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HORMONAL THERAPY OF MALE HYPOGONADISM

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Male hypogonadism occurs commonly in clinical practice and has significant effects on the well being of patients. For example, Klinefelter's syndrome, a primary testicular disorder, occurs in approximately 1 in 500 men and results in both androgen deficiency and infertility.[28] The clinical manifestations of male hypogonadism usually can be treated effectively. Androgen deficiency in men with Klinefelter's syndrome can be treated with testosterone replacement; however, the infertility is irreversible. In contrast, both androgen deficiency and infertility can be corrected using gonadotropin therapy in men with hypogonadotropic hypogonadism. Appropriate hormonal therapy of men with hypogonadism requires an understanding of the normal physiologic regulation of the testis and the pathophysiology underlying testicular dysfunction.

PHYSIOLOGY

The testis is composed of two functional compartments: the interstitial compartment, which contains Leydig cells that synthesize and secrete testosterone, the principal steroid product of the testis; and the seminiferous tubule compartment, which contains Sertoli cells surrounding developing germ cells and that produces mature spermatozoa.[28]

Testosterone has important physiologic roles during embryogenesis and pubertal development and in adults.[28] During fetal development, testosterone is required for normal differentiation of male internal and external genitalia. During puberty, testosterone is necessary for the development and maintenance of

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male secondary sexual characteristics (growth of the prostate, seminal vesicles, penis and scrotum; development of skeletal muscle; redistribution of body fat; stimulation of long bone growth and mass and closure of epiphyses; growth and development of normal male hair pattern; and enlargement of the larynx that results in deepening of the voice); stimulation of sexual behavior and function (libido and potency) and other behavioral characteristics (e.g., normal aggressiveness); and initiation of sperm production. In adults, testosterone is required for the maintenance of libido and potency, muscle mass and strength, fat distribution, bone mass, erythropoiesis, male hair pattern, certain behaviors (e.g., motivation), and spermatogenesis (and thus, fertility).

The testis is controlled primarily by the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that are secreted by the anterior pituitary gland.[28] LH binds to receptors on Leydig cells and stimulates testosterone production, and therefore has an important role in regulating both male sexual development and sperm production. FSH binds to receptors on Sertoli cells and plays an important role in the initiation and quantitative maintenance of spermatogenesis. Gonadotropin secretion by the pituitary is dependent upon stimulation by the decapeptide, gonadotropin-releasing hormone (GnRH), that is produced by the hypothalamus and stimulates secretion of both LH and FSH.[28] Pulsatile GnRH secretion and stimulation of the pituitary is necessary for normal gonadotropin secretion. It is the central nervous system activation and maintenance of pulsatile hypothalamic GnRH secretion that stimulates gonadotropin and, in turn, testosterone and sperm production at the time of puberty, and that maintains normal testis function in adults.

PATHOPHYSIOLOGY

Hypogonadism may result from either primary disorders of testis function (primary hypogonadism) or disorders of the pituitary or hypothalamus that result in inadequate gonadotropin stimulation of the testis (secondary hypogonadism).[28] The distinction between primary and secondary hypogonadism has important therapeutic implications. Men with primary gonadal failure usually present with impaired spermatogenesis that is either isolated or combined with reduced androgen production. In either case, reduced sperm production and infertility is usually not responsive to therapy, and hormonal treatment is usually directed at testosterone replacement for the androgen deficiency. In contrast, men with secondary hypogonadism usually have impairments of both sperm and testosterone production that are responsive to gonadotropin or, in the case of hypothalamic disorders, GnRH therapy, and fertility may be restored with these treatments.

THERAPEUTIC GOALS

The clinical presentation of male hypogonadism and the goals of hormonal therapy depend on the stage of development during which gonadal failure occurs. Deficiency of androgen production or defects in androgen action that occur during early fetal development result in varying degrees of ambiguous genitalia. Hormonal therapy cannot correct the ambiguous genital development, but testosterone may be used to enlarge the penis as an adjunct to surgical repair for selected cases of microphallus or hypospadias.[10, 16] High-dose testosterone therapy can also be used to improve virilization and sexual function in

patients with partial androgen resistance syndromes (e.g., 5α-reductase deficiency or certain androgen receptor defects).[33]

Prepubertal hypogonadism results in delayed onset of normal pubertal development manifested by a failure to develop normal male secondary sexual characteristics and behavior, undergo accelerated growth (pubertal growth spurt), and initiate spermatogenesis.[28] The goal in hormonal treatment of boys with hypogonadism causing delayed puberty is to induce secondary sexual characteristics, stimulate libido and potency, and induce growth in a time course that is comparable to the individual's peers.[27] It is important that hormonal therapy induce a pubertal growth spurt without prematurely closing long bone epiphyses and compromising adult height. Initiation of spermatogenesis usually is not an issue in boys with delayed puberty; it may be the major therapeutic goal, however, in young men that present with lack of pubertal development and infertility as adults.

Adult hypogonadism is manifested primarily by infertility, abnormalities in sexual function (i.e., reduced libido and potency), alterations in behavior (e.g., loss of motivation, irritability), and, to a lesser degree, by loss of certain secondary sexual characteristics (e.g., reduced axillary and pubic hair, muscle mass, hematocrit).[28] The goal of hormonal therapy in adult hypogonadal men is to restore sexual function, normal behavior, and virilization and in some men, to stimulate spermatogenesis and restore fertility.[27]

Androgen therapy is the primary treatment modality used both to induce and to maintain normal secondary sexual characteristics, sexual function, and behavior in prepubertal boys and men with either primary or secondary hypogonadism.[2, 27, 44] In boys or men with secondary hypogonadism, gonadotropin therapy (using human chorionic gonadotropin [hCG] to provide LH-like activity) or GnRH therapy can be used to induce virilization, accelerate growth, and stimulate libido and potency. Because these modalities are more expensive and complicated (requiring more frequent injections or infusion pumps) than androgen therapy, however, they are usually reserved for men with secondary hypogonadism in whom the goal of therapy is to initiate and maintain spermatogenesis sufficient to induce fertility. Rarely, gonadotropin or GnRH therapy is used in these men to increase testicular size or because it is preferred over androgen therapy.

The initiation and maintenance of spermatogenesis in humans requires relatively high concentrations of testosterone within the testes, concentrations that cannot be achieved practically by exogenous androgen administration.[25] Therefore, testosterone treatment is ineffective in stimulating spermatogenesis in hypogonadal men. In fact, it may further reduce sperm production by suppressing gonadotropin secretion through negative feedback actions on the hypothalamus and pituitary. Gonadotropin treatment (using hCG and human menopausal gonadotropin [hMG] or human FSH [hFSH] to provide LH- and FSH-like activity, respectively) or GnRH therapy are the major hormonal treatment modalities used to stimulate spermatogenesis and induce fertility in men with secondary hypogonadism.[25] These modalities are not effective in men with primary hypogonadism. Previous androgen therapy does not adversely affect subsequent testicular responsiveness to gonadotropin treatment.[7, 22]

Full hormone replacement therapy may not be appropriate in certain clinical situations. In prepubertal boys, hormonal therapy is usually started at a low dose and gradually increased to a full adult replacement dose over a period of years to stimulate growth and induce virilization without compromising adult height. Furthermore, because it is usually not possible to distinguish between constitutional delayed puberty in which normal puberty eventually occurs and

permanent gonadotropin deficiency, hormonal therapy is used intermittently to ascertain whether pubertal development will begin spontaneously. Finally, full androgen replacement may not be appropriate for some hypogonadal men, e.g., men with severe psychological disorders and mental retardation or elderly men with severe bladder neck obstruction from benign prostatic hyperplasia who are not good surgical candidates. In these instances, lower dose androgen supplementation may be used to provide anabolic effects and preserve muscle and bone mass, while minimizing stimulation of libido and potency and prostatic growth.

CONTRAINDICATIONS

Hormonal therapy with androgens, gonadotropins, or GnRH is absolutely contraindicated in men with prostate carcinoma or male breast cancer. Treatment in men with these androgen-responsive malignancies may cause rapid tumor growth that may result in increased bone pain or spinal cord compression. Therefore, a careful examination of the prostate and breast should be performed prior to institution of hormonal therapy in hypogonadal men. Measurement of serum prostate-specific antigen (PSA) may also be useful in older men at high risk for prostate cancer.

ANDROGEN THERAPY

Ideally, androgen replacement therapy should provide normal physiologic serum testosterone (~300–900 ng/dL or 10–30 nmol/L), as well as dihydrotestosterone (DHT) and estradiol (E_2) concentrations, and correct the clinical manifestations of androgen deficiency in prepubertal boys or men with hypogonadism.[28] It should be safe and specifically not have adverse effects on the prostate, serum lipids, liver, and respiratory regulation. The route of administration should permit convenient self-administration, have relatively long dosing intervals to foster compliance, and be free of local pain or irritation. Finally, an ideal androgen replacement preparation should have predictable and reliable pharmacokinetics and pharmacodynamics, and be relatively inexpensive. Unfortunately, androgen preparations that are currently available do not fulfill all of these criteria and at present, ideal androgen replacement therapy is not achievable.

Testosterone 17β-Hydroxyl Esters

Unmodified testosterone administered orally or parenterally is rapidly absorbed and metabolized by the liver, resulting in a very short circulating half-life (~10 minutes), making it impractical as a therapeutic preparation to achieve sustained physiologic serum concentrations and effects. To develop preparations of testosterone that would be clinically effective and practical for androgen replacement therapy of hypogonadal men, chemical modifications of the testosterone molecule or alternative methods of delivery have been developed to slow the rate of absorption and metabolism.

Esterification of the 17β-hydroxyl group decreases the polarity of the testosterone molecule.[28] The increased fat solubility of testosterone esters slows the rate of its release from oily injection vehicles into the circulation, prolonging the

duration of action of these depot preparations. Once absorbed, testosterone esters are hydrolyzed to free testosterone, which is biologically active and metabolized via the same pathways as the endogenous hormone. Because of poor cross-reactivity of the esters in clinical testosterone assays, testosterone levels may be used to monitor therapy.

Currently, the testosterone esters, testosterone enanthate and cypionate, are the most effective, safe, practical, and least expensive androgen preparations available and are the treatment of choice for androgen replacement therapy of hypogonadal men (Table 1). These preparations are considered clinically equivalent in terms of duration of action and therapeutic efficacy.[31]

In adult hypogonadism, androgen replacement therapy is instituted by administering either testosterone enanthate or cypionate 200 mg, intramuscularly (IM), every two weeks.[28, 40] Intramuscular injection of 200 mg of either ester results in testosterone levels at or above the normal range one to two days after

Table 1. TREATMENT OF MALE HYPOGONADISM

Condition	Treatment Goal	Modality	Dosage
Adult hypogonadism	Virilization and normal sexual function	Testosterone enanthate or cypionate	200 mg IM every 10–14 days (androgen replacement) 50–100 mg IM every 14 days (low dose androgen supplementation)
		Transdermal testosterone (Testoderm CIII)	4 mg or 6 mg testosterone patch on scrotum daily
	Initiation and maintenance of spermatogenesis	hCG	1000–2000 IU IM or SC 2–3 times weekly for 12 months
		Followed by combined administration of hCG plus:	
		hMG or hFSH	75–150 IU IM or SC 3 times weekly for 6–18 months
		GnRH	2–40 μg SC every 2 hours by automatic infusion pump
Prepubertal hypogonadism (delayed puberty)	Stimulation of growth and puberty	Testosterone enanthate or cypionate	50–100 mg IM monthly initially, increasing to 50–100 mg IM every 2 weeks and then to adult replacement
		hCG	1000–2000 IU IM or SC weekly initially, increasing to adult replacement
		GnRH	2–40 μ μg SC every 2 hours by automatic infusion pump

IM = intramuscularly; hCG = human chorionic gonadotropin; SC = subcutaneously; GnRH = gonadotropin-releasing hormone; hMG = human menopausal gonadotropin; hFSH = human follicle-stimulating hormone

administration that gradually fall over the subsequent two weeks to levels at or, at times, below the eugonadal range before the next injection (Figure 1).[40] Administration of 100 mg IM weekly or 300 mg IM every three weeks may also be used for androgen replacement of hypogonadal men, but at the expense of more frequent injections or larger fluctuations in serum testosterone levels, respectively.[40] Usually, patients or a family member or friend can be taught to give deep intramuscular injections of testosterone esters. In some hypogonadal men this is not possible and injections must then be given in a clinic setting.

The therapeutic efficacy of androgen replacement is assessed primarily by monitoring the patient's clinical response. Although there is considerable variability in response, most hypogonadal men experience a stimulation of libido

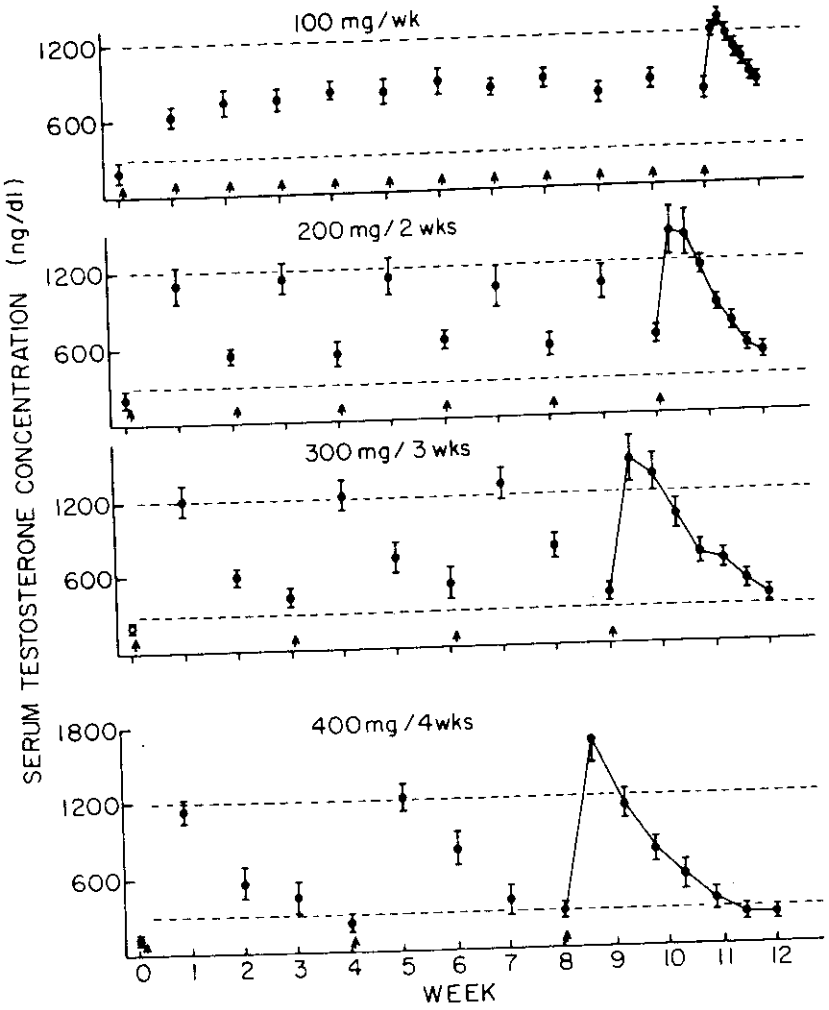

Figure 1. Serum testosterone levels in hypogonadal men receiving androgen replacement therapy using intramuscular testosterone enanthate injections for 12 weeks in four dosage regimens: 100 mg weekly; 200 mg every 2 weeks; 300 mg every 3 weeks; and 400 mg every 4 weeks. Blood was sampled weekly until the last dose and then more frequently. Serum testosterone concentrations exhibit large fluctuations but are maintained above the lower limit of the normal range *(dashed lines)* with each dosage regimen, except the 400-mg-every-4-week dosage in which testosterone levels fall below the normal range after 3 weeks. (*From* Snyder PJ, Lawrence DA: Treatment of male hypogonadism with testosterone enanthate. J Clin Endocrinol Metab 51:1335, 1980; with permission.)

and potency, resumption of sexual activity, and improved feeling of well-being, motivation, energy level, aggressiveness, and stamina during the first few weeks to months of androgen replacement therapy. Hematocrit, body hair, muscle mass and strength, and bone mass increase during subsequent months to years. In sexually immature, eunuchoidal men, androgen replacement also stimulates development of secondary sexual characteristics and, if epiphyses are still open, long bone growth within this time frame.

Ideally testosterone levels during therapy should be in the mid-normal range one week after an injection and above the lower limit of the normal range immediately prior to the next injection.[27] In some hypogonadal men treated with testosterone esters, large variations in serum testosterone concentrations between injections produce disturbing fluctuations in sexual function, energy level, and mood. Patients may complain of diminished energy level and sexual function a few days before their next testosterone injection and have serum testosterone levels below the eugonadal range at that time. In these patients the dosing interval of testosterone ester administration should be shortened from every two weeks to every 10 days. Particularly in men who have previously been severely hypogonadal for a prolonged period of time, the sexual and behavioral changes induced by testosterone replacement may be distressing to both patients and their sexual partners who have grown accustomed to his behavior. Counseling of patients and their partners prior to institution of androgen replacement may help to reduce or alleviate these adjustment problems.

In situations in which full androgen replacement is not required, e.g., elderly hypogonadal men with severe symptomatic chronic bladder neck obstruction from benign prostatic hyperplasia, low dosage androgen supplementation may be instituted gradually using testosterone enanthate or cypionate at a reduced dosage, i.e., 50 to 100 mg IM every two weeks.[27] Alternatively, a short-acting testosterone ester may be used for androgen replacement, e.g., testosterone propionate 25 to 50 mg IM three times weekly with careful monitoring of urinary symptoms and prostate examinations. Although frequent injections are required, the shorter duration of action of this preparation would permit more rapid androgen withdrawal if urinary obstruction or a prostate nodule suspicious for cancer developed during therapy.

Androgen treatment in prepubertal hypogonadism is usually withheld until patients are 14 years of age. If delayed sexual maturation and growth cause severe emotional and psychological distress in affected boys and their families, however, androgen therapy should be instituted at an earlier age. In prepubertal boys with hypogonadism who present with delayed puberty, it is usually difficult to distinguish boys with constitutional delayed puberty who eventually undergo growth and development spontaneously and thus require only transient androgen therapy from those with permanent hypogonadism who require continuous treatment to induce puberty and maintain sexual function.[27] Also, in young boys with delayed puberty who have markedly retarded bone age and are not close to predicted adult height, excessive androgen treatment causes rapid virilization and increase in long bone growth, but may lead to premature closure of epiphyses, resulting in compromised adult height.

For these reasons, androgen therapy in boys with delayed puberty is usually begun using a low dose of testosterone enanthate or cypionate, e.g., 50 to 100 mg IM monthly.[20, 44] Monthly testosterone ester injections stimulate long bone growth and induce mild virilization, but do not usually interfere with spontaneous pubertal onset. To induce adequate virilization, however, larger, more frequent doses are usually required. Therefore, dosage of testosterone ester is increased to 50 to 100 mg every two weeks and then to full adult replacement

dosages over the next 1 to 2 years to mimic the normal pubertal increase in testosterone levels and progression of development and growth. These higher dosages are continued for approximately six months and then stopped for three to six months to determine if spontaneous onset and progression of puberty will occur.

An increase in testis size to more than 8 to 10 mL is usually the first clinical indication of spontaneous puberty.[44] Increases in serum LH and testosterone levels (initially at night) also indicate the onset of puberty. Growth, virilization, and psychological adjustment are monitored carefully. If spontaneous pubertal development and growth do not occur, another round of androgen therapy is instituted. None of the dosages of testosterone esters proposed compromise attainment of predicted final adult height, if careful monitoring is performed.

Formulations containing a combination of short- and long-acting testosterone esters are available in other countries (e.g., Testoviron 50 and 100 [Schering, Berlin, Germany] and Sustanon 100 and 250 [Organon, Oss, the Netherlands]).[44] Compared with testosterone enanthate and cypionate, these preparations produce much higher peaks and larger fluctuations in serum testosterone concentrations after intramuscular injection, but do not have longer duration of action. Therefore, they are not recommended for androgen replacement therapy of hypogonadal men.

Testosterone undecanoate is an orally active, 17β-hydroxyl ester of testosterone that has been used in Europe to treat hypogonadal men.[12] Its highly nonpolar side chain and formulation in an oleic acid vehicle permit this preparation to be absorbed from the gastrointestinal tract directly into the lymphatics, bypassing initial hepatic metabolism, and then into the systemic circulation. The extremely variable serum testosterone levels and clinical responses, the high dihydrotestosterone (DHT) levels (due to intestinal 5α-reductase activity), the large doses that need to be administered frequently (four times daily), and the uncommon, but distressing, gastrointestinal side effects with testosterone undecanoate limit its practical use for long-term androgen replacement therapy of hypogonadal men. The use of this preparation for low-dose androgen supplementation in clinical situations that do not require full replacement, however, may be more feasible.

Transdermal Testosterone

A scrotal transdermal testosterone system was approved for androgen replacement therapy of hypogonadal men in the United States.[14, 32] It provides an alternative to testosterone esters in selected patients (see Table 1). The system is composed of a testosterone-containing patch that must be applied to scrotal skin to be effective. In hypogonadal men, application of the patch in the morning increases blood testosterone concentrations into the eugonadal range within two to four hours, followed by a gradual decline in levels throughout the remainder of the day, mimicking the normal circadian rhythm of endogenous testosterone levels in young men (Fig. 2).[14] The patches are available in two sizes, 40 and 60 cm^2, that deliver 4 and 6 mg of testosterone per day, respectively; the small size is used for men with a small scrotum. The patch is worn for 22 to 24 hours per day and a trial of 6 to 8 weeks of therapy is used to judge its therapeutic efficacy. Long-term daily use of this transdermal system maintains physiologic testosterone concentrations and clinical responses in hypogonadal men and is tolerated well, except for minor skin irritation. Transdermal testosterone has not been evaluated in hypogonadal patients under 18 years of age.

In addition to its favorable pharmacokinetics and pharmacodynamics, compared with testosterone esters, this transdermal system is much easier to self-

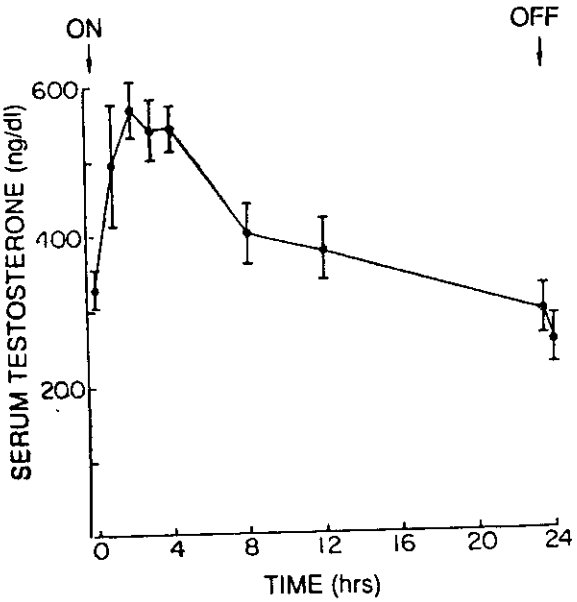

Figure 2. Serum testosterone levels in hypogonadal men receiving transdermal androgen replacement therapy using chronic daily application of a testosterone-containing patch on the scrotum. The previous day's patch was removed *(OFF)* at 8:00 AM and a new patch was applied 0.5 h later *(ON)*. Blood was sampled at 0, 1, 2, 3, 4, 8, 12, and 23.5 h after application of the new patch and 0.5 h following its removal. Serum testosterone concentrations are maintained in the normal adult range (350–1030 ng/dL) throughout the day. Peak testosterone levels occur 2 h after application of the patch in the morning and are followed by a gradual decrease in levels over the day, mimicking the circadian variation of serum testosterone observed in normal young men.[5] (*From* Findlay JC, Place V, Snyder PJ: Treatment of primary hypogonadism in men by the transdermal administration of testosterone. J Clin Endocrinol Metab 68:369, 1989; with permission.)

administer and avoids uncomfortable and occasionally painful, deep IM injections. Daily replacement of the testosterone-containing patch is required on a clean, dry and preferably shaven scrotum of adequate size.[14, 32] Thus, this system may not provide effective androgen replacement in poorly compliant patients or those with a small scrotal surface area. Furthermore, serum DHT levels are elevated relative to testosterone concentrations and above the normal range, probably as a result of application on genital skin which contains high 5α-reductase activity. Although the long-term consequences, if any, of chronically elevated DHT levels is not known, careful monitoring for development of adverse effects, e.g., on growth of the prostate gland, is necessary. Transdermal testosterone therapy is currently more expensive than androgen replacement with testosterone ester injections. The cost and convenience of this system may be justified, however, in the typical patient who requires clinic visits every two to three weeks for administration of testosterone enanthate or cypionate injections.

Testosterone Implants

Subcutaneous implantation of testosterone pellets has been used in other countries for androgen treatment of hypogonadal men.[12, 17] Implantation of three to six 200-mg testosterone pellets into hypogonadal men results in sustained,

nearly zero-order release of testosterone that maintains levels within the normal range for four to six months. Despite its favorable pharmacokinetics, this preparation is not widely used and is unlikely to be acceptable for androgen replacement therapy for many hypogonadal men because of the need to undergo a minor surgical procedure to implant the pellets, the large number of pellets implanted, the possibility of pellet extrusion, and the risk of local hematoma formation, inflammation, infection, and fibrosis.

Oral 17α-Alkylated Androgens

Alkylation of the testosterone molecule at the 17α-position, often combined with modification of the ring structure, retards hepatic metabolism, allowing effective drug levels to be reached following oral or buccal administration. Oral 17α-alkylated androgens are weak androgens, however, and it is difficult to achieve full therapeutic androgen replacement using these preparations.[27] Furthermore, compared with parenteral testosterone esters, they may cause serious hepatotoxicity (cholestasis, peliosis hepatis, benign and malignant tumors of the liver) and are more expensive. Unlike testosterone esters, the 17α-alkyl group is not removed from these preparations prior to target organ action and excretion, and thus serum testosterone levels can not be used to monitor therapy. Because oral androgens carry a greater risk and cost and have less therapeutic benefit compared with testosterone esters, they should not be used for androgen replacement therapy in hypogonadal men.

New Testosterone Preparations

To avoid the fluctuations in serum testosterone concentrations and symptoms of hypogonadism associated with testosterone enanthate and cypionate, new androgen preparations with zero-order release kinetics, more stable blood levels, and longer durations of action are being developed and tested.

Testosterone microspheres composed of unmodified testosterone encapsulated in a biodegradable lactide:glycolide copolymer show promise as a new method for androgen replacement in hypogonadal men. Intramuscular injection of this preparation results in near zero-order release of testosterone at rate of about 6 mg/day and maintenance of serum testosterone levels in the mid-normal range and normal DHT and E_2 concentrations for 10 to 11 weeks.[3] However, the discomfort associated with the two large-volume (2.5 mL) deep IM injections and batch variations in bioavailability are presently significant drawbacks of this formulation for long-term androgen treatment.

A longer acting 17β-hydroxyl ester of testosterone, testosterone buciclate or butylcyclohexylcarboxylate, also known as 20-Aet-1, has been recently been developed and tested by the World Health Organization. Intramuscular injection of 600 mg of this preparation in hypogonadal men maintains serum testosterone concentrations in the low-normal to hypogonadal range for about 12 weeks.[1] It is unclear whether the relatively low levels of testosterone achieved with testosterone buciclate administration will provide adequate androgen replacement in hypogonadal men. The large injection volume (2.4 mL) is also a limiting factor with this preparation.

A nonscrotal transdermal testosterone system is currently being evaluated for use in androgen replacement treatment of men with hypogonadism.[30] This system is composed of a mixture of testosterone and proprietary permeation-

enhancers contained within an adhesive patch and can be applied to any skin surface (e.g., abdomen, back, thigh, or chest). In hypogonadal men, daily application of two patches in the evening delivers approximately 4 to 7 mg of testosterone per day and increases blood levels into the normal range. The subsequent decline in testosterone concentrations mimics the diurnal variation in serum testosterone levels observed in normal young men.[5] In contrast to the scrotal transdermal testosterone patch, serum DHT concentrations remain within the normal range with this system. In ongoing long-term studies in hypogonadal men, this transdermal testosterone system has maintained physiologic blood testosterone levels and improvement in clinical manifestations of androgen deficiency, and except for local skin irritation, it has been tolerated well.

Sublingual administration of testosterone complexed with hydroxypropyl-β-cyclodextrin to hypogonadal men results in a rapid rise and fall of serum testosterone levels lasting approximately two hours, mimicking a normal testosterone secretory pulse.[39] The short-half life of this formulation and its bitter taste limit the practicality of this preparation for long-term androgen replacement therapy of hypogonadal men.

Side Effects of Androgen Therapy

The use of testosterone esters for androgen replacement treatment of hypogonadal men is generally tolerated very well and serious side effects are rare. Androgen therapy usually causes mild to moderate weight gain both as a result of the anabolic effects and sodium retention associated with testosterone. Because of the latter, patients with underlying edematous states (e.g., congestive heart failure, hepatic cirrhosis, and nephrotic syndrome) may develop worsening edema during testosterone therapy. Prepubertal hypogonadal boys receiving testosterone treatment to induce puberty often develop acne that is usually responsive to local skin measures and antibiotics and that nearly always resolves spontaneously. Urinary obstruction and retention resulting from stimulation of prostate growth in men with benign prostatic hyperplasia is extremely uncommon, except in the presence of coexisting prostate carcinoma.[21] Excessive stimulation of libido and potency is also very uncommon, usually occurring in young boys and in men with longstanding, severe androgen deficiency.

Stimulation of erythropoiesis by testosterone occasionally causes clinically significant erythrocytosis that may require lowering of the testosterone dosage or phlebotomy. This may occur in men with or without predisposing disorders, such as hypoxia due to chronic lung disease or sleep apnea. Replacement dosages of testosterone may induce or worsen obstructive sleep apnea.[24, 36] If clinical manifestations of obstructive sleep apnea develop during testosterone treatment, a sleep study should be performed and testosterone should be discontinued or reduced in dosage if obstructive sleep apnea is documented. Serum HDL cholesterol decreases by 10% to 15% during testosterone therapy, but the clinical significance of this decrease not known.[2] 17α-alkylated androgens cause a much greater suppression of serum HDL cholesterol than testosterone esters.[42]

As a result of aromatization of testosterone to E_2 in peripheral tissues, therapy with either testosterone esters or the scrotal transdermal system results in increased E_2 as well as testosterone concentrations in blood. However, the ratio of E_2 to testosterone levels usually remains normal. Gynecomastia (breast enlargement with or without tenderness) occasionally develops during testosterone therapy, especially in prepubertal boys receiving treatment to induce puberty and men with predisposing conditions, such as hepatic cirrhosis. Because

gynecomastia is thought to occur as a result of high E_2 relative to testosterone action, it is presumed that men that develop breast enlargement during testosterone therapy have abnormally high E_2 to testosterone ratios, although this has not been conclusively demonstrated.

All oral 17α-alkylated androgens have the potential to cause hepatotoxicity, including cholestatic liver function abnormalities and occasionally resulting in clinical jaundice, peliosis hepatis (blood-filled cyst in the liver), hepatic adenoma, hepatocellular carcinoma, and hepatic angiosarcoma.[19] In contrast, hepatotoxicity does not occur with replacement dosages of parenteral 17β-hydroxyl esters of testosterone. Occasionally, injection of testosterone esters may cause local pain and hemorrhage and scrotal transdermal testosterone may cause local itching and irritation. Rarely, patients may have an allergic reaction to the injection vehicles for testosterone enanthate (sesame oil) and cypionate (cottonseed oil).

GONADOTROPIN THERAPY

Because gonadotropin therapy is effective only in patients with secondary hypogonadism, it is important that the diagnosis of hypogonadotropic hypogonadism be firmly established prior to the institution of treatment. Occasionally, human chorionic gonadotropin is used instead of testosterone to induce puberty in boys and treat androgen deficiency in men with secondary hypogonadism. The major use of gonadotropin therapy, however, is to initiate and maintain spermatogenesis in hypogonadotropic men who desire fertility.

Treatment of Androgen Deficiency

Human chorionic gonadotropin (hCG), like LH, binds to receptors on Leydig cells and stimulates endogenous testosterone production from the testis. Thus, hCG can be used as an alternative to testosterone therapy to induce pubertal development in boys and treat androgen deficiency in men with gonadotropin deficiency. In young prepubertal boys (e.g., 13–14 years of age) who present with hypogonadotropic hypogonadism and delayed puberty, hCG is usually begun at a dosage of 1000 to 2000 international units (IU) IM or subcutaneously (SC) weekly[20] and then gradually increased over the next one to two years to adult dosages, 1000 to 2000 IU, IM or SC, two to three times weekly[11, 41] (see Table 1). Occasionally, men with hypogonadotropic hypogonadism may require either higher or lower dosages of hCG. Subcutaneous administration is usually as effective as intramuscular injections and more acceptable for self-administration.[34] Therapy is usually monitored by assessing the clinical response to treatment, i.e., the progression of virilization and growth in prepubertal boys and the correction of clinical manifestations of androgen deficiency in hypogonadotropic men. In addition, serum testosterone levels are measured to determine if they increase into and are maintained within the normal range. In the absence of coexisting primary testicular disease, treatment with hCG is nearly always effective in correcting androgen deficiency in men with secondary hypogonadism.

hCG therapy may offer several advantages over testosterone enanthate or cypionate treatment for some men with secondary hypogonadism.[4, 41] hCG stimulates testicular growth, which may be important to some patients, especially those that have never undergone puberty. Because it produces much steadier testosterone levels, hCG treatment may produce less fluctuation in

libido, mood, and energy level. When given subcutaneously, hCG injections are much easier to self-administer and better tolerated than intramuscular testosterone ester injections. Most importantly, hCG treatment is absolutely required to stimulate sufficient intratesticular testosterone production prior to the initiation of spermatogenesis (see below).

There are also significant disadvantages of hCG treatment. hCG treatment requires more frequent injections and is more expensive than testosterone ester therapy. Disproportionate elevation of E_2 relative to testosterone levels during higher dosage hCG treatment may cause gynecomastia in some patients. Although it has not been clearly demonstrated, gynecomastia may occur more frequently during hCG compared with testosterone therapy. Acne, weight gain, and occasional fluid retention similar to that observed during testosterone treatment may occur during hCG treatment. Rarely, development of neutralizing antibodies to hCG may reduce the efficacy of hCG or make it completely ineffective.[41]

Initiation and Maintenance of Spermatogenesis

The main indication for gonadotropin therapy is the stimulation of spermatogenesis and induction of fertility in men with hypogonadotropic hypogonadism. The initiation of sperm production in patients with prepubertal hypogonadotropic hypogonadism who have not completed pubertal development (whose testis size is usually < 4 mL) usually requires treatment with both LH (in the form of hCG) and FSH activity (using human menopausal gonadotropin [hMG]) to initiate spermatogenesis (Figure 3).[6, 8, 15, 22, 29, 41] Men with partial gonadotropin deficiency of prepubertal onset, however, who usually have larger testis (>4 mL) and higher serum α-immunoreactive inhibin levels at presentation (suggesting some endogenous FSH secretion) may stimulate sperm production with hCG alone. Similarly, in previously treated men with prepubertal hypogonadotropic hypogonadism who had spermatogenesis initiated with combination hCG plus hMG treatment, sperm production may be reinitiated subsequently with hCG alone. In contrast to men with prepubertal hypogonadotropic hypogonadism, men who acquire gonadotropin deficiency as an adult (postpubertal hypogonadotropic hypogonadism) who had previously maintained normal sperm production can usually reinitiate spermatogenesis with hCG treatment alone (Fig. 3).[6, 8, 15, 22, 29, 41]

Previous testosterone therapy may suppress any endogenous GnRH and gonadotropin secretion present in men with hypogonadotropic hypogonadism, but does not affect the likelihood of success of subsequent treatment with gonadotropins to stimulate sperm production.[7, 22] Gonadotropin therapy is much less likely to stimulate sufficient spermatogenesis to induce fertility, however, if cryptorchidism is present or has been corrected (see Fig. 3).[15] It is important to realize that in many men, particularly those with prepubertal hypogonadotropic hypogonadism, quantitatively normal sperm production (i.e., sperm concentrations > 20 million/mL) may not be achieved with gonadotropin therapy, probably as a result of gonadotropin deficiency during development resulting in reduced Sertoli cell number or function or underlying primary testicular dysfunction.[9, 43] Fertility may still be induced, however, often at very low sperm counts (e.g., < 1 million/mL) in these men. Despite low concentrations, sperm motility and morphology are usually normal, suggesting that spermatozoa are qualitatively normal.

Prior to institution of gonadotropin therapy, it is essential that the female

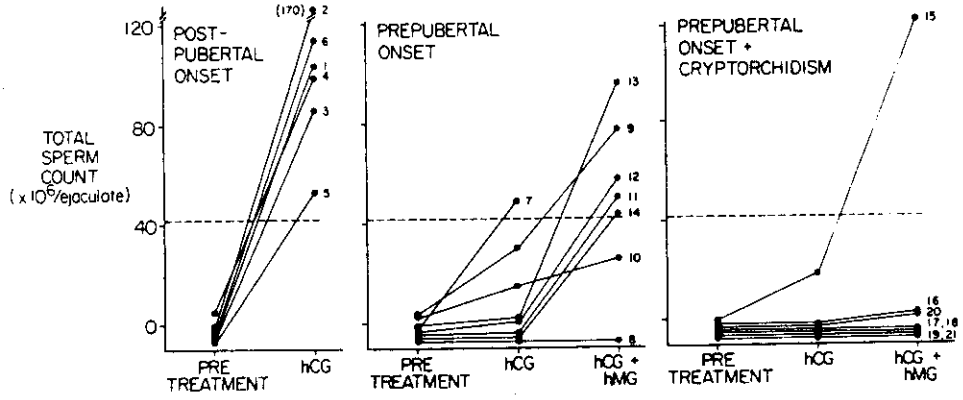

Figure 3. The effect of human chorionic gonadotropin (hCG) alone and in combination with human menopausal gonadotropin (hMG) on total sperm count in men with hypogonadotropic hypogonadism of postpubertal onset (left) and prepubertal onset, who did not (middle) or did have cryptorchidism (right). In response to treatment with hCG alone, sperm counts increased into the normal range *(dashed lines)* in all 6 men with postpubertal hypogonadotropic hypogonadism, but in only 1 of 8 patients with prepubertal hypogonadotropic hypogonadism who did not have coexisting cryptorchidism. In the latter group, sperm counts increased into the normal range with the addition of hMG to hCG (hCG + hMG) in 5 of the 7 men who did not respond to hCG alone. In men with prepubertal hypogonadotropic hypogonadism who also had cryptorchidism, sperm counts increased into the normal range in only 1 of 7 men treated with hCG + hMG. (*From* Finkel DM, Phillips JL, Snyder PJ: Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. N Engl J Med 313:651, 1985; with permission.)

partner be evaluated (e.g., reproductive and menstrual history, basal body temperature, and hysterosalpingogram) and found to have normal fertility potential or be treated concomitantly for infertility.

Gonadotropin therapy is always started using hCG treatment alone at a dosage of 1000 to 2000 IU IM or SC two to three times weekly.[11, 41] Serum testosterone levels should be monitored every month and the hCG dosage should be adjusted if serum testosterone levels are not within the normal range after three months of treatment. In addition to inducing and maintaining virilization, normal sexual function, and function of accessory sexual glands (e.g., seminal vesicles and prostate) that are needed to produce a normal ejaculate by stimulating endogenous testosterone production, hCG is an absolute requirement for the initiation of spermatogenesis.[25] Instituting gonadotropin therapy with hMG or hFSH alone does not stimulate sperm production.[35] Furthermore, hCG alone may initiate or reinitiate spermatogenesis in some men with hypogonadotropic hypogonadism, obviating the need to add the more expensive hMG.

After normal serum testosterone levels are achieved, sperm counts are monitored every month or more frequently if spermatogenesis is initiated. Because 90% of testis volume is composed of seminiferous tubules, increase in testis size (> 8 mL) is also a useful indirect indicator of initiation of spermatogenesis during gonadotropin therapy. Because the maturation of early spermatogonia to spermatozoa takes approximately 75 days in man, gonadotropin therapy to induce spermatogenesis is by necessity prolonged. During gonadotropin therapy, intercourse frequency should be maximized around the time of ovulation in the female partner. Treatment with hCG alone is usually continued for at least 12 months before hMG is added.

If sufficient spermatogenesis is not achieved to induce fertility with hCG alone, hMG is usually added, beginning at dosage of 75 IU IM or SC three times weekly. Sperm counts continue to be monitored monthly. If sperm counts sufficient to induce fertility are not achieved in six months, the dosage of hMG is increased to 150 IU three times weekly for an additional 6 to 12 months. hCG and hMG can be administered in the same syringe in a single injection.

Because hMG contains both LH and FSH, when given in combination with hCG, it may result in higher serum testosterone and E_2 concentrations and associated clinical side effects, such as weight gain, edema, acne, and gynecomastia, as discussed earlier. In the future, the use of purified urinary human FSH (hFSH) that has recently become available for use in women or recombinant hFSH that is currently being tested may offer an advantage over hMG in that regard. Rarely, neutralizing antibodies may develop against hMG which may reduce its efficacy.[41]

Once pregnancy is achieved, the patient may either continue on gonadotropin treatment or switch to testosterone therapy. Gonadotropin therapy is usually continued until delivery, in case spontaneous abortion occurs, or if the couple is considering another pregnancy within one to two years. In either case, hMG is stopped and treatment with hCG alone is continued because it is usually sufficient to maintain spermatogenesis initiated with combined therapy in these men. Monitoring of sperm counts is usually discontinued until another pregnancy is desired.

If the couple does not want any more children, both gonadotropins are discontinued and testosterone replacement therapy is usually instituted to maintain virilization and sexual function. Testosterone treatment is preferred by most patients because it is less expensive, requires less frequent injections, and does not require use of contraception. Occasionally, men prefer to remain on hCG rather than testosterone because it produces less fluctuation in symptoms of androgen deficiency. Spermatogenesis is usually maintained on hCG alone, however, and contraception is required if another pregnancy is not desired.

GnRH THERAPY

Although it is not approved in the United States for use in men, pulsatile GnRH therapy has been used to treat a subset of patients with secondary hypogonadism who have hypothalamic disorders and normal pituitary function. Men with idiopathic hypogonadotropic hypogonadism (IHH), or Kallmann's syndrome when IHH is associated with hyposmia or anosmia, who have a deficiency in GnRH secretion, are the most common group of patients to be treated with GnRH therapy.[11, 18, 38, 43] Although these men also respond to gonadotropin therapy, low-dose pulsatile GnRH replacement that mimics the normal endogenous pattern of secretion is a more physiologic treatment regimen. Normal pituitary gonadotropin secretion requires both pulsatile and low-dose GnRH stimulation. Administration of either continuous, low-dose GnRH or potent GnRH agonists produces inadequate gonadotropin responses in men with IHH.[26]

Pulsatile GnRH is administered by a portable, programmable infusion pump beginning at a dose of 2 to 5 μg per pulse SC every two hours.[11] Intravenous GnRH results in LH responses that more closely resemble endogenous secretory pulses and is more successful in inducing ovulation in women with hypothalamic amenorrhea. Because intravenous GnRH therapy requires more careful monitoring and carries a greater risk than subcutaneous treatment, however, it is usually not used for the long-term GnRH therapy that is required

in men.[41] GnRH therapy is carefully monitored by measurements of serum LH, FSH, and testosterone levels initially every two to four weeks and GnRH dose per pulse is increased until hormone levels within the normal range are achieved. A GnRH dose of 2 to 40 μg per pulse is usually required.[41] After normal hormone levels are achieved, monitoring of hormone concentrations, sperm counts (if fertility is an issue), and clinical responses (including testis size) is usually reduced to every one to two months.

GnRH therapy is usually successful in stimulating normal gonadotropin and testosterone secretion, and in inducing and maintaining pubertal development in boys and men with IHH.[11, 18, 38, 43] Stimulation of spermatogenesis and induction of fertility by GnRH are more variable, however, and may require up to two years of treatment. As with gonadotropin therapy, the overall success and rapidity of inducing spermatogenesis and fertility in IHH men with pulsatile GnRH is greater in patients with larger initial testis size (who presumably have partial gonadotropin deficiency) and less in men with cryptorchidism whether or not it is corrected. Sperm production is usually not initiated until testis size is more than 8 mL. As is the case for gonadotropin therapy, quantitatively normal spermatogenesis is usually not achieved with pulsatile GnRH treatment and the potential for fertility may be excellent despite very low sperm counts. Rarely, neutralizing antibodies to GnRH may develop and reduce the efficacy of GnRH therapy.[43]

Compared with treatment with hCG plus hMG, pulsatile GnRH therapy results in greater increases in testicular size, more rapid initiation of spermatogenesis, and less elevation in serum estradiol levels and gynecomastia, but no greater overall sperm production.[23, 37] The cost of combined gonadotropin treatment is comparable to that of GnRH therapy. Because of the greater complexity associated with long-term pulsatile GnRH treatment, it is usually reserved for intelligent, highly motivated, compliant and reliable men with IHH who can manage the problems and inconvenience of chronic infusion pump therapy or for those who do not respond to gonadotropin therapy.[13]

OTHER TREATMENT CONSIDERATIONS

In addition to hormonal replacement therapy, treatment of men with hypogonadism should be directed at the underlying etiology of gonadal failure if the cause is reversible. For example, treatment of underlying systemic illness causing delayed puberty in boys or hypogonadism in adults may eliminate the need to institute hormonal replacement. Men with secondary hypogonadism who have a destructive lesion of the pituitary and/or hypothalamus may have clinical manifestations resulting from tumor mass effects (e.g., loss of visual fields) that may require neurosurgical intervention; deficiencies in other anterior pituitary hormones that may require other hormone replacement (e.g., the need to replace both growth hormone and androgens in boys who have delayed puberty and growth caused by hypopitutarism); or excessive pituitary hormone secretion (e.g., hyperprolactinemia) that may require alternative or adjunctive medical or surgical therapy (e.g., administration of a dopamine agonist, such as bromocriptine, and/or removal of a pituitary adenoma for prolactinomas).

It is important to emphasize that a large group of men with primary hypogonadism with isolated impairment of spermatogenesis and infertility, most of whom have idiopathic oligospermia or azoospermia, are not responsive to hormonal therapy. Although some men with disordered spermatogenesis and infertility respond to other treatment modalities (e.g., surgical correction of a varicocele), most do not respond to any form of therapy.

The presence of severe gynecomastia or small testes may result in great psychological trauma and embarrassment for some hypogonadal men. Severe, well-developed gynecomastia does not reverse and may worsen during hormonal therapy of hypogonadism, and plastic surgery (reduction mammoplasty) is indicated. As discussed above, in some patients with secondary hypogonadism, gonadotropin therapy may be used to stimulate testis growth. This treatment can not be used in men with primary hypogonadism, however, such as those with Klinefelter's syndrome who have extremely small testes. Surgical implantation of testicular prostheses may be indicated in some of these men.

SUMMARY

The goals of hormonal treatment of male hypogonadism depend upon the stage of sexual development in which gonadal failure occurs. Androgen replacement therapy is used to induce and maintain normal secondary sexual characteristics, sexual function, and behavior in prepubertal boys and men with either primary or secondary hypogonadism. Parenteral testosterone esters, testosterone enanthate or cypionate, are the most effective, safe, practical, and inexpensive androgen preparations available for this purpose. They are the treatment of choice for androgen replacement therapy. A recently approved scrotal transdermal testosterone system provides an alternative to testosterone esters in selected patients.

In boys or men with secondary hypogonadism, gonadotropin or GnRH therapy may be used instead of testosterone therapy to stimulate endogenous testosterone production. Because of their greater expense and complexity, however, these modalities are usually reserved for men with gonadotropin deficiency who desire fertility and in whom spermatogenesis must be initiated and maintained. Gonadotropin therapy is begun with hCG alone. In men with partial or previously treated gonadotropin deficiency, or in men with postpubertal hypogonadotropic hypogonadism, hCG treatment alone may be sufficient to stimulate spermatogenesis and fertility. In most men with prepubertal hypogonadotropic hypogonadism, however, combined treatment with hCG plus hMG is needed to initiate sperm production and fertility. Pulsatile GnRH therapy may be used to stimulate testosterone production and spermatogenesis in men with secondary hypogonadism who have hypothalamic defects, such as idiopathic hypogonadotropic hypogonadism or Kallmann's syndrome.

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