

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE
FOR THE EVALUATION AND TREATMENT OF HYPOGONADISM
IN ADULT MALE PATIENTS—2002 UPDATE**

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ABSTRACT

In these clinical practice guidelines, specific recommendations are made for determining the most effective methods of diagnosing and treating hypogonadism in adult male patients. The target populations for these guidelines include the following: (1) men with primary testicular failure requiring testosterone replacement (hypergonadotropic hypogonadism); (2) male patients with gonadotropin deficiency or dysfunction who may have received testosterone replacement therapy or treatment for infertility (hypogonadotropic hypogonadism); and (3) aging men with symptoms relating to testosterone deficiency who could benefit from testosterone replacement therapy. Initial hormonal evaluation generally consists of a testosterone determination, in conjunction with a free testosterone or sex hormone-binding globulin level, in patients with clear symptoms and signs but normal-range total testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels. Other possible tests include semen analysis, pituitary imaging studies, genetic studies, bone densitometry, testicular ultrasonography, testicular biopsy, and specialized hormonal dynamic testing. Therapeutic options generally consist of testosterone replacement by injections, patches, or topically applied gel in hypergonadotropic patients and in hypogonadotropic patients not interested in fertility. In hypogonadotropic patients interested in fertility, gonadal stimulation options can be considered, including human chorionic gonadotropin stimulation therapy with or without human menopausal gonadotropin (or follicle-stimulating hormone) or gonadotropin-releasing hormone pump therapy. These therapies may be combined with assisted reproductive technologies such as in vitro fertilization with intracytoplasmic sperm injection, which may allow pregnancy to occur with very low numbers of sperm. (*Endocr Pract.* 2002;8:439-456)

Abbreviations:

AIDS = acquired immunodeficiency syndrome; **FDA** = Food and Drug Administration; **FSH** = follicle-stimulating hormone; **GnRH** = gonadotropin-releasing hormone; **hCG** = human chorionic gonadotropin; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **LH** = luteinizing hormone; **MRI** = magnetic resonance imaging; **PSA** = prostate-specific antigen; **SHBG** = sex hormone-binding globulin

FOREWORD

Guidelines are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

MISSION STATEMENT

Hypogonadism is defined as “inadequate gonadal function, as manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones” (1).

Men with hypogonadal disorders have symptoms that are often denied by the patient and ignored by the physician. In addition, diagnostic evaluation and therapeutic options are poorly understood. With a longer life span and with advances in the treatment of cardiovascular disease, some aging men suffer from associated decreases in testosterone levels that may increase the risk of osteoporosis, sexual dysfunction, fatigue, cardiovascular disease, and mood disturbances. Prostate cancer in men remains a common problem that demands further research efforts and also is an issue in the consideration of testosterone replacement therapy.

Of prime consideration is the paucity of long-term research studies on the identification of men at risk for complications related to a decreased testosterone level, optimal assessment of such patients, optimal treatment, and potential complications relating to long-term therapy.

These guidelines on the evaluation and treatment of hypogonadism in adult male patients represent not only a source of guidance for health-care professionals but also an appeal to clinicians to increase their awareness of the problem and to discuss these issues with their at-risk patients. With growing awareness and increased research efforts, both the duration and the quality of life for aging men will improve.

GENERAL MANIFESTATIONS

Hypogonadism may manifest with testosterone deficiency, infertility, or both conditions. Symptoms of hypogonadism depend primarily on the age of the male patient at the time of development of the condition. Hypogonadism is often unrecognized before the age of puberty unless it is associated with growth retardation or other anatomic or endocrine abnormalities.

When hypogonadism develops *before* the age of puberty, the manifestations are those of impaired puberty:

- Small testes, phallus, and prostate
- Scant pubic and axillary hair
- Disproportionately long arms and legs (from delayed epiphyseal closure)
- Reduced male musculature
- Gynecomastia
- Persistently high-pitched voice

Postpubertal loss of testicular function results in slowly evolving subtle clinical symptoms and signs. In aging men, these symptoms and signs may be difficult to appreciate because they are often attributed to "getting older." The growth of body hair usually slows, but the voice and the size of the phallus usually remain unchanged. Prostate size may decrease in hypogonadal men, but the amount of change is related to the severity of testosterone deficiency. Typical temporal hair recession and balding usually do not occur, and if they did, these manifestations would not be expected to prompt a patient to seek medical attention. Patients with hypogonadism may have the following findings:

- Progressive decrease in muscle mass
- Loss of libido
- Impotence
- Oligospermia or azospermia
- Occasionally, menopausal-type hot flushes (with acute onset of hypogonadism)
- Poor ability to concentrate

The risk of osteoporosis and attendant fractures is increased. Many cases of hypogonadism are diagnosed during the course of infertility evaluations.

EVALUATION

A comprehensive history should be elicited and a complete physical examination should be performed to help determine the cause and extent of the hypogonadism.

History

Any history of loss of libido, sexual dysfunction, a low-volume ejaculate, or impotence should be generally noted. A history of use of medications, herbal preparations, or home remedies and any history of possible exposure to diethylstilbestrol in utero should be elicited.

A history of anosmia or hyposmia, midline defects, or cryptorchidism may be suggestive of Kallmann's syndrome or other types of hypogonadotropic hypogonadism. A family history may also indicate an underlying genetic basis.

Primary testicular failure is usually associated with genetic syndromes such as Klinefelter's syndrome or congenital disorders such as anorchism. Testicular failure may also be associated with a history of testicular trauma, certain surgical procedures in the area, cryptorchidism, mumps orchitis, and, occasionally, toxic exposures, radiation treatment, or chemotherapy.

A postpubertal onset of hypogonadotropic hypogonadism, generally manifesting as loss of libido, sexual dysfunction, or impotence, should suggest the possibility of hypothalamic or pituitary disease. Evidence of other endocrine deficiencies such as central hypothyroidism or secondary adrenal insufficiency, visual field disturbances, headaches, or seizures may also be associated with pituitary tumors or other central disorders.

Physical Examination

The amount and distribution of body hair, including beard growth, axillary hair, and pubic hair, should be noted, as should the presence of a male pattern escutcheon. The ethnic origin of the patient should be considered in this assessment. Any decrease in body hair or decrease in beard growth should also be noted.

The presence and degree of gynecomastia should be recorded. The presence of galactorrhea would suggest pronounced hyperprolactinemia, usually associated with some degree of hyperestrogenism.

The testes should be measured (length and width) by using a Prader orchidometer or calipers. Some testicular disorders may selectively affect production of sperm without influencing production of testosterone. These disorders may sometimes be detected by careful physical examination, including determination of testicular size and consistency. Because approximately 85% of testicular mass consists of germinal tissue, a reduced germinal cell mass would be associated with a reduced testicular size and a soft consistency. Testicular growth is a reliable index of pubertal progression in peripubertal boys, in whom hypogonadism may frequently be difficult to distinguish from delayed puberty (2). Although ethnic and racial origin may influence testicular size, approximate ranges are as follows:

- Prepubertal testes are between 3 and 4 mL in volume and less than 2 cm long
- Peripubertal testes are between 4 and 15 mL in volume and more than 2 cm long
- Adult testes are usually between 20 and 30 mL in volume and from 4.5 to 6.5 cm long by 2.8 to 3.3 cm wide

Testicular consistency should be noted. If the germinal epithelium was damaged before puberty, the testes are generally small and firm. If postpubertal damage occurred, the testes are usually small and soft.

On examination of the scrotum, the presence of any masses or varicoceles should be noted for further evaluation. For assessment of any potentially significant varicocele, the patient should be asked to perform a Valsalva maneuver, and the scrotal contents should be examined.

In prepuberty, the length of the stretched penis is about 4 to 8 cm, and the width is less than 2 cm in a flaccid state. In the adult, the length of the penis ranges from about 10 to 17 cm, and the width in the flaccid state is more than 3 cm.

With prepubertal onset of hypogonadism, the stature may assume eunuchoid proportions, with a crown-to-pubis divided by a pubis-to-floor ratio of <0.92 and an arm span more than 3 cm greater than the height. These proportions vary with racial and ethnic background.

A nonpalpable prostate suggests low testosterone levels. A prostate that is normal for age suggests reasonably normal testosterone levels. Of note, an enlarged prostate may not substantially diminish if once-normal testosterone levels have decreased.

Laboratory Studies

Testosterone

Testosterone levels vary from hour to hour; periodic declines below the normal range can occur in some otherwise normal men (3). An overall diurnal rhythm is also present, the highest levels of circulating testosterone occurring during the early morning hours. Therefore, testosterone levels should be determined in the morning, and studies should be repeated in patients with subnormal levels, especially those with no definite signs or symptoms of hypogonadism.

Testosterone circulates principally in bound form, mainly to sex hormone-binding globulin (SHBG) and albumin. It tightly binds to SHBG and is not biologically available, whereas the testosterone fraction associated with albumin is weakly bound and can dissociate to free, active testosterone (4). In young adult men, only about 2% of testosterone is in the free form, 30% is bound tightly to SHBG, and 68% is weakly bound to albumin (5).

Although a testosterone determination is the threshold test in the evaluation of suspected male hypogonadism, the total testosterone concentration may be within the normal range in men with primary testicular disorders such as Klinefelter's syndrome. Low production of testosterone and increased estradiol stimulate production of SHBG by the liver. The increased level of SHBG results in higher circulating total testosterone than would otherwise be present with low circulating free testosterone. An increased SHBG level may also be associated with hyperthyroidism, liver disease, severe androgen deficiency, or estrogen excess. SHBG levels increase about 1% per year as men age. Male patients with hypogonadism often have high SHBG levels because of low serum testosterone levels and enhanced production of estradiol from increases in intratesticular aromatization. Therefore, if the

clinical findings indicate that hypogonadism is present and the total testosterone levels are normal or borderline low, the level of SHBG or free testosterone by equilibrium dialysis should be determined. Measurement of total testosterone values can be enhanced in borderline cases with measurement of SHBG levels. Free testosterone assays are method dependent and may be difficult to interpret. Because albumin binds testosterone weakly, the amount of free testosterone measured will vary with the technique. Determination of the serum testosterone concentration by equilibrium dialysis is usually more reliable. Equilibrium dialysis free testosterone measurements are generally available and used to determine the amount of testosterone not bound to SHBG or albumin. Free testosterone measured by an analogue displacement assay is probably not reliable and should not be used. An important research goal is to establish a consistent method for determining free testosterone levels and to verify the results so that these levels can be more widely used and trusted. This issue frequently arises in the assessment of older men with impotence, in whom free testosterone—or total testosterone interpreted with SHBG levels—may be useful for determining the threshold of therapy (6-8).

Conversely, a low testosterone level may also be misleading under some circumstances. Slightly subnormal levels of total testosterone may occur in men with low levels of SHBG and normal circulating levels of free testosterone. A low SHBG level may be associated with hypothyroidism, obesity, or acromegaly. Determination of the level of SHBG or free testosterone by equilibrium dialysis may be helpful for clarifying the underlying disorder, especially when the clinical findings are not suggestive of hypogonadism (9).

Another alternative is the use of the free testosterone index. The free testosterone index is the testosterone level (in nanomoles per liter) divided by the SHBG (in nanomoles per liter) (10).

Gonadotropins

If a low testosterone level has been established, further laboratory testing is used to determine whether the hypogonadism is related to a primary testicular disorder (hypergonadotropic hypogonadism) or to pituitary disease (hypogonadotropic hypogonadism). The primary feature of hypogonadotropic hypogonadism is the failure of a reciprocal increase in gonadotropins in the setting of a substantially decreased testosterone level. In patients with signs and symptoms indicative of hypogonadism, determining luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels together with the initial testosterone level is usually most efficient.

FSH and LH may have variable biologic activity, depending on their carbohydrate content. Unlike standard radioimmunoassays, highly sensitive, two-site radioimmunoassays for gonadotropins yield results that generally correlate well with biologic assays. Because the biologic-to-radioimmunologic ratio of activity of gonadotropins may vary in aging and various disease states, the

most accurate results will be obtained with these highly sensitive assays (5). Currently, many assays for gonadotropins lack the sensitivity to detect values below the normal range, unlike the modern thyrotropin assays for thyroid disease. Additional studies, such as gonadotropin-releasing hormone (GnRH) testing, by an endocrinologist may help in the further assessment of these patients.

Both FSH and LH are secreted in short pulses. FSH has a longer half-life than does LH and is more likely to provide adequate results on a single blood sample. In addition, most patients with progressive hypogonadism will have increased FSH levels well before LH levels increase. Because LH has a shorter half-life than does FSH, errors may be introduced in measurements made on single samples. Pooled samples for LH done 20 to 30 minutes apart are more accurate than single-sample determinations (albeit less convenient). Persistent borderline values may be further evaluated with dynamic endocrine testing. These tests may include the GnRH stimulation test, the clomiphene stimulation test, and the human chorionic gonadotropin (hCG) stimulation test. These specialized, dynamic studies should be conducted and interpreted by an endocrinologist and may have limited clinical value.

Dynamic Tests

GnRH Stimulation Test.—In the GnRH stimulation test (11,12), intravenous injection of 100 µg of GnRH causes serum LH levels to increase threefold to sixfold during a period of 30 to 45 minutes and FSH levels to increase between 20 and 50%. Various degrees of primary testicular failure cause higher than expected peak values for LH and FSH. Men with hypothalamic or pituitary disease may have a reduced or normal response that is often inadequate for distinguishing between a pituitary and a hypothalamic disorder. If the pituitary gland is primed with repeated doses of GnRH, this stimulation test may provide a more sensitive and reliable result.

Clomiphene Stimulation Test.—In the clomiphene stimulation test, 100 mg of clomiphene citrate is given for 5 to 7 days as an evocative test of the hypothalamic-pituitary axis. Clomiphene acts by interrupting the negative feedback loop and thereby stimulating release of gonadotropin from the pituitary. A doubling of LH and a 20 to 50% increase in FSH are normal results indicative of an intact hypothalamic-pituitary response (13).

hCG Stimulation Test.—Various protocols are used for hCG stimulation testing. In general for postpubertal male patients, a single dose of hCG (5,000 IU intramuscularly) is administered, and pretherapy and 72-hour posttherapy testosterone measurements are done (some protocols use 1,000 to 4,000 IU of hCG or multiday dosing) (14).

Prolactin Level

In men with acquired hypogonadotropic hypogonadism, who usually have a reduced libido and impotence,

a prolactin level should be determined to evaluate for the presence of a prolactinoma or other cause of hyperprolactinemia. High prolactin levels can reduce GnRH and testosterone levels. In addition, a high prolactin level can reduce libido and potency even in men treated with therapeutic doses of testosterone. About 5% of men who complain of impotence will have an increased prolactin level (15). Further endocrinologic evaluation with magnetic resonance imaging (MRI) scanning of the pituitary gland is indicated for unexplained hyperprolactinemia.

Semen Analysis

A semen analysis (12) is the primary test to assess the fertility potential of the male patient. Semen should be collected by masturbation after 2 to 5 days of abstinence and evaluated within 2 hours. Variability between specimens is common; with low or borderline samples, follow-up consisting of evaluation of three or more samples should be done during a 3-month period. A fertile sample is usually associated with a motility of more than 50% and a sperm count that exceeds 20 million/mL (16). In general, semen volume should range from 1.5 to 6 mL. Morphologic features should be examined for abnormalities.

A fructose test should be done on a semen sample showing azoospermia. Because fructose is secreted by the seminal vesicles, absence of fructose may indicate complete obstruction of the ejaculatory ducts or congenital absence of both vasa deferens and both ejaculatory ducts.

Most often, a semen analysis is done in an otherwise asymptomatic man during the course of an infertility evaluation. For such an assessment, a semen analysis should be done early to determine appropriate further evaluation and therapeutic options.

Other Studies

Bone Densitometry

Because hypogonadism frequently results in low bone density and increased fracture risk, baseline hip and spine bone densitometry studies should be performed to assess the initial situation and allow future interventions to be based on any deterioration in bone density that may occur over time. Such baseline studies are especially important in men treated for prostate cancer and rendered hypogonadal. In addition to addressing the underlying condition, treatment options to maintain bone mass may include testosterone therapy (but not in the setting of prostate cancer) or bisphosphonates. At present, alendronate has been approved by the US Food and Drug Administration (FDA) for use in osteoporosis in male patients. In addition, therapy should include sufficient calcium, exercise, and vitamin D. Anabolic agents, such as parathyroid hormone, may become therapeutic options in the future for men with osteoporosis. Regardless of treatment, bone density studies should be repeated in 1 to 2 years to determine whether bone mass is being appropriately maintained.

Pituitary Imaging

In cases of acquired hypogonadotropic hypogonadism (low testosterone with low-normal FSH and LH levels) not clearly attributable to a specific cause, pituitary imaging studies with MRI or computed tomography may be needed to evaluate for structural lesions in the hypothalamic-pituitary region. MRI generally provides better pituitary images, but bony changes in the sella may be better characterized by computed tomography. In general, MRI done with and without a contrast agent is recommended as the initial pituitary imaging study in patients requiring delineation of a pituitary pathologic condition. Although no published studies have clearly indicated a particular level of testosterone in the setting of hypogonadotropic hypogonadism that should prompt pituitary evaluation, a total testosterone concentration of 150 ng/dL or below has been considered a reasonable level at which to pursue pituitary imaging, even in the absence of other symptoms. Certainly other symptoms suggestive of pituitary disease necessitate appropriate further evaluation.

A considerable proportion of aged men with hypogonadism of unknown cause have a central origin for this disorder. Possible contributing factors may include aging itself, medications, and chronic illness. Further research in this area is clearly warranted.

Genetic Studies

Patients with hypergonadotropic hypogonadism and impaired pubertal development associated with small, firm testes and often with gynecomastia are likely to have Klinefelter's syndrome or a variant. Classically, a buccal smear was done to establish the diagnosis by revealing Barr bodies. We currently recommend genetic karyotype testing to confirm the diagnosis in a patient with these findings at initial assessment. Fluorescent in situ hybridization studies increase the sensitivity of detecting Klinefelter's syndrome associated with mosaicism.

Testicular Biopsy and Scrotal Exploration

Since the advent of sensitive FSH assays, germinal cell function is now most often assessed through the FSH assay alone rather than testicular biopsy. In general, however, men with azoospermia, normal FSH levels, and normal testicular size should usually undergo testicular biopsy and scrotal exploration to determine whether a germinal cell abnormality, an obstruction, or a congenital abnormality of the vasa is present.

Testicular Ultrasonography

Testicular ultrasound examination should be done in patients with clinical findings suggestive of a scrotal or testicular mass.

DIFFERENTIAL DIAGNOSIS AND SPECIAL CONSIDERATIONS

The differential diagnosis of hypogonadism includes a large and diverse group of disorders affecting the testes directly or affecting hypothalamic-pituitary regulation

of the testes. The clinical setting, history, physical examination, and clinical judgment will, to a large degree, determine which possible etiologic factors are present. These guidelines summarize the various disorders but are not intended to be comprehensive (17).

Hypergonadotropic Hypogonadism

Patients with hypergonadotropic hypogonadism may have some or all of the following characteristic findings:

- Hypogonadism
- Increased FSH level
- Increased LH level
- Low testosterone level
- Impaired production of sperm

Klinefelter's Syndrome

Klinefelter's syndrome is caused by an extra X chromosome present in the male karyotype and occurs in about 1 in every 400 men (5). The most common karyotype is 47,XXY, and mosaicism is sometimes present (18). Men with Klinefelter's syndrome classically have small (less than 2.5-cm), firm testes, gynecomastia, eunuchoid habitus, and increased gonadotropin levels. Although production of testosterone is low, high levels of SHBG may result in normal-range testosterone levels in about 40% of patients with Klinefelter's syndrome. These patients have azoospermia, but those with mosaicism may have some spermatogenesis and may produce some pregnancies early during their reproductive lives. Virilization may begin with puberty but frequently fails to progress. Gynecomastia is often present and frequently necessitates surgical therapy for cosmetic reasons or because of concerns about breast cancer, which occurs with an increased incidence in Klinefelter's syndrome. The high levels of LH and FSH stimulate testicular aromatase activity; as a result, estradiol levels are increased. Bone density is significantly lower than for age-matched male control subjects. Learning disabilities are often present, as manifested by dyslexia and attention deficit disorder. Autoimmune disorders are present with increased frequency in patients with Klinefelter's syndrome and may respond favorably to testosterone therapy (19).

Other Genetic Syndromes

47,XXX Syndrome.—The 47,XXX karyotype, which occurs in about 0.1% of males, may be associated with hypogonadism. In some men with this disorder, aggressive behavior has been noted. Affected patients may have azoospermia in association with maturation arrest of the germinal epithelium. Usually, serum FSH levels are increased, but Leydig cell function is normal, as are testosterone and LH levels.

Dysgenetic Testes.—Dysgenetic testes may occur in conjunction with mosaicism; the patient may have an XO karyotype, a mixed XO/XY karyotype, or pure XY with streak gonads. Occurrence of pure gonadal dysgenesis in association with an XY karyotype and streak gonads

imposes a substantial risk of gonadoblastoma, which necessitates gonadectomy. Such patients generally have genital ambiguity.

Androgen Receptor Defects.—Patients with androgen receptor defects have an XY genotype and variable phenotype, depending on the degree of receptor defect. Such syndromes include testicular feminization, Reifenstein's syndrome, and other partial defects, as discussed in the following paragraphs.

Testicular Feminization.—The most severe form of androgen resistance syndrome is testicular feminization. Patients with testicular feminization have a female phenotype but a blind vaginal pouch. Testosterone receptors are nonfunctional or absent. Laboratory testing shows normal to high male range testosterone and increased gonadotropin levels. The testes should be removed after puberty because of an increased risk of a malignant lesion due to cryptorchidism. Administration of testosterone yields no response.

Reifenstein's Syndrome.—In Reifenstein's syndrome, patients have a male phenotype with variable pseudohermaphroditism. A partial androgen receptor defect is present; testosterone and gonadotropin levels are increased. Abdominal testes should be removed because of the risk of a malignant lesion. If hypospadias is present, surgical correction of the genitalia may be needed. Any significant gynecomastia may also need surgical correction. Patients may respond to high doses of testosterone.

Other Syndromes.—Some male patients with gynecomastia or oligospermia may have partial androgen insensitivity in association with mild increases in testosterone and gonadotropin levels.

5 α -Reductase Deficiency.—An autosomal recessive condition, 5 α -reductase deficiency syndrome is associated with an XY genotype. Affected patients, however, have female genitalia until puberty, when increasingly male features develop. The diagnosis is based on clinical manifestations and an increased testosterone-to-dihydrotestosterone ratio, both after puberty and in response to hCG before puberty. Sexual assignment is an issue, and patients may need corrective surgical procedures that necessitate specialty consultation.

Myotonic Dystrophy.—Classically, myotonic dystrophy is an autosomal dominant disorder, characterized by hypogonadism, muscle weakness, and frontal balding, that occurs only in male patients. Recent studies have demonstrated repeat sequences of CTG in an untranslated region of the *DMPK* gene in many of these patients, but the disorder seems to be genetically and phenotypically heterogeneous (20). Testicular failure usually occurs after age 40 years; thus, patients often have children at risk for the

disease. Testosterone levels may be variably decreased in the setting of azoospermia and high gonadotropin levels.

Cryptorchidism

Unilateral or bilateral cryptorchidism can occur. The incidence of this condition is 3 to 4% at birth, but most testes ultimately descend. Thus, the 1-year incidence is about 0.8%. Because normal testicular descent requires normal pituitary function and dihydrotestosterone levels, the incidence of cryptorchidism is increased in patients with Kallmann's syndrome. Problems associated with the management of cryptorchidism include distinguishing between cryptorchidism and retractile testes and recommending medical treatment with hCG or surgical therapy in an infant (21). Generally, the objective is to bring the undescended testicle into the scrotum before 1 to 2 years of age to improve fertility potential. Because a slight risk of a malignant lesion is associated with undescended testicles, surgical placement into the scrotum offers the opportunity for thorough examination. In prepubertal boys, treatment with hCG may be used for 4 weeks to determine whether testicular descent occurs before operative intervention is considered. Discussion of these problems is beyond the scope of these guidelines; appropriate specialty consultation should be obtained.

Vanishing Testes Syndrome (Congenital Anorchism or Prepubertal Functional Castrate)

The initial manifestation of the vanishing testes syndrome is sexual immaturity in a male patient. The cause is unclear, but the syndrome may be due to testicular torsion during fetal life after sufficient testosterone exposure to produce masculinization of the reproductive tract. Impalpable testes suggest the possibility of cryptorchidism. FSH and LH levels are increased, and testosterone levels are low. If the LH levels are only minimally increased, hCG stimulation testing of the gonad should be done. With vanishing testes syndrome, no response would be demonstrated. A response to hCG stimulation would raise the possibility of intra-abdominal testes, which would necessitate further evaluation because of the potential for malignant transformation. In this setting, MRI is recommended to assess the possibility of a retained intra-abdominal dysgenetic gonad because this would be associated with an increased risk of a malignant lesion and would necessitate removal.

Hemochromatosis

Iron overload may lead to primary gonadal failure or sometimes hypothalamic-pituitary dysfunction that results in secondary gonadal failure (22). The diagnosis is made in the setting of associated findings of hemochromatosis in conjunction with an increased ferritin level and is generally confirmed with a liver or bone marrow biopsy.

External Testicular Insults

Trauma.—The patient may have a history of direct traumatic injury. Testicular torsion sometimes is

associated with a “bell-clapper” abnormality in which the testes lie horizontally because of incomplete closure of the surrounding tissues.

Mumps Orchitis.—In patients with postpubertal mumps, a 25% risk of orchitis exists. More than 50% of those patients with orchitis will be infertile. Increased FSH concentrations and oligospermia or azoospermia are present. Mumps orchitis can progress to produce low testosterone and high LH levels in some men. Unilateral testicular atrophy can progress to bilateral failure over the years.

Radiation Treatment or Chemotherapy.—With irradiation or chemotherapy, testicular exposure can occur from treatment of another disease or inadvertently. A dose-dependent recovery potential and variable Leydig cell dysfunction have been noted. Pretreatment sperm banking is possible if future “fertility” is desired and sperm counts are normal.

Autoimmune Syndromes

Anti-Leydig cell antibody-associated disorders or conditions associated with anti-sperm antibodies are autoimmune syndromes related to hypogonadism. These syndromes are poorly characterized, and further research is needed to determine diagnostic criteria and possible treatment options.

Sertoli Cell Only Syndrome

The absence of germ cells in patients with small testes, high FSH levels, azoospermia, and normal testosterone levels should suggest the presence of Sertoli cell only syndrome. The diagnosis can be made only by testicular biopsy. The presence of Leydig cell hyperplasia is common and may be responsible for high serum estradiol levels. The cause of this syndrome is currently unknown.

Hypogonadotropic Hypogonadism

The condition of hypogonadotropic hypogonadism is generally associated with the following findings:

- Low or low-normal FSH level
- Low or low-normal LH level
- Low testosterone level

Kallmann’s Syndrome

Classic Kallmann’s syndrome is a congenital disorder inherited as a sporadic condition or generally as an X-linked recessive trait manifesting as prepubertal hypogonadism. The incidence of this syndrome is about 1 in 10,000 male births. Low testosterone levels are present because of an impaired release of LH and FSH as a result of variable GnRH deficiency. LH and FSH are released in response to priming followed by stimulation with GnRH. The gene on the X chromosome for classic Kallmann’s syndrome and associated anosmia has been identified and cloned (23). Autosomal recessive and autosomal dominant

variants of hypogonadotropic hypogonadism also exist and are referred to as idiopathic hypogonadotropic hypogonadism.

Classically, Kallmann’s syndrome is associated with anosmia as a result of defective development of the olfactory tract in the brain. The GnRH-containing neurons originate in the developing olfactory tract and therefore do not develop properly in this syndrome (5). This defective development of the olfactory tract can be diagnosed by MRI scanning. In some cases, other defects such as cerebellar dysfunction, red-green color blindness, cleft palate, and congenital deafness are present (24). Cryptorchidism may occur because gonadotropins contribute to normal testicular descent. The prepubertal testes in patients with Kallmann’s syndrome tend to be larger than in patients with Klinefelter’s syndrome and are appropriate for age up to puberty, inasmuch as normal initial amounts of germinal tissue are present. Partial pubertal development may be present in patients with partial defects; thus, Kallmann’s syndrome may be difficult to distinguish from delayed puberty up through the teenage years. Once a patient with Kallmann’s syndrome has been identified, other family members at risk (on the basis of mode of inheritance) should be assessed, if possible.

Other Related Syndromes

Congenital hypogonadotropic syndromes are associated with secondary hypogonadism and other somatic findings. Prader-Willi syndrome is characterized by hypogonadism, short stature, mental retardation, hypotonia at birth, and obesity. Laurence-Moon-Bardet-Biedl syndrome is an autosomal recessive trait characterized by mental retardation, retinitis pigmentosa, polydactyly, and hypogonadism. These syndromes may be due to a hypothalamic deficiency of GnRH.

Fertile Eunuch Syndrome

Hypogonadotropic hypogonadism in patients who have modest FSH secretion and selective LH deficiency is known as the fertile eunuch syndrome. Fertility may be present in some of these patients. These men usually respond to hCG therapy.

Pituitary Disorders

Acquired hypogonadotropic hypogonadism may indicate the presence of pituitary insufficiency or a pituitary tumor. Unless the reason for the pituitary defect is clear, imaging studies of the pituitary gland and the hypothalamus are indicated to determine whether a tumor or an infiltrative disorder is present. Metastatic tumors, granulomas, abscesses, and hemochromatosis may also be discovered.

Hyperprolactinemia is a potential cause of hypogonadotropic hypogonadism and generally manifests with a low libido and impotence. A serum prolactin level should be determined in men with acquired hypogonadotropic hypogonadism. High prolactin levels are usually associated with a prolactinoma, but certain medications may also cause hyperprolactinemia.

Hypogonadotropic hypogonadism from pituitary disease may also occur with granulomatous and infiltrative disorders, cranial trauma with or without pituitary stalk transection, irradiation, and hypophysitis.

Hemochromatosis

See earlier discussion of hemochromatosis in Hypergonadotropic Hypogonadism section.

Serious Illness, Acquired Immunodeficiency Syndrome, and Stress

Transient hypogonadotropic hypogonadism may occur in patients with serious disorders or malnutrition (25). Acquired immunodeficiency syndrome (AIDS) may be associated with low testosterone levels and generally low gonadotropin levels (consistent with hypothalamic-pituitary involvement). In some patients with AIDS, gonadotropin levels are increased (consistent with testicular disease) (26).

Aging

Considerable controversy exists over the concept of a male climacteric or "andropause" (27). Growing evidence indicates that some aging men have reduced production of testosterone associated with decreased libido, impotence, decreased growth of body hair, decreased muscle mass, fatigue, increased risk of myocardial infarction (28), and decreased bone mass in conjunction with osteoporosis. Some early studies indicated that the problem may be related to coexisting conditions, but more recent evidence supports the view that an age-related decline in testicular function may occur with associated symptoms and often responds to testosterone replacement therapy (29,30). Measurements of SHBG in conjunction with total testosterone are usually needed to demonstrate the abnormality. Age-related declines in free testosterone, as measured by equilibrium dialysis, are more rapid than the decreases in total testosterone. The SHBG levels increase with advancing age, probably related to higher serum estradiol levels from increased adipose tissue. Often the FSH and LH levels are mildly increased, an indication that a primary testicular disorder may be present in conjunction with a secondary abnormality in LH burst frequency (31). Dynamic testing may disclose more subtle abnormalities of hypothalamic function. The circadian variation in serum testosterone levels, with higher values in the morning, is generally lost with aging.

Data from long-term research studies are needed to clarify the criteria for therapeutic considerations in aging men. Short-term research studies have demonstrated that testosterone replacement treatment may result in improved lean body mass, increased hematopoiesis, decreased low-density lipoprotein (LDL) levels in conjunction with a constant ratio of LDL to high-density lipoprotein (HDL), improved libido, and improved well-being in older men with low testosterone levels. Generally, prostate size and prostate-specific antigen (PSA) levels do not change in comparison with otherwise normal men, but PSA levels have been found to increase in some men (32).

Men with symptomatic hypogonadism and a total testosterone level of less than 200 ng/dL may be potential candidates for therapy, although no specific recommendations have been established at this time. Some studies have used 2.5 standard deviations below the mean testosterone values for young normal male subjects as the cutoff point for initiation of therapy, resulting in intervention at values of about 319 ng/dL (33). With use of this guideline, approximately 30% of men beyond 75 years of age would have testosterone values below this hypogonadism threshold. In general, if the potential benefit exceeds the potential risk, then the patient may be a candidate for therapy. The lack of knowledge about the exact nature of the benefit and risk remains the main problem.

THERAPY

Goals of Therapy

Restore Sexual Function, Libido, Well-Being, and Behavior

Many studies have been done to evaluate the effects of testosterone therapy on sexual function and well-being in men with hypogonadism (34). Impaired sexual behavior and mood disturbances seem to occur below a certain threshold of circulating testosterone levels, and most studies have demonstrated improved function with testosterone replacement.

In studies of testosterone treatment of men with hypogonadism, investigators have found that therapy resulted in increased sexual interest and increased number of spontaneous erections. On psychologic testing, the men with untreated hypogonadism tended to score high on depression, anger, fatigue, and confusion scales. Hormonal replacement diminished most of these traits, but although the depression score improved, it remained more of a problem in men with hypogonadism than in male control subjects (35). Further long-term studies are clearly needed in this area to establish definite criteria for therapy and response in borderline cases. Of note, erectile dysfunction associated with hypogonadism may not improve after adequate androgen replacement if other secondary causes for erectile dysfunction are present. For additional information, see the American Association of Clinical Endocrinologists Clinical Practice Guidelines for the Evaluation and Treatment of Male Sexual Dysfunction (36).

With the onset of hypogonadism before puberty, an initial low dose of testosterone should be used to avoid acute priapism, adverse psychologic effects, and aggressive behavior.

Produce and Maintain Virilization

Secondary sex characteristics such as increased muscle mass, beard growth, growth of pubic and axillary hair, and phallus growth improve with testosterone therapy.

Optimize Bone Density and Prevent Osteoporosis

In a study of elderly male nursing home residents, the incidence of hip fracture was between 5 and 15% (37). Of

those residents who had sustained a prior hip fracture, 66% were found to have hypogonadism (serum testosterone levels less than 300 ng/dL). Hypogonadism was present in up to 20% of men with vertebral crush fractures, even though many of these men did not have other clinical features of hypogonadism. In adolescent male patients with hypogonadotropic hypogonadism, testosterone therapy increases bone mineral density in comparison with that in male patients with hypogonadism not receiving testosterone (38,39). In men with prepubertal-onset hypogonadotropic hypogonadism, however, diminished bone mass may be only marginally improved by testosterone replacement (40).

Possibly Normalize Growth Hormone Levels in Elderly Men

In comparison with normal men, those with hypogonadism have significantly reduced mean growth hormone pulse amplitude but normal pulse frequency. Patients with adult-onset growth hormone deficiency also have increased cardiovascular-related mortality (41). Testosterone treatment results in a significant increase in 24-hour mean serum growth hormone value and mean growth hormone pulse amplitude. Perhaps testosterone has an important role in the control of growth hormone secretion in adulthood, and testosterone therapy may have a positive clinical influence (42). No specific recommendations on this issue are possible until further research clarifies the potential risks and benefits of therapy.

Potentially Affect the Risk of Cardiovascular Disease

Orally administered alkylated androgens are nonaromatizable and result in increased LDL and decreased HDL levels, which may increase cardiovascular risk (19,43,44). Unlike orally administered alkylated androgen preparations, testosterone is aromatized to estrogen. In men with hypogonadism treated with replacement doses of testosterone, total cholesterol and LDL levels may modestly decrease in conjunction with minimal change in HDL; thus, investigators have speculated that the risk of cardiovascular disease may be higher in men with hypogonadism not receiving testosterone replacement (45). Testosterone replacement therapy in men is not associated with major adverse lipid changes (46); in fact, endogenous testosterone and administration of exogenous testosterone may lower the atherogenic Lp(a) lipoprotein levels (47). Other studies suggest that testosterone replacement in men with hypogonadism may be associated with adverse lipid effects, and yet other studies have reported indeterminate findings (27).

Other cardiovascular effects apart from changes in lipids may be attributable to testosterone replacement therapy. A potential risk of testosterone therapy is the propensity of testosterone to increase platelet aggregation and thrombogenicity (48).

Currently, whether testosterone replacement therapy in men with hypogonadism increases, decreases, or has a neutral effect on cardiovascular risk remains uncertain. Long-term prospective research must be conducted to

assess the role of endogenous testosterone and testosterone replacement therapy on cardiovascular risk in men. No specific recommendations on this issue are possible until further research clarifies the potential risks and benefits of therapy.

Restore Fertility in Cases of Hypogonadotropic Hypogonadism

See subsequent sections on therapy for hypogonadotropic hypogonadism.

Contraindications to Testosterone, GnRH, and Gonadotropin Therapy

Testosterone replacement, pulsatile GnRH therapy, and gonadotropin therapy are contraindicated in men with prostate cancer, male breast cancer, or untreated prolactinoma. Treatment with these medications can stimulate tumor growth in androgen-dependent neoplasms. Careful examination of the male breast and prostate is required initially and at follow-up visits. In addition to prostate examination, baseline and follow-up PSA levels should be determined in older men at increased risk for prostate cancer. Men with symptomatic prostatism should undergo evaluation and treatment for this problem before testosterone replacement therapy is considered. Sleep apnea and polycythemia, which may cause hyperviscosity, are relative contraindications to the use of testosterone therapy. Testosterone treatment will tend to reduce sperm counts and testicular size and should not be used in men currently seeking fertility.

Testosterone Therapy in Adult Male Patients With Hypogonadism

Ideally, testosterone therapy should provide physiologic range serum testosterone levels (generally between 280 and 800 ng/dL) and physiologic range dihydrotestosterone and estradiol levels, which would allow optimal virilization and normal sexual function. Testosterone therapy can be used in the male patient with hypogonadism who is not interested in fertility or not able to achieve fertility. In late teenage male patients with delayed puberty, testicular size should be monitored for evidence of onset of puberty. In this setting, short-term, low-dose testosterone therapy should be withdrawn to determine whether spontaneous puberty is occurring.

The following preparations of testosterone have been approved by the FDA for clinical use:

- Long-acting intramuscular preparations
- Short-acting intramuscular preparations
- Scrotal patches
- Transdermal patches
- Transdermal gel
- Orally administered agents

Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful. The orally administered alkylated androgen preparations currently available in the

United States are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects, such as hemorrhagic liver cysts, cholestasis, and hepatocellular adenoma (19). In Europe, testosterone undecanoate may be a more acceptable oral alternative, but erratic testosterone levels, frequent dosing, and occasional gastrointestinal side effects may limit the usefulness of this preparation in the United States. Reformulation of this preparation with testing in the United States and elsewhere is currently under way.

Injectable testosterone pellets are sometimes used, and further study may prove them to be suitable for many men. For patients with hypogonadotropic hypogonadism wishing fertility, hCG with or without human menopausal gonadotropin (FSH) or pulsatile GnRH therapy and hCG with or without assisted reproduction are options.

Parenteral Testosterone Preparations

Testosterone enanthate and testosterone cypionate are long-acting testosterone esters suspended in oil to prolong absorption. Peak levels occur about 72 hours after intramuscular injection and are followed by a slow decline during the subsequent 1 to 2 weeks (49).

For complete androgen replacement, the regimen should be between 50 and 100 mg of testosterone enanthate or cypionate administered intramuscularly every 7 to 10 days, which will achieve relatively normal levels of testosterone throughout the time interval between injections (50). Longer time intervals are more convenient but are associated with greater fluctuations in testosterone levels. Higher doses of testosterone produce longer-term effects but also higher peak levels and wider swings between peak and nadir circulating testosterone levels; the result is fluctuating symptoms in many patients (51).

The use of 100 to 150 mg of testosterone every 2 weeks is a reasonable compromise. Use of 300-mg injections every 3 weeks is associated with wider fluctuations of testosterone levels and is generally inadequate to ensure a consistent clinical response. With use of these longer-interval regimens, many men will have pronounced symptoms during the week preceding the next injection. In such instances, a smaller dose at closer intervals should be tried. As a guide, testosterone levels should be above the lower limit of normal, in the range of 250 to 300 ng/dL, just before the next injection (52). Excessive peak levels and side effects should also be monitored and used to adjust the dosing regimens.

When full androgen replacement is not required, patients should receive lower doses of testosterone. One such category includes adult male patients with prepubertal onset of hypogonadism who are going through puberty for the first time during therapy and who often may require psychologic counseling, especially when a spouse is involved as well. In these patients, testosterone therapy should be initiated at 50 mg every 3 to 4 weeks and then gradually increased during subsequent months, as tolerated, up to full replacement within 1 year. Men with appreciable benign prostatic hypertrophy who have hypogo-

nadism and symptoms may be given 50 to 100 mg of testosterone every 2 weeks as an initial regimen and maintained on this dosage with careful monitoring of urinary symptoms and prostate examinations; therapy can be withdrawn if necessary.

Attaining full virilization in the patient with hypogonadism may take as long as 3 to 4 years. Follow-up intervals should be between 4 and 6 months to monitor progress, review compliance, and determine whether any complications or psychologic adjustment problems are present. Often, patients can learn how to administer their own injections. A spouse or significant other may also be instructed in this technique.

Transdermal Testosterone Therapy

Transdermal Testosterone Delivery System: Normal Skin.—A testosterone patch with permeability enhancement allows testosterone delivery through normal skin. Daily evening application generally results in normal-range serum testosterone levels, which mimic the normal diurnal changes in testosterone in normal men. In contrast to the situation with use of the scrotal patch, dihydrotestosterone levels remain within the normal range (53). Estradiol and bioavailable testosterone levels also remain within the normal range. Skin irritation may be a problem in some patients. Therapy consists of one to two patches applied daily to normal skin. As with scrotal patches, this treatment is more expensive than injections, but convenience of use, maintenance of normal diurnal testosterone levels, and elimination of office visits for injections may make this form of treatment useful in many patients. Testosterone levels should be monitored periodically to ensure the appropriate range is being maintained.

Scrotal Patch Testosterone Delivery System.—Scrotal testosterone patches are available in 40 and 60 cm² sizes, which deliver, respectively, 4 and 6 mg of testosterone daily. Scrotal skin absorbs testosterone better than does nonscrotal skin. The patch is applied to the scrotal skin after preparation of the scrotum with dry shaving. The patch is nonadhesive, and a new patch is applied each morning. The testosterone levels mimic the diurnal rhythm present in normal men. Testosterone levels are generally maintained in the normal range and are usually well tolerated. These levels should be assessed in the morning before patch application to ensure that they are above the lower limit of the normal range at the nadir. If the scrotum is small or the skin surface is abnormal, absorption may be limited. Because genital skin contains high concentrations of 5 α -reductase, the dihydrotestosterone levels in treated patients increase initially but may return to normal in some men. In most men treated with the scrotal patch, however, these levels remain higher than normal (54). The HDL-to-cholesterol ratio in treated patients does not change significantly from before to after therapy (55). The long-term potential effects of increased levels of dihydrotestosterone are unknown at this time, and careful monitoring of prostate growth is recommended. Further research may

clarify any possible adverse effects of such increased levels occurring in men who receive this type of therapy. The cost of using the scrotal patch exceeds that for testosterone injections, but the convenience of use may make this therapeutic option acceptable for many patients.

Transdermal Testosterone Gel.—Transdermal testosterone in a hydroalcoholic gel for once-daily administration to the nongenital skin is available in packets labeled 2.5 G (containing 25 mg of testosterone) and 5 G (containing 50 mg of testosterone). After application of the gel, blood levels of testosterone seem to be constant over 24 hours, and levels are adequate in most patients (56). Positive effects on libido, mood by about 30 days of therapy, and muscle mass and strength by 90 to 180 days of therapy have been noted (57). The gel is well tolerated and is generally associated with minimal skin irritation in comparison with testosterone patches (58). The gel dries quickly after application. One potential problem is transfer of the gel from person to person if direct skin contact occurs. Transdermal testosterone use has been shown to decrease bone resorption markers and increase bone formation markers; in addition, small increases in bone density have been noted after 6 months of use (59).

Monitoring Issues and Side Effects of Testosterone Therapy

Periodic follow-up of patients receiving testosterone therapy is needed. During the first year of such therapy, the clinical response and the side effects should be monitored at 3- to 4-month intervals.

For patients receiving testosterone injections, a serum testosterone level should be measured at the midpoint between injections to ensure that the value is near the middle of the normal range. Most patients using testosterone gel have constant blood levels of testosterone over 24 hours; thus, the time of measurement is usually not critical. The testosterone patch preparations usually yield peak serum testosterone values within 4 to 8 hours after application.

Examination of the prostate should be done routinely, along with a prostate-related symptom assessment every 6 to 12 months. PSA levels should be determined annually in older men receiving testosterone replacement therapy. High PSA levels should be further evaluated with a highly specific PSA assay, if available. If results are abnormal, a urologic consultation should be sought, and testosterone replacement therapy should be terminated. Men receiving testosterone replacement therapy and finasteride should be considered for further evaluation even with PSA values in the upper normal range. Testosterone treatment should not be administered to men with high PSA values or significantly increasing PSA levels. Testosterone, and especially dihydrotestosterone, stimulates growth of the prostate and seminal vesicles. In a study that assessed the effect of exogenous testosterone administration by patch or by injection on the serum levels of PSA and prostate-specific membrane antigen in men with hypogonadism, the results

demonstrated no correlation with therapy and thus no testosterone dependence of PSA or prostate-specific membrane antigen (60). Testosterone treatment of men with hypogonadism also resulted in growth of the prostate and seminal vesicles, but this growth did not exceed the volumes expected in normal men (61). No clear relationship has been established between testosterone replacement therapy and prostate cancer, although anecdotal reports have been published (62). Men in whom symptomatic prostatism develops should undergo assessment before testosterone replacement therapy is continued. Long-term studies are needed to clarify this issue.

Gynecomastia may result from the aromatization of testosterone to estradiol and changes in SHBG levels. Surgical therapy may be considered for some patients. Men with a genetic susceptibility to alopecia may note worsening of this problem with testosterone therapy.

Testosterone stimulates the bone marrow production of erythrocytes. The result is an increased hematocrit in some men, with the possibility of hyperviscosity side effects (63). The hematocrit should be determined every 6 months for the first 18 months and then yearly thereafter if it is stable and normal. Testosterone therapy should be decreased or discontinued if the hematocrit increases to above 50%.

Lipid disturbances in testosterone-treated male patients are generally not a problem because of the aromatization of testosterone to estradiol. The ratio of HDL to total cholesterol generally remains constant. Anabolic steroids, used in oral testosterone preparations, that are not aromatized increase LDL and lower HDL levels and thus could increase cardiovascular risk. An initial lipid profile should be recorded, and a follow-up profile should be obtained after 6 to 12 months of therapy and then yearly thereafter.

Sleep apnea may also be a problem in some men, and testosterone therapy should be discontinued until the sleep apnea problem can be adequately addressed (64). The patient should be asked about fatigue during the day in addition to disordered sleep. A sleep study should be done if symptoms are present.

Because pharmacologic use of testosterone will suppress spermatogenesis, the use of testosterone preparations may substantially reduce fertility in otherwise normal men. This adverse effect is often an issue with the illicit use of testosterone.

Gonadal Stimulation in Hypogonadotropic Hypogonadism

Because gonadotropin or GnRH therapy is effective only in hypogonadotropic hypogonadism, this diagnosis must be firmly established before consideration of therapy. Although these agents may also be used to induce puberty in boys and to treat androgen deficiency in hypogonadotropic hypogonadism, the major use of these preparations is in the initiation and maintenance of spermatogenesis in hypogonadotropic men who desire fertility.

Gonadotropin Therapy in Androgen Deficiency

It is known that hCG binds to Leydig cell LH receptors and stimulates the production of testosterone. Peripubertal boys with hypogonadotropic hypogonadism and delayed puberty can be treated with hCG instead of testosterone to induce pubertal development. The initial regimen of hCG is usually 1,000 to 2,000 IU administered intramuscularly two to three times a week (65). The clinical response is monitored, and testosterone levels are measured about every 2 to 3 months. Dosage adjustments of hCG may be needed to determine an optimal schedule. Increasing doses of hCG may reduce testicular stimulation by down-regulating the end-organ; thus, a more optimal result may occur with less frequent or reduced dosing. The half-life of hCG is long.

The advantages of hCG over testosterone in this setting include the stimulation of testicular growth, which may be an important issue for some men. Use of hCG may also yield greater stability of testosterone levels and fewer fluctuations in hypogonadal symptoms (66). In addition, hCG treatment is necessary for stimulating enough intratesticular testosterone to allow the initiation of spermatogenesis. The disadvantages of hCG include the need for more frequent injections and the greater cost.

Gonadotropin Therapy for Induction of Spermatogenesis

Male patients with onset of hypogonadotropic hypogonadism before completion of pubertal development may have testes generally smaller than 5 mL. These patients usually require therapy with both hCG and human menopausal gonadotropin (or FSH) to induce spermatogenesis. Men with partial gonadotropin deficiency or who have previously (peripubertally) been stimulated with hCG may initiate and maintain production of sperm with hCG therapy only. Men with postpubertal acquired hypogonadotropic hypogonadism and who have previously had normal production of sperm can also generally initiate and maintain spermatogenesis with hCG treatment only (67). Fertility may be possible at sperm counts much lower than what would otherwise be considered fertile. Counts of less than 1 million/mL may be associated with pregnancies under these circumstances. It is imperative that the female partner undergo assessment for optimal fertility before or concurrently with consideration of therapy in the man.

Therapy with hCG is generally begun at 1,000 to 2,000 IU intramuscularly two to three times a week, and testosterone levels should be monitored monthly to determine whether any therapeutic adjustments are needed to normalize the levels. It may take 2 to 3 months to achieve normal levels of testosterone. When normal levels of testosterone are produced, examinations should be conducted monthly to determine whether any testicular growth has occurred. Sperm counts should also be assessed monthly during a 1-year period. Because of the high cost of human menopausal gonadotropin (or FSH) preparations, hCG should be the initial therapy of choice for at least 6 to 12 months. Use of hCG, in the absence of

exogenous FSH, can often complete spermiogenesis in men with partial gonadotropin deficiency (68). In general, the response to hCG can be predicted on the basis of the initial testicular volume—the greater the initial testicular volume, the greater the chance of responding to hCG only (69). In one study, however, investigators demonstrated that most patients will respond to hCG alone regardless of initial testicular volume (70). Studies have shown that combining purified FSH and testosterone without LH or hCG does not stimulate spermatogenesis in truly hypogonadotropic men (71).

If spermatogenesis has not been initiated by the end of 6 to 12 months of therapy with hCG or LH, administration of an FSH-containing preparation is initiated in a dosage of 75 IU intramuscularly three times a week along with the hCG injections. After 6 months, if sperm are not present or are present in very low numbers (<100,000/mL), the human menopausal gonadotropin (or FSH) dosage can be increased to 150 IU intramuscularly three times a week for another 6 months. If pregnancy occurs, the patient's regimen can be switched to only hCG to allow continued spermatogenesis for subsequent potential pregnancies. After delivery, if no further pregnancies are desired, the patient can be switched to testosterone therapy if desired, or long-term hCG therapy can be continued in conjunction with appropriate contraceptive measures, if needed. Rarely, antibodies against hCG may arise and prevent any response to therapy; in such a case, human LH may be effective (72). Recombinant LH has recently become available and may be of use in selected patients.

GnRH Therapy

In patients with an otherwise intact pituitary gland and hypogonadotropic hypogonadism, synthetic GnRH can be given in a pulsatile fashion subcutaneously through a pump every 2 hours. GnRH therapy is monitored by measuring LH, FSH, and testosterone levels every 2 weeks until levels are in the normal range, at which point monitoring can be adjusted to every 2 months. GnRH can be used to initiate pubertal development, maintain virilization and sexual function, and initiate and maintain spermatogenesis. In most patients, these effects may take from 3 to 15 months to achieve sperm production (73). As with gonadotropin therapy, fertility can be achieved with very low sperm counts—often in the range of 1 million/mL. GnRH may be more effective than gonadotropin stimulation in increasing testicular size and initiating spermatogenesis in many patients with hypogonadotropic hypogonadism (74).

Other Treatment Considerations***Antiandrogen Therapy in Oligospermia***

Long-term use of low-dose clomiphene citrate at 25 mg daily to increase pituitary stimulation of testicular function has often been attempted in men with oligospermia (75). Tamoxifen has been used in countries other than the United States. The results are unpredictable, and

no long-term, prospective studies have demonstrated efficacy. Studies have generally shown no significant changes in semen variables or pregnancy rates (76). Currently, we do not recommend the general use of clomiphene citrate or tamoxifen for treatment of oligospermia in male patients.

Assisted Reproductive Technology

The ability to perform in vitro fertilization with intracytoplasmic sperm injection directly into the egg has revolutionized the approach to male subfertility. A single sperm or immature form retrieved from the testicle is sufficient to fertilize an egg and provide a reasonable chance at pregnancy. In vitro fertilization with intracytoplasmic sperm injection may be a viable option in many men with hypogonadism who cannot otherwise be induced to produce enough sperm to result in pregnancy as well as in the presence of a female factor that may further make pregnancy by the couple difficult or impossible. The procedure is expensive and seldom covered by health insurance; therefore, this technology will generally not replace conventional gonadal stimulation protocols. Intrauterine insemination may also be a low-cost option in suitable women when the man has mild to moderate oligospermia.

Pituitary Tumors

Patients with acquired hypogonadotropic hypogonadism may require assessment for a possible pituitary tumor with appropriate pituitary imaging studies, such as MRI, and determination of a prolactin level. Depending on the presence or absence of a tumor, other hormonal testing may be indicated, including thyroid and adrenal function tests. Further evaluation and treatment options would depend on what hormonal deficits are present, the size and site of the tumor, the operability of the tumor, and the patient's preferences in specific circumstances.

If a prolactinoma is present, therapy would be directed toward correcting this problem before initiation of other therapy. Medical therapy with bromocriptine, pergolide, or cabergoline may effectively reduce prolactin levels sufficiently to allow gonadal function to resume or allow stimulation with gonadotropins. Even when prolactin levels cannot be normalized, hCG therapy alone or in conjunction with human menopausal gonadotropin (or FSH) therapy may stimulate spermatogenesis in treated prolactinomas and result in pregnancies (77).

Surgical therapy should especially be considered for significant pituitary tumors that are not prolactin-secreting microadenomas. Surgical treatment may also be an option in prolactin-secreting microadenomas if patients have severe side effects from medications or prefer this approach after being appropriately informed of the risks and benefits of medical versus surgical management.

Gynecomastia

Many men have psychologic problems resulting from gynecomastia. This problem should be taken seriously and discussed with the patient. Use of aromatase inhibitors,

such as testolactone, has been tried but has yielded limited benefit. A breast reduction surgical procedure is often required for psychologic well-being.

Psychologic Counseling

Men with hypogonadotropic disorders frequently have associated mood disturbances, including depression, aggression, poor self-esteem, and learning problems. In such cases, psychologic counseling is often needed to allow proper identification and treatment of these problems. Counseling should also include significant others, if possible.

SUMMARY

The major objectives of the initial assessment of a patient with possible hypogonadism are to distinguish primary gonadal failure (hypergonadotropic hypogonadism with low testosterone and increased FSH and LH levels) from hypothalamic-pituitary disorders (hypogonadotropic hypogonadism with low testosterone and low to normal FSH and LH levels) and to make a specific diagnosis. The initial clinical manifestations may vary, depending on whether the onset of the disorder was prepubertal or postpubertal. Men with hypogonadotropic disorders may achieve fertility with gonadal stimulation. Men with hypergonadotropic disorders are treated with testosterone to achieve virilization and are usually, but not invariably, incapable of achieving fertility.

History and Physical Examination

- A history of major medical problems, medications, toxic exposures, fertility problems, and developmental milestones should especially be noted. Low libido, impotence, fatigue, impaired concentration, and sexual dysfunction are important presenting problems and need to be asked about specifically because most men will not seek medical attention for these symptoms alone.
- The degree of pubertal development, eunuchoid proportions, anosmia, hyposmia, gynecomastia, abnormal hair growth and distribution, abnormal genitalia, presence of varicocele, findings on prostate examination, and testicular size and consistency, in particular, are important physical manifestations for differential diagnosis.

Laboratory and Ancillary Evaluation

- Laboratory testing is directed toward determining whether the patient has abnormalities of reproductive hormones and whether the abnormalities are indicative of testicular or hypothalamic-pituitary disease. The initial laboratory testing should include a morning blood sample for testosterone, prolactin, FSH, and LH levels. A semen analysis is needed if fertility potential is at issue.
- If testosterone levels are low-normal and the symptoms and signs indicate hypogonadism, the testosterone

study should be repeated, and SHBG or a free testosterone level by equilibrium dialysis should be determined to help diagnose a hypogonadal state because total testosterone levels may be normal in the setting of hypogonadism if the SHBG levels are increased.

- For the diagnosis of hypergonadotropic hypogonadism, FSH is especially important because FSH has a longer half-life, is more sensitive, and demonstrates less variability than LH. Pooled LH samples (three preferred) may help reduce problems with LH variability associated with a short half-life and pulsatile secretion.
- Dynamic testing of the hypothalamic-pituitary-testicular axis should be done by an endocrinologist and reserved for patients in whom the results of baseline diagnostic testing are equivocal, although interpretation of the results of dynamic testing may be poorly defined.
- In acquired hypogonadotropic hypogonadism, a prolactin level and pituitary imaging study should be done to assess the patient for a possible hypothalamic-pituitary disorder such as a pituitary tumor. Testing of the thyroid, adrenal, and growth hormone axes is also indicated.
- Chromosomal analysis should be considered in men with prepubertal-onset hypergonadotropic hypogonadism to evaluate for Klinefelter's syndrome and related disorders.
- Bone densitometry should be done in men with chronic, untreated hypogonadal disorders to aid in decision making about treatment options to prevent and treat osteoporosis.
- Testicular ultrasonography should be done in patients with clinical findings suggestive of a scrotal or testicular mass.
- In the evaluation of abnormal semen findings, testicular biopsy should be reserved for patients with normal results of hormonal studies and azoospermia to evaluate for obstruction or congenital absence of the vasa and possible surgical repair or for possible use of in vitro fertilization with intracytoplasmic sperm injection.

Diagnosis and Treatment

An overall summary of clinical and laboratory findings, potential diagnoses, and recommended evaluation or treatment strategies in adult male patients with hypogonadism is presented in Table 1.

CONCLUSION

The recognition, evaluation, and treatment of hypogonadism in the male patient are often dismissed by the patient and overlooked by the physician. The symptoms and signs of hypogonadism should be identified through appropriate questioning of the patient and a directed physical examination. Hormonal and ancillary testing should be performed in a cost-efficient and clinically appropriate manner to allow pertinent treatment considerations. Testosterone replacement therapy can often enable the

patient to function in a more normal manner and decrease the risk of future problems with fertility, mood disturbances, fatigue, impaired virilization, and osteoporosis. Further studies are needed to determine the influence of testosterone replacement therapy on cardiovascular risk. Of importance, these guidelines demonstrate the need for meaningful, long-term studies of hypogonadal disorders in general and of aging men in particular. The ultimate goals are to improve not only the duration but also the quality of life and to allow people to reach their full potential regardless of age.

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Table 1
Summary of Findings, Potential Diagnoses, and Recommended Strategies
in Adult Male Patients With Hypogonadism*

Testicular size†	FSH	LH	Testosterone‡	Semen analysis	Diagnosis	Evaluation or treatment
Not palpable	↑	↑	↓	Azoospermia	Anorchism	Surgical exploration
Not palpable	↑	↑	N‡ or ↓	Azoospermia	Bilateral cryptorchidism	Surgical exploration
<5 mL	↓	↓	↓	Azoospermia, oligospermia	Kallmann's syndrome, hypogonadotropic hypogonadism	T for virilization; hCG ± hMG (or FSH) or GnRH for spermatogenesis
<5 mL	↑	↑	N‡ or ↓	Azoospermia	Klinefelter's syndrome, other hypergonadotropic syndromes	Karyotype to confirm; T for virilization
8-15 mL	↑	N	N	Azoospermia, oligospermia	Germinal damage: toxins, idiopathic	Fertility: IVF with ICSI (?)
10-20 mL	↓	↓	↓	Oligospermia	Adult acquired hypogonadotropic hypogonadism	Pituitary MRI; prolactin. Treat pituitary disorder if present; otherwise treat as Kallmann's syndrome
10-20 mL	N or ↑ (variable)	N or ↑ (variable)	N‡ or ↓	Variable	Senescence	T if symptomatic with low T‡
15-20 mL	N or ↑	N	N	Oligospermia	Varicocele, drugs, idiopathic	Fertility: varicocele repair if significant varicocele present. Optimize female factor; IVF with ICSI
Variable phenotype	↑ (variable)	↑ (variable)	↑	Variable	T receptor defects, Reifenstein's syndrome	Variable (depending on degree): medical or surgical therapy
20-30 mL	N	N	N	Azoospermia	Obstruction	Fertility: surgical repair; IUI, IVF with ICSI

*FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; IVF = in vitro fertilization; LH = luteinizing hormone; MRI = magnetic resonance imaging; N = normal; SHBG = sex hormone-binding globulin; T = testosterone.

†Normal testicular size is 20-30 mL. Testicular size is used here as a clinical finding to help narrow the differential diagnosis. Some variation beyond the listed ranges may exist for a specific condition. Use of this variable is optional; the diagnosis should be based on the total clinical picture.

‡Because of changes in SHBG levels, total testosterone may be in the normal range in the setting of low testosterone production. Level of SHBG or free testosterone should be used in this setting to determine whether treatment options should be considered.

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