

HYPOGONADISM: COMORBIDITIES AND LABORATORY CONFIRMATION

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ABSTRACT

The steady rise in life expectancy has brought mankind one step forward in the everlasting search for the fountain of youth, and yet, one step back when it comes to the quality of this longevity. Life after 60 brings not only a growing list of chronic conditions, but also the daunting state of comorbidities. And, although major diseases, such as hypertension and diabetes, are under the spotlight in regard to proper diagnosis and management, other, seemingly less prominent, age-related conditions, such as hypogonadism, fall well under the radar screen, especially when present as a comorbidity of a more threatening disease state.

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PREVALENCE

It is estimated that 20% of men 60 to 80 years of age have testosterone levels below the lower limit of normal and approximately 2 to 4 million men suffer from overt hypogonadism.^{1,2} Yet, despite the quite common prevalence of this condition, 95% of affected men go untreated. Factors, such as limited amount of literature on the topic and a reluctance among patients in reporting symptoms, appear to be largely responsible

for this disparity. Before discussing the different forms of hypogonadism and their causes, it's pertinent to understand the normal physiological process surrounding testosterone production.

HYPOTHALAMIC-PITUITARY COMPLEX

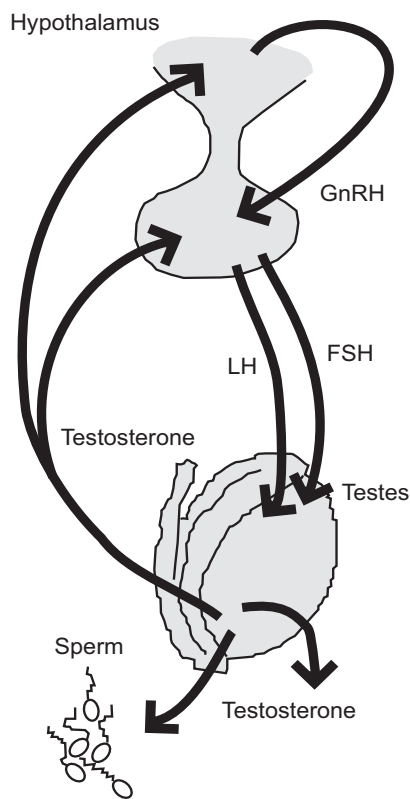
Testosterone, the main androgen in humans, is synthesized and secreted primarily by testicular Leydig cells. However, control over this process takes place at the hypothalamic-pituitary-gonadal axis (Figure) via a negative feedback mechanism. The hypothalamus periodically releases gonadotropin-releasing hormone (GnRH), which interacts with the pituitary gland by binding to the GnRH receptor on the gonadotrope surface and stimulating the synthesis and pulsatile secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Although FSH initiates spermatogenesis, LH acts on testicular Leydig cells to produce testosterone.³⁻⁷ Increasing concentrations of testosterone inhibit further secretion of GnRH through a negative feedback mechanism. Testosterone is important in maintaining normal sexual and reproductive function, skeletal growth, and muscle development. It is converted to dihydrotestosterone, a more potent androgen involved in facial/body hair growth, acne, and prostate development. Testosterone can also be converted by aromatase to estradiol, which plays a role in bone formation and breast tissue development, and is important for negative feedback regulation of several central endocrine processes.³⁻⁶

Testosterone is highly bound (60%) to sex-hormone-binding globulin (SHBG) and, to a lesser extent, other serum proteins, including albumin (38%). Only 2% exists unbound as free testosterone.⁸ Bioavailable testosterone refers to non-SHBG-bound forms (including free testosterone) and generally is considered to be the biologically active fraction. As

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Figure. Production and Regulation of Testosterone



FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

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one ages, the amount of SHBG increases, which means that more testosterone is bound and not biologically active.⁸ This results in progressively lower levels of active or bioavailable testosterone, which is associated with primary gonadal failure and hypothalamic-pituitary failure.⁸ Also with age, Leydig cells decrease, steroid hormone biosynthesis and blood supply to the gonads become impaired, and steroid output after administration of human chorionic gonadotropin is decreased.⁸

Low-testosterone states are associated with a syndrome in men (typically at an advanced age) called andropause, a term that is akin to menopause in women. The syndrome has also been referred to as male climacteric, viropause, low-testosterone syndrome, androgen deficiency in the aging male, partial androgen deficiency in the aging male, and aging-associated androgen deficiency.⁸ Growing evidence sug-

Table 1. Common Causes of Hypogonadism

Primary Hypogonadism (testicular failure)

Congenital causes:

- Klinefelter's syndrome
- Vanishing testis syndrome
- Fetal testicular loss
- Anorchia

Acquired causes:

- Obesity
- Severe systemic illness
- Castration
- Mumps orchitis
- Malnutrition
- Respiratory disorders
- Trauma

Secondary Hypogonadism (pituitary failure)

Congenital causes:

- Kallmann's syndrome
- Prader-Willi syndrome

Acquired causes:

- Pituitary adenoma
- Inflammatory disease (ie, Crohn's disease, ulcerative colitis, and rheumatoid arthritis)
- Respiratory diseases (ie, asthma and COPD)
- Metabolic syndrome/diabetes
- Other endocrine disorders (ie, hypothyroidism)

COPD = chronic obstructive pulmonary disease.

Adapted with permission from *Pharmacy Times*. Nov 2004:90.⁸

gests that age-related reduction in testosterone production is associated with a constellation of physical, sexual, and emotional symptoms brought about by a complex interaction of hormones, psychiatric situations, and physical factors. The complications range from decreased libido, impotence, decreased muscle mass, and fatigue to more concerning problems, such as increased risk of myocardial infarction and decreased bone mass in conjunction with osteoporosis.⁸ Earlier studies indicated that andropause was potentially related to coexisting conditions; however, more recent research supports the view that age-related decline in testicular function may occur with associated symptoms and often responds to testosterone replacement therapy.⁹ However, besides age, a number of other factors, such as hypothalamic-pituitary-gonadal axis defects, may induce hypogonadism (Table 1).

CAUSES OF HYPOGONADISM AND ASSOCIATED COMORBIDITIES

Hypogonadism is typically discerned as either primary or secondary, depending on the source of the dysfunction. The term primary (hypergonadotropic) hypogonadism refers to testicular disorders and is characterized by low serum testosterone levels, despite high levels of FSH and LH. Causes of primary hypogonadism may be congenital or acquired and may include genetic conditions (eg, Klinefelter syndrome and gonadal dysgenesis), anatomic defects, tumors, and alcohol abuse.¹⁰ Secondary (hypogonadotropic) or central hypogonadism involves deficient release of GnRH and is characterized by low-normal or low levels of FSH, LH, and testosterone. Similar to primary hypogonadism, secondary hypogonadism has congenital and acquired causes, but unlike primary hypogonadism, secondary hypogonadism often has a cause that can be treated.¹¹ Causes or manifestations of secondary hypogonadism may include hyperprolactinemia, GnRH deficiency, lesions in the hypothalamus or pituitary glands, and certain medications (Table 2). Common conditions that are important to recognize as either potential causes or consequences of hypogonadism include type 2 diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, cancer, cardiovascular disease, prostate disease, AIDS, morbid obesity, and depressive disorders.¹²

Diabetes and obesity are not only intertwined with each other, but the 2 conditions have also been widely associated with hypogonadism. Obesity in men can be accompanied by a significant decrease in testosterone levels. In moderate obesity, total testosterone levels may appear to be low because of the decrease in SHBG binding capacity. However, free testosterone is usually normal. Massively obese men may have true hypogonadotropic hypogonadism, including decreased free testosterone and total testosterone levels.¹³ It has been estimated that 20% of men with diabetes have a low serum testosterone level and 36% of men with diabetes older than 70 years of age have low testosterone levels.¹⁴ Type 2 DM is an established risk factor for the development of atherosclerotic vascular disease. Insulin resistance is the hallmark feature of type 2 diabetes and is also an important component of the metabolic syndrome. There is evidence to suggest that testosterone is an important regulator of insulin sensitivity in men. Observational studies have shown that

testosterone levels are not only low in men with diabetes, but they are also reduced in those with coronary artery disease and metabolic syndrome.¹⁵ In a recent study, hypogonadism was observed in 33% of men with type 2 DM, who had a mean body mass index of 33.4 kg/m², and a hemoglobin A_{1c} of 8.4%.¹⁶ Short-

Table 2. Drugs Affecting the Hypothalamic-Pituitary-Testicular Axis

Drugs that Inhibit Steroid Synthesis

Spironolactone
 Imidazole fungicides (ketoconazole, soconazole, miconazole, econazole, and clotrimazole)
 Aminoglutethimide
 Chemotherapeutic drugs (cyclophosphamide, melphalan, chlorambucil, busulfan, and procarbazine)
 Ethanol

Drugs that Inhibit Release of LH or FSH

GnRH agonists (eg, leuprolide)
 Estrogens
 Anabolic steroids
 Calcium channel blockers
 Reserpine
 Amiodarone
 ACE inhibitors
 Tricyclic antidepressants
 Dopamine (increase or decrease, depending on concentration)
 Antipsychotics
 Major tranquilizers
 Opioids
 Ethanol
 Isoniazide
 Penicillamine
 Corticosteroids

Drugs that Block the Androgen Receptor

Spironolactone
 Cimetidine
 Digoxin

Drugs that May Either Increase the Metabolism of Testosterone or Alter the Levels of SHBG

Anticonvulsants (ie, phenobarbital): increases SHBG and increases metabolism
 Other drugs that induce hepatic microsomal liver enzymes
 Insulin: decreases SHBG
 Thyroid hormone: increases SHBG

ACE = angiotensin-converting enzyme; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; SHBG = sex-hormone-binding globulin.

Adapted with permission from Plymate SR. Available at: http://merck.micromedex.com/index.asp?page=bpm_brief&article_id=CPM02EN318. Accessed June 7, 2006.²⁸

term interventional studies demonstrating that testosterone replacement therapy produces an improvement in insulin sensitivity have led researchers to suspect that hypotestosteronemia may have a role in the pathogenesis of insulin-resistant states and that androgen replacement therapy could potentially improve glycemic control in men with diabetes.¹⁶

For several years, various studies have been confirming the suspicion of an association between hypogonadism and rheumatoid/autoimmune diseases (RADs). In one trial, researchers found that men with rheumatoid arthritis had lower levels of bioavailable testosterone and a large proportion were considered to have central hypogonadism (as evidenced by low levels of LH).¹⁷ Another study found a high frequency of RADs, such as lupus erythematosus, dermatomyositis, rheumatoid arthritis, and ankylosing spondylitis, in a small group of patients with untreated hypogonadism and very low serum testosterone levels. The presence of RADs in these patients was independent of the etiology of their hypogonadism and was associated with marked gonadal failure.¹⁸

Some studies have indicated that low circulating levels of testosterone are common in males with COPD. One trial reported a 30% incidence of hypogonadism among these patients.¹⁹ Still, little is known about the actual prevalence, underlying causes, and functional consequences of hypogonadism in patients with COPD. The frequent use of systemic glucocorticosteroids in these individuals and the influence of the systemic inflammatory response have been suggested as contributing to low testosterone levels.²⁰ Researchers do recognize that glucocorticoid treatment appears to aggravate hypogonadism and they suggest implementing a therapeutic study using testosterone in patients with COPD who are receiving glucocorticoids.²¹

End-stage renal disease (ESRD) is often accompanied by marked hypothalamus-pituitary axis (HPA) dysfunction that is reversed by renal transplantation, but not hemodialysis.²² Approximately 50% of all males with ESRD complain of erectile dysfunction and decreased libido.²³ These patients typically have signs of primary and secondary hypogonadism, displaying low levels of free and total testosterone along with elevated levels of LH, FSH, and estradiol. Testosterone replacement in these individuals has been shown to benefit libido, bone mineral density, and red cell mass, all common complications of ESRD. However, it should be noted that testosterone is not eliminated through hemodialysis.²⁴

HIV infection and AIDS wasting are commonly associated with hypogonadism. Approximately 20% to 40% of HIV-positive men and 50% of men with AIDS are diagnosed with hypogonadism.²⁵ Several mechanisms appear to be involved in these cases. Direct viral infection of the testes may cause testicular failure in some instances. Some men with HIV infection and subnormal serum testosterone concentrations have inappropriately low serum concentrations of LH. This may be the result of conditions, such as malnutrition, opiate abuse, opportunistic infections, and megestrol acetate administration, all of which are known to cause secondary hypogonadism.²⁶ Other men with HIV infection lack known risk factors for secondary hypogonadism but have elevated serum concentrations of LH, indicating primary hypogonadism. Hypogonadism in HIV-infected men has been observed less commonly since the introduction of retroviral therapy.²⁷

A variety of medications from virtually all classes of drugs may have diverse effects on the HPA. Drugs may influence this system by altering gonadotropin release, inhibiting testosterone synthesis, altering testosterone transport by influencing SHBG production, modifying the metabolic clearance rate of testosterone, affecting mechanisms of feedback at the hypothalamus or pituitary, and interacting with the androgen receptor. Table 2 lists a few of the drugs from several classes that could inhibit testosterone at the receptor level, inhibit testosterone synthesis, or suppress gonadotropin release.²⁸

Chemotherapeutic drugs (especially alkylating agents) or radiation therapy to the inguinal lymph nodes often damages the seminiferous tubules and, less often, the Leydig cells. Radiation causes damage, despite shielding of the testes, because of radiation scatter. The degree of damage is usually proportionate to the radiation dose; in cases of less extensive treatment, the damage may be reversible.²⁹ The various treatments used to manage prostate cancer are very commonly associated with hypogonadism. Androgen suppression therapy with GnRH agonists (eg, leuprolide) can lead to severe and sustained secondary hypogonadism by suppressing GnRH via negative feedback mechanism.³⁰ Radiation therapy directed at the prostate bed can cause prominent and permanent testicular damage, resulting in primary hypogonadism.

Ketoconazole, in addition to other imidazole fungicides (soconazole, miconazole, econazole, and clotrimazole), are known to demonstrate a direct and

reversible inhibition of testosterone biosynthesis. However, metronidazole and levamisole do not appear to influence testosterone biosynthesis.³¹ Corticosteroid therapy is known to have a profound suppressive effect on serum testosterone levels, both at the hypothalamic-pituitary and testicular level. This effect may occur at 10-mg doses of prednisone; however, the decrease in testosterone is not seen with moderate doses of inhaled steroids.³²

Ethanol intoxication (in addition to cirrhosis) significantly affects testicular function—even acutely. In one of the mechanisms, ethanol has a higher affinity for alcohol dehydrogenase than for retinol, which prevents formation of retinoic acid. When this occurs, at a serum ethanol level of 0.10 mg/dL, testosterone production is decreased and the serum LH level increases.³³ These changes revert to normal soon after serum ethanol levels decline. Long-term ingestion of ethanol increases serum estradiol, resulting in decreased gonadotropin levels, serum testosterone, and SHBG—all of which decrease free testosterone levels.^{33,34} Other common offenders include anticonvulsants and other hepatic microsomal liver enzyme inducers, which are known to augment testosterone metabolism. GnRH agonists, estrogens, anabolic steroids, psychotropic medications, and post-transplant immunosuppressants all reduce gonadotropin secretion.³⁵ Opioids are also associated with androgen deficiency due to their inhibitory effects on the release of LH and FSH. In fact, the introduction and widespread use of controlled-release forms of opioids for chronic-pain management has contributed significantly to the commonality of drug-induced hypogonadism.¹¹

Having access to patients' medication profiles, pharmacists are undoubtedly the primary health professionals when it comes to medication management. Simply being aware of patients' drug therapy and concomitant conditions can place pharmacists in a unique position to increase detection of this under-recognized and undermanaged disorder.

LABORATORY CONFIRMATION

Detection of hypogonadism is often challenging. Although the clinical signs are readily identified in males who have not undergone puberty, they are far less apparent in men who have lost testicular function after reaching sexual maturity. This is largely because many testosterone-dependent physical features, such

as muscle mass, beard, and genital development, are maintained long after the onset of testicular failure. As a result, the currently accepted diagnostic criteria are both the presence of hypogonadal symptoms and laboratory evidence of a subnormal serum testosterone level.³⁵ The most common symptoms of testosterone deficiency in men can be nonspecific, including loss of libido, sexual dysfunction, fatigue, loss of stamina, and depressed mood. Because pharmacists are often the first healthcare providers to hear patient's symptoms, they can optimize detection of hypogonadism by routinely asking at-risk patients (older men with comorbidities, such as ESRD or diabetes) about symptoms, such as libido and stamina. Of course, it helps to be familiar with the patient prior to asking about such personal complaints.

Laboratory confirmation of hypogonadism requires the demonstration of a subnormal level of circulating testosterone. Because young and middle-aged men exhibit higher testosterone secretion in the morning than in the evening, total testosterone values are evaluated in the morning on at least 2 different days. Laboratory values consistently below the lower limit of normal (usually 200 ng/dL [6.9 nmol/L]) are considered confirmatory.³⁶ However, a number of men, particularly older individuals, who have true hypogonadism may have total testosterone values in the lower end of the normal range.³⁷ Because decreased sensitivity to androgens may occur in target organs, absolute serum levels of testosterone can sometimes be misleading. Also, the range is often not age-adjusted, which poses a dilemma because patients may have low-normal levels and yet display symptoms, which are reversed after androgen supplementation. This phenomenon suggests the possibility of "relative hypogonadism," in which normal levels are individualized for each.³⁸ Another reason to look beyond the numbers is the tendency for testosterone levels to vary throughout the course of the day. Frequent sampling of testosterone in a study of 20 healthy men revealed levels ranging from 105 to 1316 ng/dL (3.64–45.67 nmol/L).³⁷

Other instances where total testosterone may be within the normal range is in men with primary testicular disorders, such as Klinefelter's syndrome. Low production of testosterone and increased estradiol stimulate the 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. Essentially, if clinical findings indicate the presence of hypogonadism, yet testosterone levels are normal or borderline low, more extensive testing is indicated to establish a clearer diagnostic picture.⁹

Finally, if tests confirm testosterone deficiency, other pathologic causes of hypogonadism should be ruled out. Serum prolactin, thyroid-stimulating hormone, and gonadotropin levels should be measured. If the patient is hypothyroid, L-thyroxine replacement should be started. Low gonadotropin levels indicate central hypogonadism, and an elevated prolactin level may indicate the presence of a pituitary tumor. In both circumstances, magnetic resonance imaging of the pituitary is indicated.⁸

CONCLUSIONS

The relationship between hypogonadism and various comorbidities is a growing area of interest in medicine. Research efforts aimed at better understanding this relationship will not only provide more information on hypogonadism, but may also offer insight into the pathophysiologic factors involved in several major disease states. Detection of hypogonadism is another area that can be optimized with intervention. Because pharmacists are often at the forefront of patient access, they can help improve detection by being knowledgeable about the causes of hypogonadism, particularly with regard to implicated medications.

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