Introduction

Testicular failure or hypogonadism in a male may be defined as a clinical syndrome that results from a decrease in either of the two major functions of the testes i.e. sperm production or testosterone production.

When these abnormalities result from a disease of testes it is called primary hypogonadism. If the pituitary or the hypothalamus is the source of dysfunction, then the disease is known as secondary hypogonadism.

Measurement of LH and FSH help to distinguish between these two forms of hypogonadism. In primary hypogonadism, sperm count and total testosterone (T) are decreased, and the resultant loss of negative feedback leads to elevated LH and FSH. In secondary hypogonadism, sperm count and total testosterone (T) are also low, but LH and FSH are low or normal.

### Causes of hypogonadotrophic hypogonadism

<table>
<thead>
<tr>
<th>Tumors:</th>
<th>Miscellaneous causes involving pituitary/hypothalamic area</th>
<th>Miscellaneous Acquired Disorders</th>
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<tbody>
<tr>
<td>• Cranioopharyngioma</td>
<td>• Langerhans histiocytosis</td>
<td>• AIDS</td>
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<td>• Germioma</td>
<td>• Post infectious lesions of the CNS</td>
<td>• Chronic systemic diseases and malnutrition like chronic renal disease, Cirrhosis, Chronic lung disease, critical illness</td>
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<td>• Other germ cell tumors</td>
<td>• Vascular abnormalities of the CNS</td>
<td>• Strenuous exercise induced hypogonadism</td>
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<td>• Hypothalamic and optic glioma</td>
<td>• Radiation therapy</td>
<td>• Psychogenic hypogonadism</td>
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<td>• Astrocytoma</td>
<td>• Congential abnormalities (Especially associated with craniofacial abnormalities)</td>
<td>• Hyperprolactinemia</td>
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<td>• Pituitary Tumors</td>
<td>• Head Trauma</td>
<td>• Cushing syndrome</td>
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<td></td>
<td>• CNS Surgery</td>
<td>• HIV Infection / AIDS</td>
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<td></td>
<td>• Morbid Obesity</td>
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<td>• Type II Diabetes Mellitus</td>
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<td></td>
<td></td>
<td>• Medications – Chronic Glucocorticoids, Heavy psychotropic medications resulting in Hyperprolactinemia, anabolic steroids, Ketoconazole use</td>
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<td>• Chronic opioids use, Methadone, Heroin, Marijuana</td>
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<td></td>
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<td>• Trauma to Pituitary gland and Hemorrhage in Patient</td>
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### Symptoms

First thing is to differentiate between constitutional delay in puberty and hypogonadism. There is family history of delay in puberty, in constitutional delay of puberty. This will clinch the diagnosis.

Symptoms depend on the age when testicular failure develops, either before or after puberty. Symptoms may include:

- Decrease in height
- Enlarged breast
- Anosmia
- Infertility
- Loss of muscle mass
- Loss of armpit or public hair
- Loss of libido
- Slow development or lack of secondary male sex characteristics (hair growth, scrotum enlargement, penis enlargement, voice changes)
- If men don't need to shave often

**Arrested puberty in the presence of gynaecomastia suggests gonadal failure and Klinefelter syndrome should be ruled out in such case**

If the disorder begins after puberty then sexual dysfunction, fatigue, difficulty in concentration, hot flushes, anemia, osteoporosis, breast development can occur.
Signs and symptoms suggesting prepubertal-onset hypogonadism.

<table>
<thead>
<tr>
<th>Small testes</th>
<th>Eunuchoid habitus</th>
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<tbody>
<tr>
<td>Cryptorchidism</td>
<td>Sparse body hair/facial hair</td>
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<tr>
<td>Gynaecomastia</td>
<td>Infertility</td>
</tr>
<tr>
<td>High-pitched voice</td>
<td>Low bone mass</td>
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<tr>
<td>Unclosed epiphyses</td>
<td>Sarcopenia</td>
</tr>
<tr>
<td>Linear growth into adulthood</td>
<td>Reduced sexual desire/activity</td>
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</table>

**On Physical examination**

- Decreased height
- Enlarged breast
- Loss of Muscle mass
- Loss of armpit or pubic hair (Staging to be done using Tanners criteria)
- Loss of sense of smell
- Size of penis – Microphallus
- Presence of one or both testes
- Position of testes in scrotum
- Size of testes
- Consistency of testes
- Abnormal mass in testes or scrotum
- Look for hypospadias
- Low bone mineral density and fractures (Assess by dual radiographic absorptiometry)

**Investigations**

- Low testosterone levels
- High Prolactin levels
- FSH and LH
- Semen Analysis, Urine analysis
- Thyroid Function test
- Karyotyping as indicated
- WBC, ESR, Metabolic Panel
- Celiac Screening
- USG of testes, Testicular biopsy

Anosmia and Microphallus suggest Klinefelter syndrome or pan hypopituitarism

In post pubertal males, morning serum testosterone should be done. Testosterone levels on two Occasions should be measured. Free testosterone done if total testosterone is at lower level than normal.
• MRI of pelvis done to rule out defects of testes and genitals
• MRI of Brain to look for pituitary defects
• Bone age determination
• ACTH stimulation test to look for adrenal hyperplasia
• Administer HCG and look for testosterone levels

Treatment and Management

First, treat the underlying cause, do surgery where required. Patients with hypogonadism are treated with sex steroids replacement. The goals of treatment are

• To promote the development of and maintain secondary sex character and sexual function.
• To build and sustain normal muscle and bone mass.
• To assist in proper psychosocial adjustment of adolescents with hypogonadism.
• Infertility can be treated in consultation with endocrinologist. LHRH or gonadotropins therapy can induce fertility in people with hypogonadotrophic hypogonadism.

Medical care

• In Pre-pubertal patients with hypogonadism, treatment is directed at initiating pubertal development at appropriate age
• Take into account, psychological needs, current growth and growth potential
• Testosterone used in males.
• Testosterone enanthate injections 50 mg monthly, increasing every 15 days up to 200-250 mg every 2 weeks, which is a typical adult replacement.
• Adult replacement dose can be adjusted to maintain serum testosterone levels in normal adult range.
• Sex Steroid (testosterone) replacement ensures development of secondary Sexual characteristics and maintain sexual function.
• In Patients with Hypergonadotrophic hypogonadism fertility is not possible.
• In Patients with hypogonadotrophic hypogonadism fertility is possible.
• Therapy with testosterone does not confer fertility or stimulate testicular growth and spermatogenesis.
• Initiate and maintain virilisation with testosterone
• When fertility is desired, testosterone is stopped and pulsatile LHRH or injection HCG and FSH can be given.
• Oral testosterone (Methyl testosterone is discouraged because of liver toxicity)
• Transdermal testosterone gel, nasal testosterone is also available.
• Because risk of gonadoblastoma and carcinoma, gonadal tissue should be removed in Males with nonfunctioning testicular tissue.
• Monitor hematocrit values to look for polycythemia, Polycythemia is a complication of testosterone replacement
• Prostate examination and prostate specific antigen measurements should be done before testosterone therapy and periodically after treatment with testosterone is stared
• Refer to urologist to look for prostate cancer.
<table>
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<tr>
<th>Formulation</th>
<th>Administration</th>
<th>Advantage</th>
<th>Disadvantage</th>
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</thead>
<tbody>
<tr>
<td>Testosterone undecanoate</td>
<td>Oral; 2-6 cps every hours.</td>
<td>Absorbed through the lymphatic system, with consequent reduction of liver involvement.</td>
<td>Variable levels of testosterone above and below the mid-range (69). Need for several doses per day with intake of fatty food.</td>
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<tr>
<td>Testosterone cypionate</td>
<td>Intramuscular; one injection every two to three weeks.</td>
<td>Short-acting preparation that allows drug withdrawal in case of onset of side-effects.</td>
<td>Possible fluctuation of testosterone levels</td>
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<td>Testosterone enanthate</td>
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<td>Short-acting preparation that allows drug withdrawal in case of onset of side-effects.</td>
<td>Fluctuation of testosterone levels</td>
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<tr>
<td>Testosterone undecanoate</td>
<td>Intramuscular; one injection every 10-14 weeks</td>
<td>Steady-state testosterone levels without fluctuation.</td>
<td>Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effect</td>
</tr>
<tr>
<td>Transdermal testosterone</td>
<td>Gel or skin patches; daily application</td>
<td>Steady-state testosterone level without fluctuation</td>
<td>Skin irritation at the site of application and risk of interpersonal transfer</td>
</tr>
<tr>
<td>Sublingual testosterone</td>
<td>Sublingual; daily doses</td>
<td>Rapid adsorption and achievement of physiological serum level of testosterone</td>
<td>Local Irritation</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>Buccal table; two doses per day</td>
<td>Rapid absorption and achievement of physiological serum level of testosterone level.</td>
<td>Irritation and pain at the site of application</td>
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<tr>
<td>Subdermal depots</td>
<td>Subdermal implant every five to seven months</td>
<td>Long duration and constant serum testosterone level</td>
<td>Risk of infection and extrusion of the implants</td>
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If Testosterone is contraindicated

- Lose weight if overweight
- Exercise to increase muscle tone
- Reduce ETOH (ETOH enhances aromatase converting testosterone to estrogen)
- Avoid opioids
- Avoid xenobiotics (Bisphenol A [BPA] increases aromatase)
- Let the testicles dangle. cool testicles mean more testosterone production (Victory Pose)
**Conclusion**

Testicular failure 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.

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