Acquired causes of testicular failure

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ENDOCRINE OUR LIFE LINE

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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 hypogonadatrophic hypogonadism

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

Causes of Hypergonadotropic hypogonadism

Acquired causes:	Congenital Causes:
• Chemotherapy • Radiation therapy • Gonadectomy • Mumps orchitis • Testicular torsion • Testicular cancer • Varicocoele • Hemochromatosis due to multiple transfusions • Anorchism or cryptorchidism • Constant injury to testicles while riding motorcycle or bicycle.	• Klinefelter syndrome • Inactivating mutations • Testicular biosynthesis defect • Gonadal dysgenesis • Ovotesticular DSD, XX males • LH resistance.

Symptoms

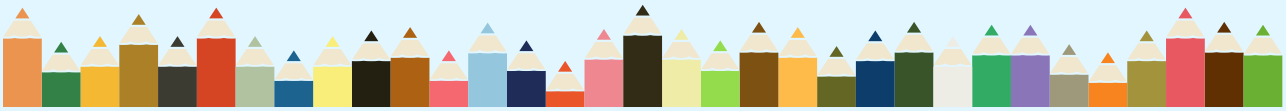
First thing is to differentiate between constitutional delay in puberty and hypogonadism. There is family history of delay in puberty, in constitutional delay of puberty. This will clinch the diagnosis.

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

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

- 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

It 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.

Small testes	Eunuchoid habitus
Cryptorchidism	Sparse body hair/facial hair
Gynaecomastia	Infertility
High-pitched voice	Low bone mass
Unclosed epiphyses	Sarcopenia
Linear growth into adulthood	Reduced sexual desire/activity

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)

Anosmia and Microphallus suggest Klinefelter syndrome or pan hypopituitarism

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

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

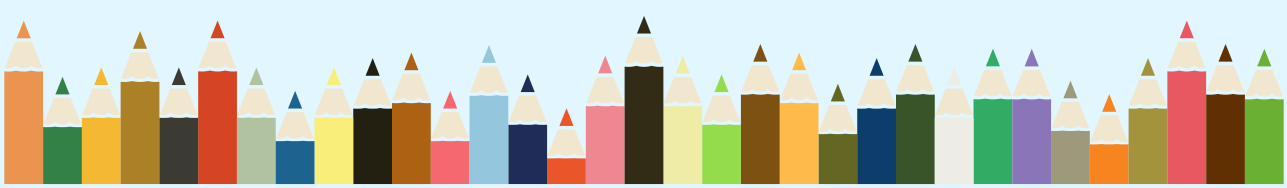
First, treat the underlying cause, do surgery where required.

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 hypogonadatrophic 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 Hypergonadotropic hypogonadism fertility is not possible.
- In Patients with hypogonadatrophic 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.



Testosterone preparations for replacement therapy

Formulation	Administration	Advantage	Disadvantage
Testosterone undecanoate	Oral; 2-6 cps every hours.	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range {69}. Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every two to three weeks.	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible fluctuation of testosterone levels
Testosterone enanthate	Intramuscular; one injection every two to three weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels
Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effect
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation	Skin irritation at the site of application and risk of interpersonal transfer
Sublingual testosterone	Sublingual; daily doses	Rapid adsorption and achievement of physiological serum level of testosterone	Local Irritation
Buccal testosterone	Buccal table; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone level.	Irritation and pain at the site of application
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level	Risk of infection and extrusior of the implants

Recommendations for testosterone replacement therapy

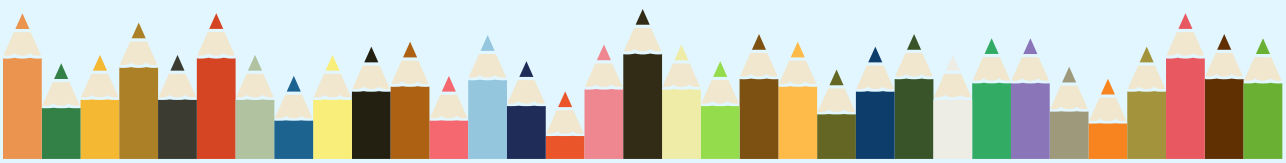
Recommendations	LE	GR
Fully inform the patient about expected benefits and side-effects of the treatment options. Select the preparation with a joint decision by an informed patient and the physician.	3	A
Use short-acting preparations rather than long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Do not use testosterone therapy in patients with male infertility and active child wish since it may suppress spermatogenensis.	1b	A
Only use HCG treatment for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, only attempt testosterone in men with major symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	2	A

Contraindications against testosterone treatment

Prostate cancer
Male breast cancer
Servere sleep apnoea
Male infertility-active desire to have children
Haematocrit > 0.54%
Servere lower urinary tract symptoms due to benign prostatic hyperplasia
Severe chronic cardiac failure/New york Heart Association Class IV

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)



Recommendations for follow-up

Recommendations	LE	GR
Assess the response to treatment at three, six and twelve months after the onset of treatment, and thereafter annually	4	C
Monitor haematocrit at three, six and twelve months and thereafter annually. Decrease the testosterone dosage or switch testosterone preparation from parenteral to topical or venesection, if haematocrit is above 0.54. If haematocrit remains elevated, stop testosterone and reintroduce at a lower dose once haematocrit has normalized.	4	C
Assess prostate health by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at three, six and twelve months and thereafter annually.	4	C
Assess men with cardiovascular disease for cardiovascular sumptoms before TRT is initiated and continue close clinical assessment during TRT.	1b	A

BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

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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