



A Systematic Review On Testicular Failure/Male Hypogonadism

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Abstract: Testicular failure or male hypogonadism is an uncommon disorder in which the body does not synthesized enough of the hormone testosterone, which is important for male growth and development throughout puberty, or enough sperm, or both. This paper will review the symptoms, cause, diagnosis and possible management of the condition by modern science and herbs.

Index Terms - Testicular failure, testosterone, herbs, management

1 INTRODUCTION

Testicular failure, also well-known as primary hypogonadism, is an unusual condition that is characterized by the lack of ability of the testicles to produce sperm and testosterone. Decreased testosterone, resulting in delayed puberty, reproductive unfitness, or both. The diagnosis of testicular failure is done via measurement of serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) and by stimulation tests with human chorionic gonadotropin (hCG). Many factors have been claimed as causes of the condition, which give rise to a wide-ranging array of signs and indications. These factors can occasionally make the diagnosis as well as treatment/management of testicular failure a challenging problem (Ferri FF, 2020).

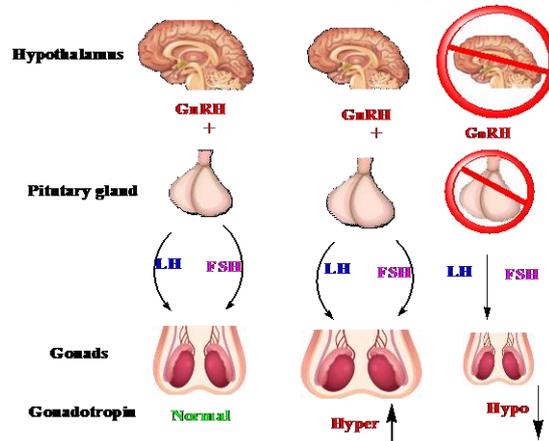
2 CAUSES

Male hypogonadism means the testicles don't produce an adequate amount of the male sex hormone-Testosterone. Scientists divide this condition into two parts.

- **Primary:** This type of hypogonadism also known as primary testicular failure initiates from a problem in the testicles. It may result in endocrine failure, foremost to testosterone insufficiency or exocrine failure causing weakened spermatogenesis and later male infertility.
- **Secondary:** This type of hypogonadism indicates a problem in the hypothalamus or the pituitary gland that signals the testicles to produce testosterone.

The hypothalamus produces gonadotropin-releasing hormone, which signals the pituitary gland to make a follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Luteinizing hormone then signals the testes to produce testosterone (AskMayoExpert, 2018).

Figure 1 Male hypogonadism



Both types of hypogonadism can be caused by a congenital trait or something that happens later in life (acquired), such as an injury or an infection. At times, primary and secondary hypogonadism arise together.

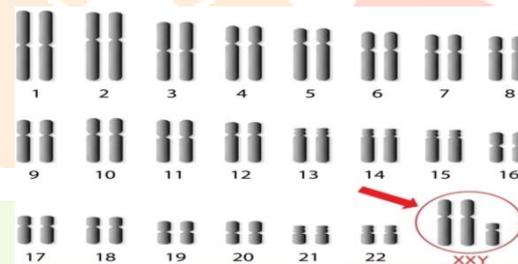
2.1 Primary Hypogonadism

Common causes of primary hypogonadism include:

2.2 Klinefelter syndrome

This condition results from a congenital defect of the sex chromosomes, X and Y. A male usually has one X and one Y chromosome. In Klinefelter syndrome, two or more X chromosomes are present in addition to one Y chromosome.

Figure 2 Congenital defect of the sex chromosomes

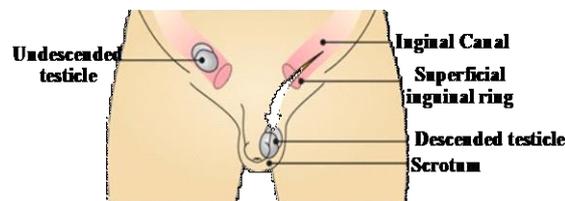


The Y chromosome contains the genetic material that determines the sex of a child and associated development. The extra X chromosome that occurs in Klinefelter syndrome causes nonstandard development of the testicles, which results in the underproduction of testosterone.

2.1.2 Undescended testicles

Before birth, the testicles develop inside the abdomen and normally move down into their long-lasting place in the scrotum. Sometimes one or both of the testicles aren't dropping away at birth (Sargis RM et al., 2018).

Figure 3 Undescended testicles



This condition often modifies itself within the first few years of life without treatment. If not corrected in the initial stage, it can lead to failure of the testicles and reduced production of testosterone.

2.1.3 Mumps orchitis

The mumps infection involving the gonads that occur during puberty or maturity can damage the gonads, affecting the role of the testicles and testosterone production.

2.1.4 Hemochromatosis

Too much iron in the blood can cause testicular failure or pituitary gland dysfunction, results in low production of testosterone.

2.1.5 Injury to the testicles

Testicles are outside the abdomen, they are prone to injury. Damage to normally developed testicles can cause hypogonadism. But the damage to one testicle might not harm total testosterone production.

2.1.6 Treatment of cancer

Chemo or radiation therapy for the treatment of cancer can restrict testosterone and sperm production. The effects of both treatments often are short-term, but everlasting infertility may occur. Although many men recover their fertility within a few months after treatment, preserving sperm before starting cancer therapy is an option for men (Gardner DG et al., 2019).

2.2 Secondary hypogonadism

In secondary hypogonadism or T. failure, the testicles are normal but don't function well due to disbalance in pituitary or hypothalamus messenger signaling. Several conditions are also responsible for secondary hypogonadism, including:

2.2.1 Kallmann's syndrome

It is a situation that causes hypogonadotropic hypogonadism and anosmia and deuteranopia. Hypogonadotropic hypogonadism disturbs the production of the hormones desired for sexual development. It is a birth defect that occurs due to a deficiency of GnRH. Kallmann's syndrome is often diagnosed at the time of puberty due to undeveloped sexual parts i.e. undescended testicles or a small penis in the male. Untreated, adult males may include reduced bone density and muscle mass; small testicles; erectile dysfunction; Low libido; and infertility (Dodé C., et al. 2009).

2.2.2 Hypophysis disorders

An abnormality in the pituitary gland can impair the release of hormones from the gland to the testicles, affecting normal testosterone production due to drugs, infectious hypophysis lesions, hyperprolactinemia, encephalic injury, pituitary/brain radiation therapy or surgery, very tiring exercise, alcoholism, or illicit drug intake, and systemic diseases like hemochromatosis/ Iron overload, sarcoidosis, and Eosinophilic granuloma (Fraietta, R., et al. 2013).

2.2.3 Inflammatory disease

2.2.3.1 Sarcoidosis: Sarcoidosis affects the lungs, skin, liver, spleen, lymph nodes, upper respiratory tract, heart, and nervous system. Due to inflammation in the limbic system, it affects the hormone signaling brane to gonads that result in a low level of testosterone, which leads the testicular failure (Rashi Jain et al., 2020).

2.2.4 Histiocytosis: Histiocytoses involve a group of various proliferative disorders characterized by the accumulation and infiltration of variable numbers of monocytes, macrophages, and dendritic cells in the affected tissues. Langerhans cell histiocytosis is uncommon cancer that initiates in langerhans cell histiocytosis cells. LCH cells are a type of dendritic cell that encounters foreign substances (Kurtulmus N., et al. 2015).

LCH can affect any organ such as the lungs, liver, brain, spleen, or lymph nodes. When it affects the brain a disbalance of hormone occur which may affect the sex hormone production and sex organs (Eberhard Nieschlag., et al., 2009)

2.2.5 Tuberculosis: The tuberculous infection of the master gland, sellar region, and genitals is characterized by the existence of a critical or long-lasting inflammatory reaction (Swelling, irritation, and pain in the testicles) that can affect testosterone production that results in delayed poverty and undeveloped organs (Dulce Bonifacio-Delgadillo et al., 2014).

2.2.6 HIV/AIDS: Secondary hypogonadism occurs in HIV-infected men due to deficiency of nutrition, severe infection, an AIDS-related wound, pituitary dysfunction (tumor, hyperprolactinemia) cause androgen deficiency that results in loss of hair, decrease in strength and muscle mass, increase in body fat, low sex drive, erectile dysfunction, testicular atrophy, infertility, and sometimes gynecomastia (Gomes A. C., et al., 2017).

2.2.7 Medications: Taking medication like leptin, opioids (codeine, Dihydrocodeine, morphine, oxycodone, methadone, fentanyl, hydromorphone, etc.) ghrelin, and high-dose chemotherapeutic agents (cyclophosphamide, busulphan, carmustine, lomustine, carboplatin, mercaptopurine, vinblastine, etc.), hormones eg. Cortisol for the treatment and management of medical conditions are also responsible for low testosterone production and secondary hypogonadism or T. failure (Burney B. O., et al., 2012, Mitchell R.T., et al., 2017, Brownlee K. K., et al., 2005).

2.2.8 Obesity: Obesity at any age causes a rise in levels of leptin, insulin, proinflammatory cytokines, and estrogen can cause functional hypogonadotropic hypogonadism with the defect present at the level of the hypothalamic GnRH neurons (Fernandez C. J., et al. 2019).

2.2.9 Age: Male hypogonadism becomes more common with increasing age due to dropping in total serum testosterone concentration, enhancement in sex hormone-binding globulin concentration, and dropping in free testosterone. With age SHBG (level increase) binding more testosterone and less free testosterone available to act on target tissues that result in low libido, low bone density, decreased energy, depressed mood, reduction in muscle strength and bulk, etc. (Stanworth R. D., & Jones, T. H. et al. 2008).

2 COMPLICATIONS

The complications of untreated hypogonadism/ T. failure depending on the stage of life i.e. fetal development, puberty or adulthood.

Complications might be-

- Undeveloped genitalia
- Gynecomastia
- Infertility
- Erectile dysfunction
- Lack of libido

- Osteoporosis
- Poor self-image (Tang C., et al. 2020).

4 SYMPTOMS

Hypogonadism can begin during gestational age, before puberty, or during adulthood. Signs and symptoms depend on the condition.

4.1 Gestational age

If the body doesn't produce an adequate amount of testosterone during fetal development, the result may be impaired development of the external sex organs. A child who is genetically male may be born with ambiguous genitals or underdeveloped male genitals.

4.2 Before puberty

It can delay the normal development of the body. It can be interrupted:

- Development of muscle mass
- Voice deepening
- Growth of body and facial hair
- Growth of the penis and testicles
- It may cause unnecessary growth of the arms and legs
- Gynecomastia (Ferri FF., 2020).

4.3 Adulthood

In adults, T. failure can modify certain masculine physical characteristics and impair normal reproductive activities. Initial signs and symptoms might include:

- Reduced sex drive
- Reduced energy
- Sadness

Signs and symptoms: without management

- Decrease in hair growth on the face and body
- Decrease in muscle mass
- Hot flashes
- Erectile dysfunction
- Infertility
- Gynecomastia
- Osteoporosis
- Low level of testosterone results in poor mental health
- Lack of concentration (Khera M., et al. 2016)

5 DIAGNOSES

Timely diagnosis in boys can help prevent complications from delayed puberty. This offers better protection against osteoporosis and other related conditions.

5.1 Physical examination- The development of sexual characters can be examined through a physical exam for pubic hair, muscle mass and size of testes is consistent with age.

5.2 Blood test- The level of testosterone can be measured through a blood serum test if any symptom of hypogonadism is observed in Physical examination. If results revealed a low testosterone level in the blood, to know the reason further tests for testicular disorder or a pituitary abnormality can be done. (Carnegie C. 2004).

5.3 Semen analysis- Semen analysis should be done in boys and men who are suffering from T. failure. Generally, sperm count, morphology, and motility of sperm is observed during analysis.

5.4 Pituitary imaging- Pituitary MRI and CT scans in men with isolated hypogonadotropic hypogonadism have LH < 4 Iu/l. The presence of low gonadotrophins indicates undesirable testosterone deficiency (Fraietta R., et al. 2013, Hirsch D., et al. 2014).

5.5 Genetic studies- Genetic testing involves a test for DNA, the chemical database that carries instructions for body functions. Genetic testing can disclose mutations in genes that may responsible for that type of medical condition. When results are not favorable the genome sequencing is done. It is a complex procedure for analyzing a sample of DNA taken from blood. Every person has a unique genome, made up of DNA. it can support identify genetic variants that may relate to health. This testing is usually partial to just looking at the protein-encoding parts of DNA named the exome (Xu C., et al. 2017, Kim J., et al. 2018).

5.6 Testicular biopsy- A diagnostic testicular biopsy may be performed in men with azoospermia, normal testicular volume, and normal reproductive hormones to differentiate between obstructive and non-obstructive azoospermia. A biopsy may show CIS of the testis, the precursor of a testicular tumor. Furthermore, in men with signs of testicular dysgenesis on ultrasound, such as an inhomogeneous testicular design and testicular microlithiasis (Dohle G. R., et al. 2012).

6 THERAPIES AND MANAGEMENT OF TESTICULAR FAILURE

Typically for the treatment of testicular failure, testosterone replacement therapy is suggested to maintain an adequate concentration of testosterone in the blood. The adequate concentration of testosterone in the blood can help counter the signs and symptoms of male testicular failure/hypogonadism. The benefits are observed with, testosterone replacement therapy, such as an increase in libido, increase in energy level, positive effects on bone density, strength, and muscle mass, etc. (Osterberg E. C., et al. 2014).

Oral testosterone preparations have not been used for the treatment of t. failure/hypogonadism because oral preparations can cause severe liver complications. And they don't keep testosterone levels steady.

The FDA approved an oral testosterone replacement preparation (testosterone undecanoate) that is absorbed by the lymphatic system. It might avoid liver complications as compared to other oral forms. Other preparations are available such as gel, solutions, nasal spray, buccal tablets, implantable pellets containing testosterone, transdermal patch, parental: testosterone cypionate (IM), and testosterone enanthate (IM) testosterone undecanoate (IM) (Shoskes J. J., et al. 2016).

6.1 Treatment for postponed puberty

Treatment of postponed puberty in boys depends on the basic cause. Testosterone supplementation (injection) can stimulate puberty and help in the development of secondary sex characteristics, such as improved muscle mass, increase the growth of facial and pubic hair, and growth of the penis (Tang C. et al., 2020).

6.2 Herbs for management of T. failure

6.2.1 *Tribulus terrestris* (Zygophyllaceae)

It is an annual plant, widely distributed everywhere in the world. It is adapted to grow in dry weather localities in which rare other plants can survive. It has long been used as a folk medicine in China and Indian for the treatment of a lot of complaints and also claimed to improve sexual functions in man. The whole plant extract contains a steroidal saponin compound called protodioscin which has an aphrodisiac property (Gauthaman K. et al. 2003, Cibin F. W. S. et al., 2018).

6.2.2 *Epimedium sagittatum* (Berberidaceae)

It is an ornamental herb and also known as Epimedium barrenwort, bishop's hat, fairy wings, horny goat weed, or yin yang huo. It is used in traditional Chinese medicine to stimulate male and female hormones. *Epimedium sagittatum* extract contains a prenylated flavonol glycoside called icariin, that blocks phosphodiesterase type 5 associated with erectile dysfunction (Dell'Agli M. et al., 2008, Zhao H. et al., 2020).

6.2.3 *Pausinystalia johimbe* (Rubiaceae)

It is an evergreen tree commonly known as yohimbe, found in western and central Africa. Yohimbe extracts have been used in traditional medicine as an aphrodisiac and dietary supplement. Its bark contains an indole alkaloid called yohimbine that is widely used as therapy for erectile dysfunction (Yan J. et al., 2000).

6.2.4 Ginseng

It is the root of the perennial herbs of *Panax quinquefolium*/*Panax ginseng*. It is used as traditional Chinese medical practices to treat sexual dysfunction as well as to enhance sexual behavior. Ginseng having a series of tetracyclic triterpenoid saponins (ginsenosides) as active ingredients. It has reputed as an aphrodisiac due to ginsenosides VII-X (Nocerino E. et al., 2000, Leung K. W. et al., 2013).

6.2.5 *Withania somnifera* (Solanaceae)

It is one of the chief herbs in Ayurveda known commonly as ashwagandha, Indian ginseng, poison gooseberry, or winter cherry. Whole-plant extract reduces lipid peroxidation and protein carbonyl concentration; improve sperm quality and seminal plasma levels in infertile males (Mahdi A. A. et al., 2011, Durg S. et al., 2018).

6.2.6 *Mucuna pruriens* (Fabaceae)

Alkaloids generated from *Mucuna pruriens* seeds, according to Sachin Saksena and V.K. Dixit (1987) may increase testosterone levels in the seminiferous tubules, with effects on pituitary function or Leydig cells, which store testosterone for gonadal function regulation. *Mucuna pruriens* was proven in a study to effectively recover spermatogenic loss caused by ethinyl estradiol treatment in male rats, and the herb's therapeutic effects were mediated by reduced ROS, apoptotic regulation, and an increase in the number of germ cells. L-DOPA, the main component of *Mucuna pruriens*, is largely responsible for its pro-spermatogenic characteristics (Singh et al., 2013).

Suresh et al. (2012) found that *Mucuna pruriens* seed extract improved sexual potency and behaviour, libido, sperm parameters, and endocrine levels significantly. In infertile men, *Mucuna pruriens* increases testosterone, LH, dopamine, adrenaline, and noradrenaline levels while decreasing FSH and PRL levels. *Mucuna pruriens* treatment of infertile men improves steroidogenesis and sperm quality (Shukla et al., 2008).

6.2.7 Shilajit (Asphaltum, mineral pitch)

Shilajit was tested in healthy volunteers aged 45 to 55 years old in a randomised, double-blind, placebo-controlled clinical research at a dose of 250 mg twice a day for its influence on male androgenic hormone, testosterone. Shilajit treatment for 90 days increased total testosterone, free testosterone, and dehydroepiandrosterone (DHEAS) levels significantly ($P < 0.05$) when compared to placebo. The levels of gonadotropic hormones (LH and FSH) were stable (Pandit et al., 2016).

6.2.8 *Curculigo orchoides* (Hyoxidaceae)

The effect of an ethanolic extract of rhizomes on sexual behaviour in rats was investigated in this study. The effects of 100 mg/kg of extract on sexual behaviour were determined by measuring measures such as penile erection, mating performance, mount frequency, and mount delay. Weight gains in reproductive organs also indicated a strong anabolic and spermatogenic impact. The medication had a significant impact on the animals' sexual behaviour, as evidenced by a decrease in mount latency, an increase in mount frequency, and increased attractability to females. In the treated group, the penile erection index was likewise increased (Chauhan et al., 2007).

6.2.9 *Cynomorium coccineum* (Cynomoraceae)

Cynomorium coccineum is a parasitic plant with no leaves and no chlorophyll. This herb's aqueous extract has been proven to improve sperm count, percentage of viable sperm, and sperm motility, decrease the number of aberrant sperm, and increase spermatogenesis (Abd El-Rahman et al., 1999).

6.2.10 *Chlorophytum borivilianum* (Asparagaceae)

The goal of this study was to see how the water soluble extract of *Chlorophytum borivilianum* root tubers affected sperm and testosterone levels in healthy adult males. The study was intended as a randomised, double-blind, placebo-controlled trial on volunteers aged 20 to 40 years old who were registered at the outpatient department (OPD). Water extracts of *Chlorophytum borivilianum* and placebo were given in two divided dosages of 500 mg to participants in groups A and B for 12 weeks. Semen (Volume, Liquefaction Time, Sperm Count, Sperm Motility) and Serum Testosterone levels were used to make the assessment. In comparison to the Placebo, there was a highly significant improvement in the aforesaid parameters after administration of *Chlorophytum borivilianum* extract (Rath et al., 2013).

7 CONCLUSIONS

Male T. failure is a uncommon condition of male reproductive system but it affects the self-image and relationships. Counseling with the medical practitioner about the causes, diagnosis and current status of condition or family counseling may improve the confidence and reduce anxiety. According to the researches herbs are the best option for the management of testicular failure and related conditions.

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