, 52nd Edition			
**Source: 1997 Red Book			

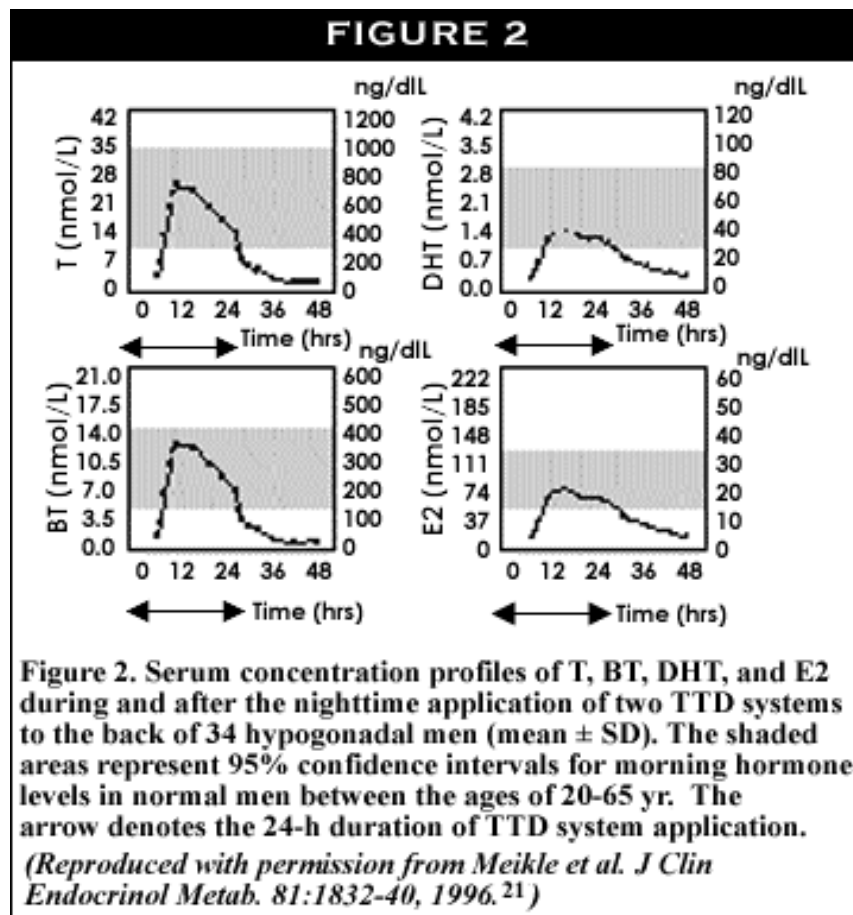


Table 6

Comparison of Percentage of Normal Range Values with Androderm or Testosterone Enanthate Injections		
Androderm IM p value		
T	82% 72%	0.05
BT	87% 39%	<0.001
DHT	76% 70%	0.06
E2	81% 35%	<0.001

Table 7

Treatment of Male Hypogonadism				
Group	Goal of Therapy	Plasma Testosterone	Preparation	Usual Dose
Delayed adolescence	Short term maintenance, initial	100-300 ng/dL	hCG	500 IU IM 1-2 times/wk

			Androderm	2.5 mg patch 12 h at night
			TE or TC	50-100 mg q 3-4 weeks
	subsequent	300-400 ng/dL	Androderm	2.5 mg/day
			TE or TC	100 mg q 2 week
Adult	Long-term maintenance	400-1000 ng/dL		
Hypogonadotropic hypogonadism		GnRH*		5-30 µg SC q 2 h
Hypogonadism			hCG	1000-4000 IU IM 1-3 times/wk
			Androderm	5 mg/day
			Testoderm	4 or 6 mg/day
			TE or TC	200 mg q 2wks or 100 mg q 1 wk IM
	Subreplacement		Fluoxymesterone	5-10 mg/day p.o.
			Methyltestosterone	5-25 mg daily
			Testosterone Undecenoate**	200 mg p.o. qid
<p>* <i>Experimental, requires programmed pump.</i> ** <i>Not available in United States</i> <i>hCG, human chorionic gonadotropin; GnRH, gonadotropin-releasing hormone; TE, testosterone enanthate;</i> <i>TC, testosterone cypionate.</i></p>				