



INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

HYPOGONADISM

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ABSTRACT :

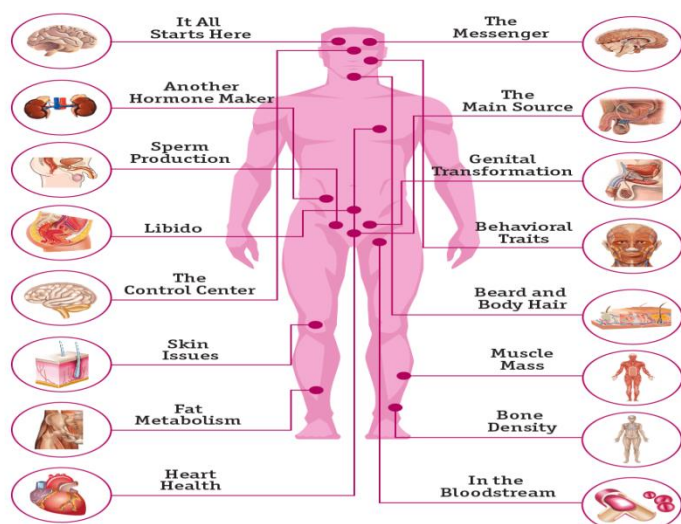
Testosterone is primary sex hormone in male .which regulates primary and secondary characteristic in male. Testosterone is secreted by interstitial cells of Leydig between seminiferous tubule and from adrenal gland. If testosterone level decrease then it leads to the Hypogonadism. It causes erectile dysfunction, anemia, muscle stiffness, psychological problem. It detects by various hormone test such as LH and FSH level prolactin level and also hypogonadal symptoms. There is a testosterone replacement therapy available to overcome Hypogonadism. It includes intramuscular injections, transdermal patches, transdermal gels, subcutaneous pellet. Normal level of testosterone gives better libido, improve mood, reduces fats and maintain bone mineral density. Testosterone replacement therapy also contra indicated in prostate cancer. We can also give alternative for testosterone replacement therapy and some lifestyle modification and non pharmacological treatment is also gives good benefits in hypogonadal men.

KEYWORDS : Testosterone , Hypogonadism, Hormone, Transdermal patches, prostate cancer

INTRODUCTION:

Testosterone is a primary male sex hormone in male which regulates the primary and secondary characteristics in male. Primary sexual characteristics regulated by the testosterone are testicular descent , spermatogenesis , enlargement of penis and testes. Testosterone also increases libido. Regularity of secondary sexual characteristics of male is seen during puberty. Secondary characteristics such as facial hair growth , deepening of voice , enlargement of larynx(Adam's apple). Testosterone is an anabolic hormone which stimulate protein synthesis, increases tissue growth at the epiphyseal plate at early stage of puberty . Testosterone also induces erythrocytosis .Testosterone is secreted by the Interstitial cells of the Leydig between seminiferous tubules and from adrenal gland in little amount.

Benefits of Testosterone:



Hypogonadism is a clinical syndrome in which a human body does not produce enough amount of testosterone which plays important role in masculine growth and spermatogenesis during puberty in male.

Types of Hypogonadism :-

There are mainly 2 types of Hypogonadism;

1. Primary Hypogonadism or Primary testicular failure or Hypergonadotropic Hypogonadism .
2. Secondary Hypogonadism or secondary testicular failure or Hypogonadotropic Hypogonadism

Primary Hypogonadism:

There is decrease in total serum testosterone, high –normal or high level of luteinizing hormone(LH) and follicle stimulating hormone(FSH).

Secondary Hypogonadism

There is decrease in total serum testosterone, normal to level of luteinizing hormone(LH) and follicle stimulating hormone(FSH).

Etiology For Primary Hypogonadism: Congenital primary hypogonadism occurs due to the chromosomal defect Ex:-**Klinefelter syndrome** –

In this syndrome there is defect in sex chromosome. Person with this syndrome consists of two ‘X’ chromosomes with additional one ‘Y’ chromosome.

- Acquired hypogonadism is mainly associated with various conditions
 - mumps orchitis:**
Infection occurs in testes which effect normal testicular function & production of testosterone.
- surgical removal of testes
- chemotherapy or radiation may alter the production of testosterone & sperms which may result in permanent infertility.
- normal ageing.

Etiology of Secondary Hypogonadism

- **kallmann syndrome:**

Abnormal development of hypothalamus associated with the deficiency of gonadotropic releasing hormone.

- **Pituitary Gland Disorder:**

There is decrease in LH & FHS level. Pituitary tumor (or) brain tumor located near to the pituitary gland affects the testosterone by decreasing LH & FSH secretion which results in hypogonadism.

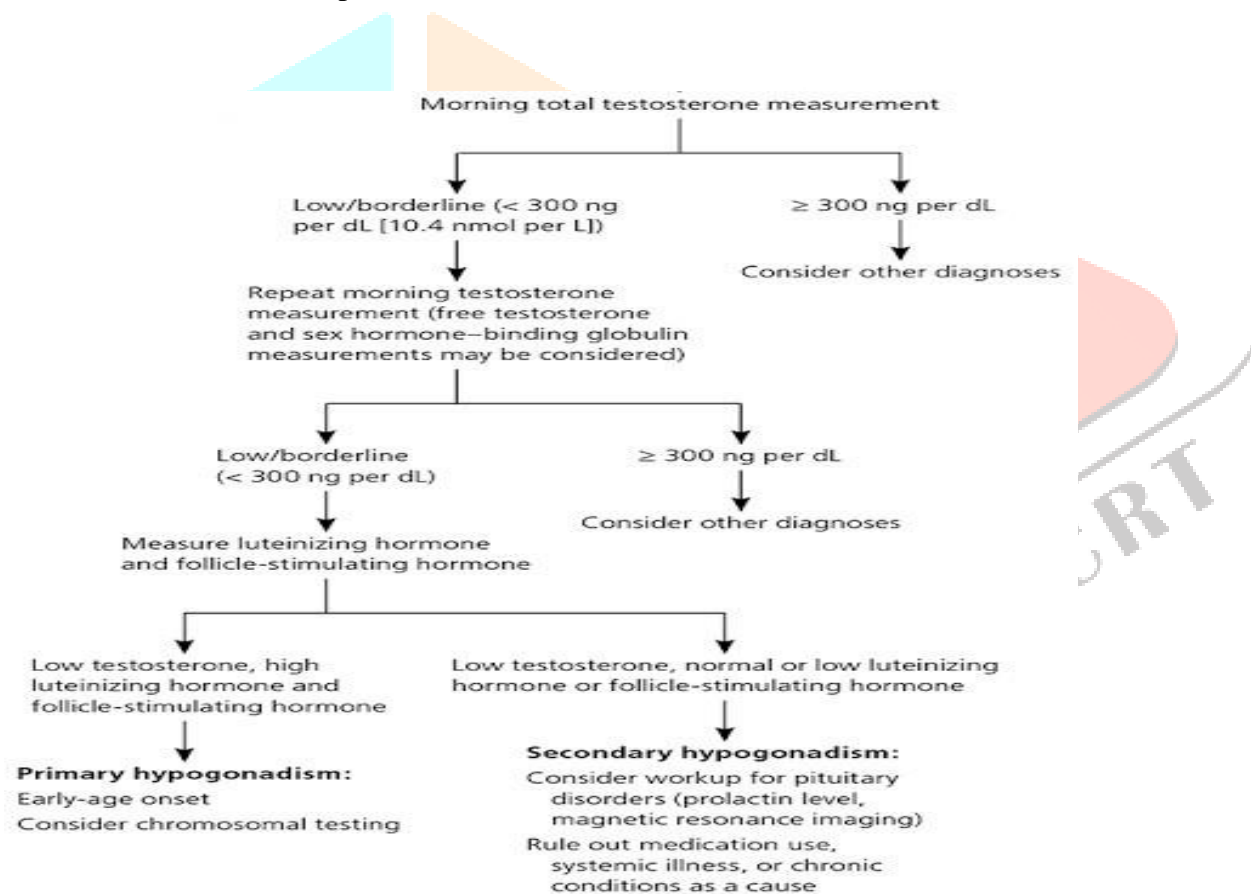
- **Inflammatory Condition:**

Such as sarcoidosis , histocytosis and tuberculosis affects the testosterone production.

- **HIV-AIDS , Type2-Diabetes Mellitus , chronic renal failure , glucocorticoid therapy, etc these are acquired causes of secondary hyposonadism.**

- **Obesity:**

There is excess production of aromatase enzyme in obese patient which converts testosterone into estradiol which results in increase of blood serum estrogen level and excess availability of blood serum estrogen decreases the testosterone production.



Decrease In Testosterone Levels Leads To Following Complications:

- **Reproductive System:**

If testosterone level decreases then it badly affect on reproductive system. Because it decreases sex drive (means man loose his desire for sex), it also cause erectile dysfunction, low libido, diminish penis sensation , reduce ejaculation, decrease sperm production.

- **Central Nervous System:**

If testosterone level decreases then it badly affect on central nervous system. Because low levels of testosterone leads to depression, aggression, decrease confidence, decrease concentration, feels lack of energy.

- **Muscle, Fat, Bone:**

If testosterone level decreases then it badly affect on muscles.

Because it cause for muscle stiffness and it also leads to muscle strength reduction.

Low testosterone leads to decrease in fat metabolism which ultimately results in increase in body fat.

Decrease in testosterone levels leads to decrease in bone mineral density and sometimes ageing patient may also experience bone fracture.

Diagnosis:

A. Health Examination:

Anosmia (lose of ability to smell)

Mumps after puberty

History of head trauma

Injury to patient's testicles

Family history of diseases relating to low testosterone

B. Physical Examination:

Abnormality Prostate size

Gynecomastia (Enlarged breasts in male)

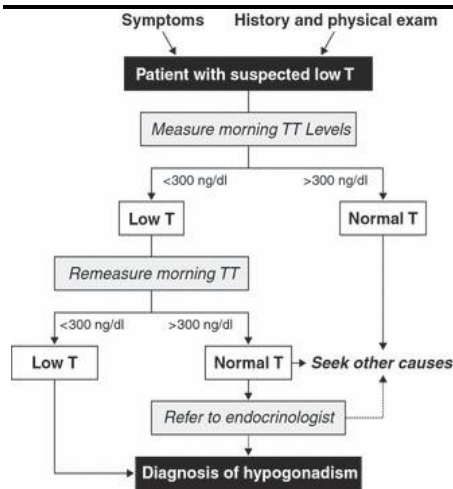
Increased BMI or west circumference for obesity

Whether testicles are present and their size

C. Lab Investigations :

- **Testosterone level in blood:**

Two different Samples are taken in early morning. If there is decrease in total testosterone level (<300ng/dl) at both the time, then it is considered the penitent is suffering from Hypogonadism.



• **LH and FSH Level :**

Increase LH and FSH shows primary Hypogonadism.

Low or low normal- levels of these hormones is seen in secondary Hypogonadism

Low Testosterone with normal LH and FSH level is associated with defect in hypothalamus and/or pituitary gland

FSH level me also determine sperm production functioning.

• **Prolactin level :**

High prolactin level may be sign of pituitary gland defect or tumor in pituitary gland.

• **Estradiol :**

There is enlarged breast size in male. Then estradiol level are checked.

• **Karyotype (chromosomal test) :**

Mostly done in young teenager or infertile male to diagnose klinefelter syndrome.

• **Bone density test :**

• **MRI**

• **Hemoglobin**

Testosterone replacement therapy:-

Testosterone replacement therapy is primary treatment for hypogonadal male which having aim to restored normal hormonal level it is the therapy approved by the united state food and drug administration as a treatment of Hypogonadism.

(1) **Transdermal patches :**

2mg/24 hr or 4mg/24hr patch of endoderm is applied on the dry intact skin of arms with usual dosing of 2 to 6 mg daily .There is a risk of developing reactions of skin (purities, blistering, indurations, erythematic vesicles) with the use of Transdermal patch. Some patient may also develop headache, depression & GI bleeding.

Now a day's scrotal or non scrotal patches are available in market scrotal patches produces high level of dihydrotestosterone (DHT) which increases the activity of 5 -alpha reductase enzyme on scrotal skin resulting in uniform delivery of serum testosterone for 24 hours.

(2) **Transdermalgel:** -

Transdermal gel formulation such as androgen, testim, fortesta, axiron are available in market they are provided in sachets, tubes or in metered dose pump amid it can be also applied on arms with the help of hands. Transdermal gels are applied on dry intact skin on back, abdomen, upper thighs or on arms. These formulations maintain steady serum testosterone concentration. Adverse events associated with Transdermal gel is skin irritation, do not achieve normal testosterone, risk of transfer of skin to skin testosterone. While using gel preparation patient should be instructed to wash hands, avoid skin to skin transfer to other on a gel treated area. Gels are only effective in management of symptoms of hypogonadism.

Daily dosing require to treat hypogonadism is

1. Ander gel and testing 50 - 100 mg daily.
2. Fortesta 10-17 mg daily.

(3) **Tablet:-**

1. Sublingual and Buccal tablet: - By using buccal tablet hypogonadism can be treated. Striant SR 30 mg buccal tablet is given to the patient.

Cyclodextrin- complex testosterone formulation of buccal tablet rapidly absorbed into the circulation. The tablets are applied on the upper oral cavity about the lateral incisors in the morning and evening.

Risk associated with buccal tablet is transient gum irritation, dry mouth, toothache, bitter taste stomatitis. Patient also report shifting of tablet in mouth while talking.

2. **Oral tablet:** -

Oral testosterone tablet are available under a brand name andriol, testroid both are methyl testosterone product.

Usual dosing of andriol is 40-80mg orally 3-times a day. Oral testosterone tablet is taken with fat containing meal. Oral preparations undergoes first pass metabolism due to which frequent dosing is require. Oral products can leads to elevation of liver enzyme, GI intolerance, acne, gynecomastia as an adverse drug reaction.

(4) **Intra muscular :-**

Injection cypionate , testosterone enanthate are administered by intra muscular route within 72hrs of administration it achieves peak level testosterone cypionate , testosterone enanthate achieve supra-physiological testosterone level within first few days of administration ,near the end of dosing interval it achieves sub-physiological level , such fluctuations results in mood swings , variation in energy and sexual activity. Other risks such as irritation at the site of application. These preparations are applied on thighs or buttock area of the human body.

Usual dosing of testosterone cypionate and testosterone enanthate is 100-200mg every 2 week or 50-100mg every 1 week.

(5) Implantable pellet :-

Testopel pellet with usual dosing of 150-450mg every 3-6 months is implanted into subcutaneous fat of buttock, lower abdominal wall or thighs. There is no need for daily treatment while using implantable pellet. Adverse drug reaction associated with subcutaneous testosterone pellet is infection , fibrosis at pellet site , extrusion.

Benefits of Testosterone replacement therapy

Testosterone replacement therapy shows the improvement in many of the effects of hypogonadism which includes beneficial effect on lean body, muscle strength, bone mineral density, libido & erectile functioning, improvement in mood & energy level, well being. Improvement of symptoms of the hypogonadism by restoring a normal

testosterone level. Testosterone replacement therapy shows some beneficial effects on metabolic syndrome, type2- diabetes and some cardiovascular diseases

1. Improve erectile functioning, sexual desire performance: -

in comparison of younger men with elder men they require higher level of circulating testosterone for libido & erectile function. The candidates for testosterone therapy are those persons who are suffering with erectile dysfunctioning & diminished libido and testosterone deficiency. Frequent etiological cause of erectile dysfunctioning in elder men is venous leakage in the corpus cavernosum which is restored by testosterone therapy.

2. Bone mineral density, improve muscle mass, muscle strength: -

In a chronic hypogonadal male patient having both androgen deficiency and decrease bone mass. Elder men with hypogonadism are more prone to osteopenia , osteoporosis. Testosterone supplementation increase the bone density at lumbar spine there is no increase in density of hip bone but it is only for the middle aged men with hypogonadism. In older men there is increased bone density at both lumbar- spine and hip.

3. Mood, energy,depression: -

in older patient it has been seen that there is significant relation between decreased testosterone level leads to depression or emotional disturbance. For these patients administration of supra-physiological testosterone in small proportion is enough.

4. Improving cardiovascular diseases, metabolic syndrome: - many of the metabolic syndrome such as obesity, hypertension, dyslipidemia , impaired glucose regulation and insulin resistance seen in androgen deficient male. Male with base line testosterone level having high association with the cardiovascular morbidity and mortality. Treating these patients with the testosterone treatment may decrease the risk of these syndromes.**Risk of testosterone replacement therapy**

- Testosterone replacement therapy(TRT) normalizes serum testosterone but according to the age , circumstances of life and several medical conditions of the patients some risks are associated with the TRT includes prostate cancer , worsening symptoms of Benign prostatic hyperplasia(BPH) , causes gynacomastia , erythrocytosis , skin diseases , worsening of sleep apnea.
- In Prostate cancer there is increase in prostate volume due to stimulation of androgen so exogenous testosterone is contraindicated in patient with prostate cancer.

Several studies and Meta analysis cannot be able to establish significant relation between exogenous testosterone supplementation and prostate cancer. During exogenous testosterone administration there is increase in prostate specific antigen(PSA) is observed in small amount but no urinary retention is observed at higher rate so further studies are required to find out relation between prostate cancer and testosterone supplement.

- The endogenous androgen increases erythropoiesis. Testosterone therapy particularly the intra muscular esters increases the risk of polycythemia. In pre-existing polycythemia where hematocrit level is more than 54% testosterone therapy is absolutely contraindicated. Testosterone therapy increases the hemoglobin level and treats anemia in significant proportion but excess of the hemoglobin production due to exogenous testosterone leads to polycythemia.
- Orally taken tablets follows first pass metabolism. So in oral testosterone forms some hepatic problems(exception is of testosterone undecanoate) are seen including Hepatic tumor, intrahepatic cholestiasis ,liver toxicity .

Alternative treatment for testosterone replacement therapy

Dihydrotestosterone gel (DHT):-

testosterone is metabolize to dihydrotestosterone by 5-alpha reductase enzyme. Dihydrotestosterone have a stronger affinity for androgen receptor at prostate tissue skin and external genitalia. Dihydrotestosterone gel decrease risk of adverse prostate outcomes because DHT does not translate into intra prostatic DHT concentration. Due to non-aromatized property of DHT is reduces the risk of gynecomastia. Improve sexual activity , muscle mass , lowers body fat. DHT gel is expensive.

Human chorionic gonadotropin (HCG) therapy: -

HCG is homologous to LH. Due to its homogeneity HCG shares receptor with LH. HCG stimulates the production of testosterone by Leydig cells. HCG directly stimulates spermatogenesis . If there is no change seen in sperm concentration after 6 months from initiation of HCG therapy then FSH therapy i.e. human menopausal gonadotropin (hMG) or recombinant human FSH (rhFSH) therapy is added with HCG therapy.

rhFSH have absence of contaminating urinary compound , more stability , more efficacy to restore fertility in a men with low testosterone , it is administered 3 times a week due to its short half life. HCG is administered through intra muscular or subcutaneously with usual dosing of 1000-2000 IU 2(or) 3 times a week. Indication of HCG therapy is to stimulate sperm production, increase fat free mass,decrease total cholesterol level, decrease very low density lipoprotein level. Adverse drug reaction associated with this therapy is gynecomastia , increase hematocrit.

Aromatase inhibitor: -

The conversion of testosterone to estradiol is blocked by aromatase inhibitors by inhibiting the aromatase enzyme. These actions can directly raise the level of serum testosterone. The inhibition of aromatase results in increasing level of gonadotropin releasing hormone , LH & FSH hormone level , subsequently result in increase in serum testosterone level.

Selective estrogen receptor modulators (SERM):-

the SERM agents act as estrogen receptor antagonists and agonists depending on the tissue. The clomiphene citrate (Clomiphene) is one of the SERMs which act as an estrogen antagonist in the hypothalamus and pituitary gland. The stimulation of LH& FSH secretion is done by clomiphene, by the prevention of inhibitory effect of estrogen on gonadotropin production. The use of clomiphene is done as off-label in the men suffering with hypogonadism. The clomiphene is tolerable agent. It shows only mild symptoms such as dizziness, fatigue, and headache. When proper dose of clomiphene citrate is followed then it can be considered as an effective and safe alternative to testosterone replacement therapy. This therapy has positive effect on skeletal muscle and bone. But having negative effect on erythrocytes, prostate, hair (alopecia), skin.

Non-pharmacological therapy:-

Testosterone production also can be improved by the lifestyle modification, change in diet, exercise, taking peace, full sleep, reduce stress.

- **Diet:** - Food including garlic, egg, pomegranate, oysters, spinach, tuna, ginger, broccoli, can also increase testosterone naturally.

1 Garlic: - Allicin present in a garlic lowers the cortisol level in the body. As cortisol level decreases increase testosterone production.

2 Tuna: - Tuna is a rich source of vitamin- D. and vitamin D plays significant role in increase testosterone level and maintain sperm count.

Salmon or sardines are a good alternative for tuna.

3 Zinc supplement: - Oysters, beans (kidney beans, black beans, chickpeas) pumpkin seeds are a zinc supplement, increases testosterone and also increases growth factor hormone both of these increase muscle growth and physical performance.

4 Pomegranate:- Increases testosterone level up to 24%. It includes dietary nitrates which might improve exercise performance, person may feel more active and less fatigue.

Pomegranate may help in slow down metastasis in prostate cancer and decrease risk of prostate cancer in male.

5 eggs: - Whole egg contains amino acids and aspartic acid stimulates the production of testosterone. Egg yolk is dietary cholesterol and cholesterol is a building block for testosterone production.

6 Green leafy vegetables: - Spinach is a rich source of magnesium it promotes better blood flow by better penile erection and also involved in development of muscle.

7 Broccoli:- It is rich in indoles and anti cancer compounds which boost testosterone production by breaking the process of estrogen production. Estrogen inhibits the production of male sex hormone.

1 GET HIGH QUALITY SLEEP
Sleeping on time and keeping to 7 to 8 hours sleep is the most important first step to boosting your testosterone. This is on the basis that your sleep remains uninterrupted throughout the night.

2 WATCH WHAT YOU PUT IN YOUR MOUTH
Get whole natural food and healthy fats into each meal. If it doesn't grow out from Mother Earth, it's definitely not natural. (P.S.: you won't find a Bagel tree in the garden, right?)
Rule of thumb, on your plate, you should have 50% greens, 25% protein, 25% carbohydrates.

3 MINDFUL TO YOUR STRESS LEVEL
Consider mindfulness practises to keep your stress level at bay. We shouldn't be chased by a bear all the time! (Figuratively)
A walk in nature, meditation, yoga are just some helpful ways to calm your nerve.

4 MOVE MORE, LIFT WEIGHTS
The more active you are, the more testosterone you have. However, packing a heavy morning of exercise, and sit for the rest of the day won't work. Constant movement sprinkled throughout the day is the key.

Lifting weights is definitely helps as well. When muscle mass increases, your body will produce more testosterone.

5 DON'T FORGET THE SUN
A study published in Journal of Hormone and Metabolic Research found that consuming vitamin D supplement contribute to increase in testosterone levels.

If nature allows, go out in direct sunlight between 10am-2pm for 15 minutes can help keep vitamin D levels in check. Let your body do their job because only your body knows what you need and how much you need it.

6 SUPPLEMENTS CAN HELP
We might not get all the nutrients our body need from our normal meals, so supplementing can definitely help make sure our body get sufficient material to do its job.

Zinc helps contribute to over 100 chemical processes within your body. It's also effective for men with low testosterone.
Ashwagandha is your other choice to boost testosterone too.

5 NATURAL TESTOSTERONE BOOSTER
Ginger, Oysters, Pomegranates, Leafy Green Vegetables, Fatty Fish and Fish Oil, Extra Virgin Olive Oil, Onions are your power packed natural food that can give your favourite hormone a lift.

- **Have a peaceful sleep :**

Due to apnea, nocturnal hypoxia can occur which decreases LH level which ultimately affects on testosterone level. Some studies shows that treating a patient of obstructive sleep apnea with uvulopalatopharyngoplasty and observes 3 months post operative testosterone level it seems to be increased. Increasing the duration of sleep effects positively on testosterone level.

- **Decreasing stress: -**

It is well known that the age related hypogonadism is more prone to mood swings and some theories are also explained the cortisol disturbs steroidogenesis in testicular leydig cells through inhibitory enzymatic effect. So minimizing stressful situation can also improve testosterone level.

- **Varicocele repair: -**

Presence of varicocele leads to the pathospermia and secondary infertility, testicular atrophy which exacerbates hypogonadism. Surgical treatment of varicocele improves serum testosterone level. Resulting in improvement of sexual activity, spermatogenic and hormonal function in testosterone deficient male.

- **Bariatric surgery: -**

In recent studies it has been seen that the patient with BMI 35 or more are gone through the surgery which shows the weight loss in those patients. It requires further studies and researches.

• **Food should avoid in low testosterone:-**

1 Soya: - Edamame, tofu, isolated soya protein contain phytoestrogens which is similar to estrogen structurally and act similarly to it as well

but further studies are needed to establish a significant roll of soya and soya products in low testosterone.

2 Alcohols:- heavy amount of alcohol of regular drinking of alcohol can reduces fertility of also make changes in amount of other reproductive hormone along with testosterone its linked to the low testosterone level.

3. Packed and processed food:-

Contain high amount of Trans fats which impaired testicular function by reducing testosterone level.

Conclusion:

Testosterone is primary male sex hormone. If testosterone level decrease then it leads to Hypogonadism. It's prevalence increase day by day. So physician have bulk number of patients of this disease. Physician must be aware of this disease symptoms and severe conditions about it . Don't skip patients without treatment. Because TRT (Testosterone replacement Therapy) is available. Before administration of treatment explain benefits and risk of TRT. Along with TRT non -pharmacological therapy and life style modification can also help in improve testosterone level.

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