REVIEW ARTICLE

www.japtr.org

Male hypogonadism: Symptoms and treatment

Peeyush Kumar, Nitish Kumar, Devendra Singh Thakur, Ajay Patidar

SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur -495 009 (C.G), India

DOI: 10.4103/0110-5558.72420

J. Adv. Pharm. Tech. Res.

ABSTRACT

Male hypogonadism is a condition in which the body does not produce enough of the testosterone hormone; the hormone that plays a key role in masculine growth and development during puberty. There is a clear need to increase the awareness of hypogonadism throughout the medical profession, especially in primary care physicians who are usually the first port of call for the patient. Hypogonadism can significantly reduce the quality of life and has resulted in the loss of livelihood and separation of couples, leading to divorce. It is also important for doctors to recognize that testosterone is not just a sex hormone. There is an important research being published to demonstrate that testosterone may have key actions on metabolism, on the vasculature, and on brain function, in addition to its well-known effects on bone and body composition. This article has been used as an introduction for the need to develop sensitive and reliable assays for sex hormones and for symptoms and treatment of hypogonadism.

Key words: Male hypogonadism, pituitary, sex hormone, testosterone, testis

INTRODUCTION

Hypogonadism is a medical term for decreased functional activity of the gonads. The gonads (ovaries or testes) produce hormones (testosterone, estradiol, antimullerian hormone, progesterone, inhibin B, activin) and gametes (eggs or sperm).[1] Male hypogonadism is characterized by a deficiency in testosterone — a critical hormone for sexual, cognitive, and body function and development. Clinically low testosterone levels can lead to the absence of secondary sex characteristics, infertility, muscle wasting, and other abnormalities. Low testosterone levels may be due to testicular, hypothalamic, or pituitary abnormalities. In individuals who also present with clinical signs and symptoms, clinical guidelines recommend treatment with testosterone replacement therapy.

CLASSIFICATION OF MALE HYPOGONADISM

There are two basic types of hypogonadism that exist:
Primary: This type of hypogonadism — also known as primary testicular failure — originates from a problem in the testicles.
Secondary: This type of hypogonadism indicates a problem in the hypothalamus or the pituitary gland — parts of the brain that signal the testicles to produce testosterone. The hypothalamus produces the gonadotropin releasing hormone, which signals the pituitary gland to make the follicle-stimulating hormone (FSH) and luteinizing hormone. The luteinizing hormone then signals the testes to produce testosterone. Either type of hypogonadism may be caused by an inherited (congenital) trait or something that happens later in life (acquired), such as an injury or an infection.

Address for correspondence
Dr. Peeyush Kumar,
SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur - 495 009 (C.G), India.
E-mail: peeyushkumar037@gmail.com

Primary Hypogonadism

Common causes of primary hypogonadism include:
Klinefelter's Syndrome: This condition results from a congenital abnormality of the sex chromosomes, X and Y. A male normally has one X and one Y chromosome. In Klinefelter's syndrome, two or more X chromosomes are present in addition to one Y chromosome. The Y chromosome contains the genetic material that determines the sex of a child and the related development. The extra X chromosome that occurs in Klinefelter's syndrome causes abnormal development of the testicles, which in turn results in the underproduction of testosterone.

Undescended testicles

Before birth, the testicles develop inside the abdomen and normally move down into their permanent place in the scrotum. Sometimes, one or both of the testicles may not descend at birth. This condition often corrects itself within the first few years of life without treatment. If not corrected in early childhood, it may lead to malfunction of the testicles and reduced production of testosterone.

Mumps orchitis
If a mumps infection involving the testicles in addition to the salivary glands (mumps orchitis) occurs during adolescence or adulthood, long-term testicular damage may occur. This may affect normal testicular function and testosterone production.

Hemochromatosis
Too much iron in the blood can cause testicular failure or pituitary gland dysfunction, affecting testosterone production.

Injury to the Testicles
Because of their location outside the abdomen, the testicles are prone to injury. Damage to normally developed testicles can cause hypogonadism. Damage to one testicle may not impair testosterone production.

Cancer treatment
Chemotherapy or radiation therapy for the treatment of cancer can interfere with testosterone and sperm production. The effects of both treatments are often temporary, but permanent infertility may occur. Although many men regain their fertility within a few months after the treatment ends, preserving sperm before starting cancer therapy is an option that many men consider. Howell *et al*. reported that hypogonadism was seen in 30% of the men with cancer and 90% of these gentlemen had germinal epithelial failure.[2]

Normal aging
Older men generally have lower testosterone levels than younger men do. As men age, there's a slow and continuous decrease in testosterone production. The rate that testosterone declines varies greatly among men. As many as 30% of men older than 75 have a testosterone level that is below normal, according to the American Association of Clinical Endocrinologists. Whether or not treatment is necessary remains a matter of debate.[3]

Secondary Hypogonadism
In secondary hypogonadism, the testicles are normal, but function improperly due to a problem with the pituitary or hypothalamus. A number of conditions can cause secondary hypogonadism, including:

Kallmann syndrome
Abnormal development of the hypothalamus — the area of the brain that controls the secretion of pituitary hormones — can cause hypogonadism. This abnormality is also associated with the impaired development of the ability to smell (anosmia).

Pituitary disorders
An abnormality in the pituitary gland can impair the release of hormones from the pituitary gland to the testicles, affecting normal testosterone production. A pituitary tumor or other type of brain tumor located near the pituitary gland may cause testosterone or other hormone deficiencies. Also, the treatment for a brain tumor such as surgery or radiation therapy may impair pituitary function and cause hypogonadism.

Inflammatory disease
Certain inflammatory diseases such as sarcoidosis, Histiocytosis, and tuberculosis involve the hypothalmus and pituitary gland and can affect testosterone production, causing hypogonadism.

HIV/AIDS
This virus can cause low levels of testosterone by affecting the hypothalamus, the pituitary, and the testes.

Medications
The use of certain drugs, such as, opiate pain medications and some hormones, can affect testosterone production.[4]

Obesity
Being significantly overweight at any age may be linked to hypogonadism.

Stress-induced Hypogonadism
Stress, excessive physical activity, and weight loss have all been associated with hypogonadism. Some have attributed this to stress-induced hypercortisolism, which would suppress hypothalamic function.[5]

ROLE OF TESTOSTERONE

Throughout the male lifespan, testosterone plays a critical role in sexual, cognitive, and body development. During fetal development, testosterone aids in the determination of sex. The most visible effects of rising testosterone levels begin in the prepubertal stage. During this time, body odor develops, oiliness of the skin and hair increase, acne develops, accelerated growth spurts occur, and pubic, early facial, and axillary hair grows. In men, the pubertal effects include enlargement of the sebaceous glands, penis enlargement, increased libido, increased frequency of erections, increased muscle mass, deepening of voice, increased height, bone maturations, loss of scalp hair, and growth of facial, chest, leg, and axillary hair. Even as adults, the effects of testosterone are visible as libido, penile erections, aggression, and mental and physical energy.

Pathophysiology of Testosterone and Hypogonadism
The cerebral cortex — the layer of the brain often referred to as the gray matter — is the most highly developed portion of the human brain. This portion of the brain, encompassing about two-thirds of the brain mass, is responsible for the information processing in the brain. It is within this portion of the brain that testosterone production begins.

The cerebral cortex signals the hypothalamus to stimulate production of testosterone. To do this, the hypothalamus releases the gonadotropin-releasing hormone in a pulsatile fashion, which stimulates the pituitary gland — the portion of the brain responsible for hormones involved in the regulation of growth, thyroid function, blood pressure, and other essential body functions. Once stimulated by the gonadotropin-releasing hormone, the pituitary gland produces the follicle-stimulating hormone and the luteinizing hormone. Once released into the bloodstream, the luteinizing hormone triggers activity in the Leydig cells in the testes. In the Leydig cells, cholesterol is converted to testosterone. When the testosterone levels are sufficient, the pituitary gland slows the release of the luteinizing hormone via a negative feedback mechanism, thereby, slowing testosterone production. With such a complex process, many potential problems can lead to low testosterone levels. Any changes in the testicles, hypothalamus or pituitary gland can result in hypogonadism. Such changes can be congenital or acquired, temporary, or permanent.

Recent studies have found that testosterone production slowly decreases as a result of aging, although the rate of decline varies. Unlike women who experience a rapid decline in hormone levels during menopause, men experience a slow, continuous decline over time. The Baltimore Longitudinal Study of Aging reported that approximately 20% of men in their 60s and 50% of men in their 80s are hypogonadal.[6] The New Mexico Aging Process Study showed a decrease in serum testosterone of 110 ng/dL every 10 years.[7] As hormone levels decline slowly, this type of hypogonadism is sometimes referred to as the partial androgen deficiency of the aging male (PADAM). With the growing elderly population, the incidence of PADAM may increase over the next few decades.

Regardless of the age or comorbid conditions, obesity is associated with hypogonadism. The Baltimore Longitudinal Study of Aging found that testosterone decreased by 10 ng/dL per 1-kg/m^2 increase in body mass index.[6] Another study also showed reduced testosterone levels in men with increased total abdominal adiposity.[8] The proposed causes for the effects of obesity on testosterone level include increased clearance or aromatization of testosterone in the adipose tissue and increased formation of inflammatory cytokines, which hinder the secretion of the gonadotropin-releasing hormone.[9] Similar to the projections for an aging population, the increasing incidence of obesity may lead to an increased incidence of secondary hypogonadism. When the risk factors of obesity and age are removed, diabetes mellitus still remains an independent risk factor for hypogonadism. Although diabetes mellitus–related hypogonadism was previously thought to be associated with testicular failure, study results show one-third of diabetic men had low testosterone levels, but also had low pituitary hormone levels.[10] Population projections expect the number of cases of diabetes mellitus to rise from 171 million in 2000 to 366 million in 2030.[11] This drastic increase in cases will impact the prevalence of hypogonadism as well. Certain medications are shown to reduce testosterone production. Among the medications known to alter the hypothalamic-pituitary-gonadal axis are spironolactone, corticosteroids, ketoconazole, ethanol, anticonvulsants, immunosuppressants, opiates, psychotropic medications, and hormones.

Symptoms

Hypogonadism is characterized by serum testosterone levels < 300 ng/dL in combination with at least one clinical sign or symptom. Signs of hypogonadism include absence or regression of secondary sex characteristics, anemia, muscle wasting, reduced bone mass or bone mineral density, oligospermia, and abdominal adiposity. Symptoms of post pubescent hypogonadism include sexual dysfunction (erectile dysfunction, reduced libido, diminished penile sensation, difficulty attaining orgasm, and reduced ejaculate), reduced energy and stamina, depressed mood, increased irritability, difficulty concentrating, changes in cholesterol levels, anemia, osteoporosis, and hot flushes. In the prepubertal male, if treatment is not initiated, signs and symptoms include sparse body hair and delayed epiphyseal closure.

Testing

Early diagnosis and treatment can reduce risks associated with hypogonadism. Early detection in young boys can help to prevent problems due to delayed puberty. Early diagnosis in men helps protect against the development of osteoporosis and other conditions. The diagnosis of hypogonadism is based on symptoms and blood work, particularly on testosterone levels. Often the first step toward diagnosis is the Androgen Deficiency in Aging Male (ADAM) test — a 10 item questionnaire intended to identify men who exhibit signs of low testosterone. Testosterone levels vary throughout the day and are generally highest in the morning, so blood levels are typically drawn early in the morning. If low testosterone levels are confirmed, further testing is done, to identify if the cause is testicular, hypothalamic, or pituitary. These tests may include hormone testing, semen analysis, pituitary imaging, testicular biopsy, and genetic studies. Once the treatment starts, the patient may continue to have testosterone levels drawn to determine if the medication is helping to produce adequate testosterone levels.

TREATMENT OPTIONS

Testosterone replacement therapy is the primary treatment option for hypogonadism. Ideally, the therapy should provide physiological testosterone levels, typically in the range of 300 to 800 ng/dL. According to the guidelines from the American Association of Clinical Endocrinologists,[12] updated in 2002, the goals of therapy are to:

(1) Restore sexual function, libido, well-being, and behavior
(2) Produce and maintain virilization
(3) Optimize bone density and prevent osteoporosis
(4) In elderly men, possibly normalize growth hormone levels
(5) Potentially affect the risk of cardiovascular disease
(6) In cases of hypogonadotropic hypogonadism, restore fertility[13]

To achieve these goals, several testosterone delivery systems are currently available in the market. Clinical guidelines published in 2006, by the Endocrine Society, recommend reserving treatment for those patients with clinical symptoms, rather than for those with just low testosterone levels.

Transdermal Patch

Transdermal testosterone patches are available in India under the brand name Androderm. Transdermal patches deliver continuous levels of testosterone over a 24-hour period. Application site reactions account for the majority of adverse effects associated with transdermal patches, with elderly men proving particularly prone to skin irritation. Local reactions include pruritus, blistering under the patch, erythema, vesicle formation, indurations, and allergic contact dermatitis. Approximately 10% of the patients discontinue patch therapy due to skin reactions.[14] In one study, 60% of the subjects discontinued the patch between weeks four and eight due to skin irritation.[15] A small percentage of patients may also experience headache, depression, and gastrointestinal (GI) bleeding. Some patients report that the patch easily falls off and is difficult to remove from the package without good dexterity. Transdermal patches are more expensive than injections, but the convenience of use and maintenance of normal diurnal testosterone levels are advantageous. Some patients report that the patch is noisy and therefore they feel stigmatized by its presence.

Topical Gel

Currently, two topical testosterone gels — Androgel and Testim, are available in India. Application in the morning allows for testosterone concentrations that follow the normal circadian pattern. Topical testosterone gels also provide longer-lasting elevations in serum testosterone, compared to transdermal patches.[16] Similar to patches, testosterone delivered via gels does not undergo first-pass metabolism. Adverse effects associated with therapy include headache, hot flushes, insomnia, increased blood pressure, acne, emotional labiality, and nervousness. Although application site reactions occur, skin irritation is approximately 10 times less frequent with gels than with transdermal patches.[17] Advantages associated with topical gel include maintenance of normal diurnal testosterone levels and documented increases in bone density.[18] Potential problems associated with the gel are the potential for transfer of the gel from person to person and the cost.

Buccal Tablets

Buccal testosterone tablets, marketed as Striant, release testosterone in a pulsatile manner, are similar to endogenous secretion. With this route, the peak testosterone levels are rapidly achieved and a steady state is reached by the second dose following twice-daily dosing. Similar to gel and transdermal products, buccal administration avoids first-pass metabolism. Food and beverage do not alter drug absorption. Although well-tolerated, transient gum irritation and a bitter taste are the chief adverse effects associated with this route. Gum irritation tends to resolve within the first week. Other adverse effects include dry mouth, toothache, and stomatitis. Some patients find the buccal tablet uncomfortable and report concern about the tablet shifting in the mouth while talking.

Implantable Pellet

Testosterone has also been formulated into an implantable pellet, marketed as Testopel. This surgically implanted pellet slowly releases testosterone via zero-order kinetics over many months (up to six months), although peak testosterone levels are achieved within 30 minutes. The chief complaints associated with this formulation are pellet extrusion, minor bleeding, and fibrosis at the site.

Intramuscular Injections

Intramuscular formulations are also available, sold as Depo-Testosterone (testosterone cypionate) and Delatestryl (testosterone enanthate). The testosterone is suspended in oil to prolong absorption. Peak levels occur within 72 hours of administration, but intramuscular administration is associated with the most variable pharmacokinetics of all the formulations. In the first few days after administration, supraphysiological testosterone levels are achieved, followed by subphysiological levels near the end of the dosing interval. Such fluctuations, are often associated with wide variations in mood, energy, and sexual function, and prove distressing to many patients. To reduce fluctuations, lower doses and shorter dosing intervals (two weeks) are often used. Injection site reactions are also common, but are rarely the reason for discontinuation of therapy. Despite the fluctuations in testosterone levels, intramuscular injections provide a cost-effective option and the convenience of two- to four-week dosing intervals. Disadvantages associated with injections include visits to the doctor's office, visits for dose administration, and lack of physiological testosterone patterns.

Oral Tablets

Although not currently available in the India, oral testosterone tablets, under the brand name Andriol, are

available in other countries. In India, Android and Testroid — both methyl testosterone products are FDA approved oral formulations. Although relatively inexpensive, oral products undergo extensive first-pass metabolism and therefore require multiple daily doses. Oral products are associated with elevated liver enzymes, GI intolerance, acne, and gynecomastia. Regardless of the treatment option, patients should be aware of the risks associated with testosterone therapy, including:

- Worsening of the prostatic hypertrophy
- Increased risk of prostate cancer
- Lower sperm count with large doses
- Swelling of ankles, feet, or body, with or without heart failure
- Gynecomastia
- Sleep apnea
- Blood clots

Patients should be educated on the signs and symptoms of these adverse effects and instructed to notify their doctor if any of these occur.

CONCLUSION

Hypogonadism affects men of all ages, either through congenital or acquired causes. For patients who have clinical symptoms associated with their low testosterone levels, treatment is essential for the prevention of sexual, cognitive, and bodily changes. A variety of treatment options are available, utilizing different dosage formulations, and providing patients with choices that best meet their needs. Therefore, there is a clear need to increase the awareness of hypogonadism throughout the medical profession, especially in primary care physicians who are usually the first port of call for the patient.

In summary, there is a need for doctors to have an awareness of hypogonadism as a common clinical condition. Key triggers for the physician to consider investigating for hypogonadism are reduced libido, fatigue, osteoporosis and fractures, and erectile dysfunction.

REFERENCES

1. Yialamas MA, Hayes FJ. Androgens and the ageing male and female. J Clin Endocrinol Metab 2003;17:223-36.
2. Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: Evidence of leydig cell insufficiency. J Clin Oncol 1999;17:1493-8.
3. Harman SM. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31.
4. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain 2002;3:377-84.
5. Cumming DC, Quigley ME, Yen SS. Acute suppression of circulating testosterone levels by cortisol in men. J Clin Endocrinol Metab 1983;57:671-3.
6. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31.
7. Morley JE, Kaiser FE, Perry HM. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 1997;46:410-3.
8. Haffner SM, Valdez RA, Stern MP, Katz MS. Obesity, body fat distribution and sex hormones in men. Int J Obes Relat Metab Disord 1993;17:643-9.
9. Zumoff B, Strain GW, Miller LK. Plasma free and non-sex-hormone-binding globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. J Clin Endocrinol Metab 1990;71:929-31.
10. Dhindsa S, Prabhaker S, Sethi M, Bandyopadhyay A, Chaudhari A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004;89:5462-8.
11. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
12. AACE Hypogonadism Task Force. Medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients -2002 updated. Endocr Pract 2002;8:434-56.
13. Bhasin S, Cunningham GR, Hayes FJ. Testosterone therapy in adult men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995-2010.
14. Jordan JR. Allergy and topical irritation associated with transdermal testosterone administration: A comparison of scrotal and nonscrotal transdermal systems. Am J Contact Dermatol 1997;8:108-13.
15. Parker S, Armitage M. Experience with transdermal testosterone replacement therapy for hypogonadal men. Clin Endocrinol (Oxf) 1999;50:57-62.
16. Swerdloff RS, Wang C, Cunningham G. Long-term pharmacokinetics of transdermal testosterone gal in hypogonadal men. J Clin Endocrinol Metab 2000;85:4500-10.
17. Wang C, Swedloff RS, Iranmanesh A.Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypgonadal men. J Clin Endocrinol Metab 2000;85:2839-53.
18. Wang C, Swerdloff RS, Iranmanesh A. Effects of transdermal testosterone gel on bone turnover makers and bone mineral density in hypogonadal men. Clin Endocrinol (Oxf) 2001;54:739-50.

Source of Support: Nil, **Conflict of Interest:** Nil.