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Testosterone Deficiency in the Older Male

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Abstract **Review Article**

Testosterone deficiency (TD) in the older male is a difficult diagnosis to make with potentially life changing treatment. Awareness of the normal hormonal pathways, and an understanding of the corrective homeostatic mechanisms, can help in understanding the downstream effects of potential physiologic disturbances. Depending on age, the signs and symptoms of TD can vary from under developed external genitalia in the fetus, to lack of normal pubertal changes in the young adolescent up to an alteration in certain masculine physical characteristics present in the normal adult male. For the adult male, multiple treatment options are available, with newer ones being refined and developed. Monitoring for effective response to Testosterone Replacement Therapy (TRT) and screening for complications is not an onerous task and has the potential to improve the lives of many men.

Keywords: Testosterone deficiency (TD), homeostatic mechanisms, Testosterone Replacement Therapy (TRT).

INTRODUCTION

Unhelpful expressions such as 'the male menopause' or 'Andropause' suggest a termination in Testicular function which is not representative of the reality of the situation [1]. There is a gradual fall in testosterone levels in men starting around the age of 35 and this is as a result of a steady Testicular failure [2]. Diagnosing TD in the elderly male can be difficult as the symptoms are non-specific, develop progressively and overlap with those associated with normal physiological ageing [3]. The changes associated with ageing are like those seen in men with Hypogonadism due to a known disease process. This has led to the theory that the decline in testosterone is behind the changes associated with ageing. Studies also show that 25% of men see no decline in testosterone with age, and indeed there are many instances of men fathering children in older age [1]. These points together pose the question of whether TD is due to a disorder (or disorders) that results in declining testosterone production or if it is a part of the natural ageing process that men experience.

Hypothalamic-Pituitary-Gonadal (HPG) Axis

Testicular deficiency can occur from either Testicular failure or a disturbance (or disturbances) within the HPG axis (see Figure 1). It can be classified in two main categories, Primary (Hypergonadotropic) Hypogonadism and Secondary (Hypogonadotropic) Hypogonadism.

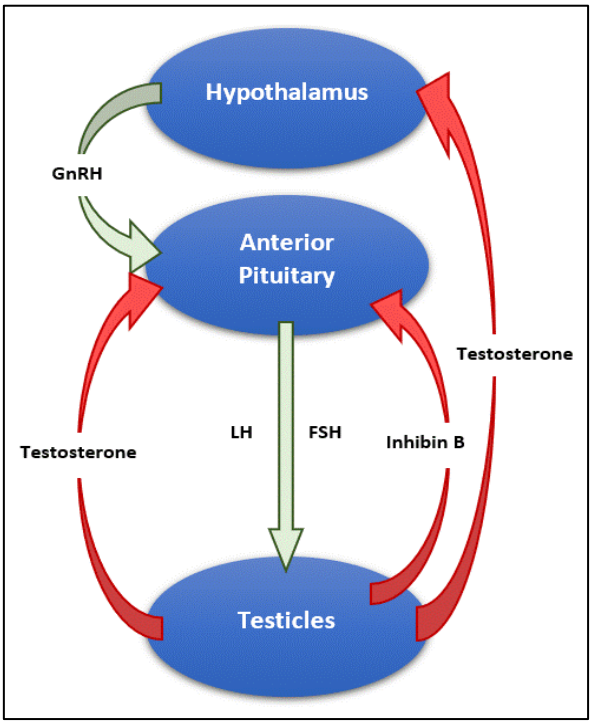

Figure 1: Simplified diagrammatic representation of the Hypothalamic-Pituitary-Gonadal Axis

Causes of Primary (Hypergonadotropic) Hypogonadism

- Testicular dysgenesis syndrome
- Chromosomal abnormalities—Klinefelter's syndrome (can go undiagnosed until detected during infertility investigations)
- Undescended testicles
- Haemochromatosis
- Testicular Injury - torsion, acute trauma, burns or repeated low-level injury such as that seen in cyclists
- Tumors - Childhood leukemia, treatment for other malignancy using chemotherapy agents or radiotherapy, testicular cancer
- Infection – especially with HIV and mumps
- Drugs – e.g., Ketoconazole, glucocorticoids, opioids, chemotherapy agents, frequent and heavy use of marijuana

Box 1: Causes of Primary (Hypergonadotropic) Hypogonadism

When the TD is Testicular in origin, it is deemed "Primary". Due to low production in testosterone, there is a homeostatic response causing an elevated Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH). In men, Primary Hypogonadism is associated with Testicular failure.

Causes of Secondary (Hypogonadotropic) Hypogonadism

- Malnutrition or obesity
- Medications – e.g., Opioids, gonadotrophin releasing hormone (GnRH) analogues, steroids.
- Hyperprolactinemia
- Serious systemic illnesses, (including HIV and TB infections)
- Pituitary tumors (10% of intracranial tumors are pituitary tumors) or treatment for brain tumors elsewhere
- Aging

Box 2: Causes of Secondary (Hypogonadotropic) Hypogonadism

In Secondary (Hypogonadotropic) Hypogonadism, the levels of LH and FSH produced by the Anterior Pituitary are low. This will occur as a result of Pituitary gland or Hypothalamus disease. Due to low levels, there is insufficient LH and FSH to stimulate the Testes to produce testosterone from the normal Testes. Where hypothalamic disease is present, the patient would be expected to have low levels of testosterone in association with low GnRH and LH/FSH.

Most cases of Hypogonadism in men between 50 and 70 years of age are of a mixed form i.e., both central defects of the HPG axis and Testicular failure [4]. This type is thought to have several possible causes, ranging from acute and chronic illnesses, ageing, diabetes, alcoholism, drugs and sickle cell disease. The biochemical abnormalities demonstrated in this form are variable gonadotrophin levels. The levels of gonadotrophin found depend on whether the low testosterone levels are predominantly of primary or secondary origin [5].

Table 1: Testosterone deficiency biochemical changes

Source of Dysfunction	Testes	Hypothalamus or Pituitary	Testes + Hypothalamus/Pituitary
Type of Testosterone Deficiency	Primary Hypergonadotropic Hypogonadism	Secondary Hypogonadotropic Hypogonadism	Mixed
Biochemical consequences	↓ Testosterone ↑ LH (+/- FSH)	↓ Testosterone ↓ (or low-normal) LH (+/- FSH)	↓Testosterone ↓ or ↑ LH and FSH

Clinical Features / Presentation

The clinical manifestations of TD can vary depending on age of onset. A considerably different presentation will be seen in a fetus, prepubertal child and adult. The focus of this review will be maintained on the adult male. The commonest reasons for men seeking medical help are related to sexual performance (Erectile Dysfunction, decreased libido) [6] and increased fatigue. These sets of symptoms are frequently the earliest symptoms felt. The signs and symptoms could be grouped into somatic, sexual and psychological (Box 3).

Signs and symptoms of Testosterone deficiency in older men

- Somatic
  - Slowed growth of secondary body hair in the axillae, genital and beard area.
  - Progressive decrease in muscle mass and strength
  - Increased upper body and central body fat
  - Lethargy and/or poor ability to concentrate
  - Increased fatigue
- Sexual
  - Decreased libido
  - Decreased performance
  - Lack of early morning erection
  - Erectile Dysfunction
  - Difficulty in achieving orgasm
- Psychological
  - Poor concentration and memory
  - Sleep disturbance
  - Depressed mood
  - Lack of motivation
  - Irritability
  - Anxiety
  - Anger
  - Aggression

Box 3: Signs and symptoms of Testosterone deficiency in older men

It is worth noting that male pattern baldness is not associated with TD [1]. The size of the penis usually remains the same, as does the individual's voice. Hot flushes are rare and typically occur when the degree of TD is severe, especially if the rate of progression is rapid.

Diagnosis

Older symptomatic men, those with examination findings and those with lab findings (e.g., anemia, low bone mineral density) should be evaluated for TD.

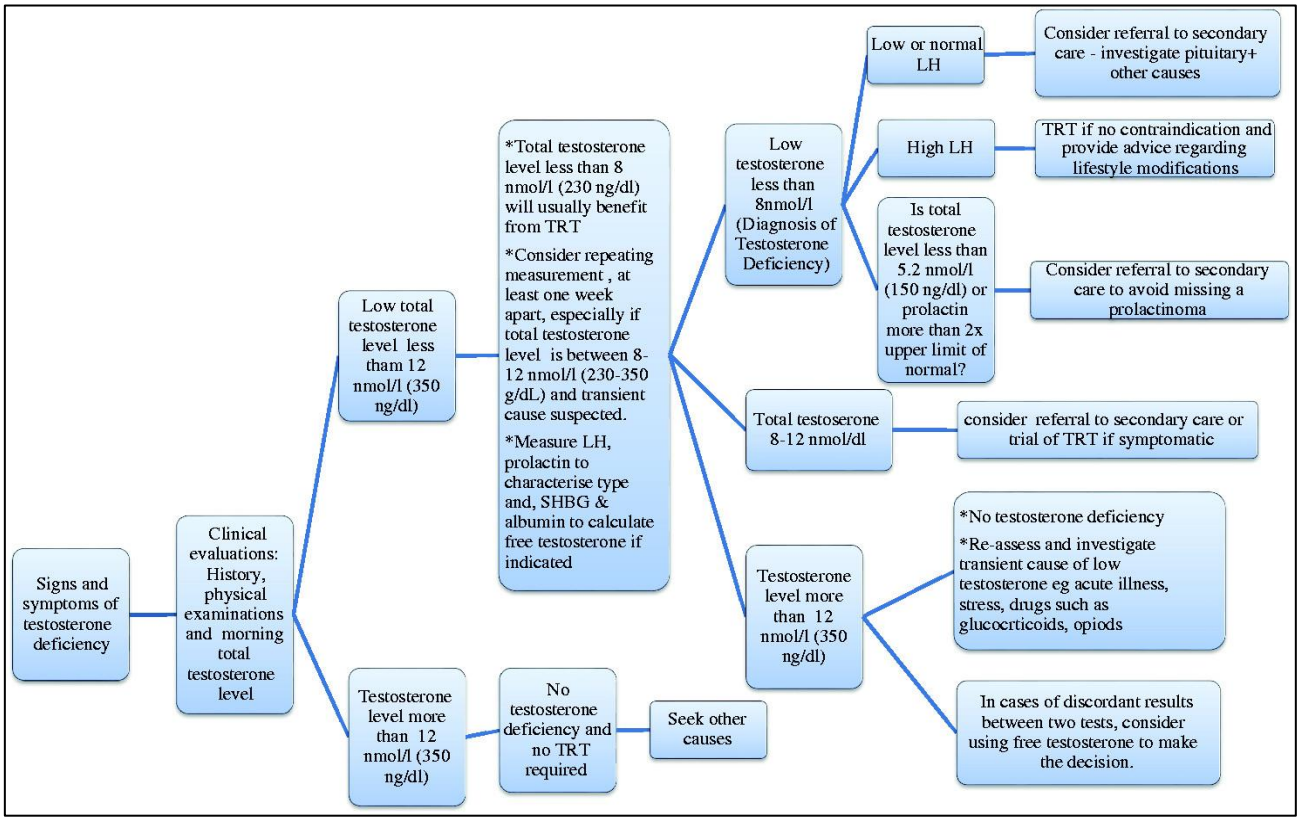

Figure 2: Flow chart for the assessment and diagnosis of Testosterone deficiency [7]

Testosterone is mostly bound to sex hormone-binding globulin (SHBG) and albumin only a small fraction circulates freely [3]. Albumin bound testosterone can dissociate easily becoming bioavailable, compared to testosterone bound to SHBG which is tightly bound and not utilizable. SHBG levels increase with age by around 1% per year. As a result of this physiological fact, younger men have a higher ratio of usable testosterone than the older man [7]. SHBG levels are increased liver disease, severe androgen deficiency, hyperthyroidism or estrogen excess. Low levels a tend to be associated with obesity, acromegaly and Hypothyroidism.

It is commonly accepted that a total serum testosterone level above 12 nmol/L is normal and would not require TRT. Other causes for the patient's symptoms should be explored. Likewise, a level below 8 nmol/L would typically respond well to treatment. For levels between 8 and 12 nmol/L generally a repeat total testosterone along with albumin and SHBG levels is advised in order to calculate free testosterone [8]. Estimations on the bioavailable testosterone can be made using these results, but they should be interpreted with a degree of caution; seemingly normal results can occur where both testosterone levels and SHBG levels are low despite the patient being deficient. Directly measuring free testosterone is possible and can be done in situations with abnormal levels of SHBG [9].

A few points worth keeping mind when performing testosterone investigations. There is an obvious diurnal variation in the serum testosterone demonstrated in young men. This reaches a maximum concentration at 0600 and drops to lower levels during rapid eye movement [10]. This diurnal variation is noticeably dulled in men over 40 years in age [11]. Short lived altered levels can occur also e.g., a reduction with acute illness, consumption of large amounts of alcohol the day prior to testing and an increase if fasting. Such factors should be excluded by clinical evaluations and repeat testosterone measurement [8]. TD cannot be diagnosed with the presence of symptoms alone; there must be an accompanying reduction in serum levels to make the diagnosis.

Checking Gonadotropin levels helps to differentiate between primary and secondary Hypogonadism. If LH and FSH levels are repeatedly low then a referral to secondary care for further investigations is warranted.

Treatment

As with other hormone replacement therapies, the aim of treatment is to improve symptoms and so improve quality of life. Before initiating treatment, screening for contraindications is required (Box 4).

Contraindications against TRT

- Benign prostatic Hyperplasia with severe LUTS
- Male Breast Cancer
- Prostate Cancer
- Hematocrit > 54%
- Severe sleep apnoea
- Male infertility with active desire to have children

Box 4: Contraindications against TRT

Baseline investigations and examination should be performed including hematological, breast, prostatic and cardiovascular assessments. The current consensus is that testosterone does not cause Prostate Cancer but may exacerbate pre-existing malignancy [3]. The prostatic assessment should involve an International Prostate Symptoms Score (IPSS), Serum PSA and an examination of the prostate gland. Patients should be seen by Urologist if the IPSS is >19, there is an elevated PSA or if there is any suspicion of malignancy.

Who to Treat?

Amongst different Urological societies and associations, there is an acceptance that screening the general population for TD is not recommended [14]. It is felt that elderly men with multiple symptoms and/or conditions suggestive of TD should be investigated. Men without either of these factors, who happen to have reduced testosterone levels, should not be treated. It is a controversial scenario without a clear way forward.

Which Preparation to Choose?

Different methods of administering TRT are available, with varying pharmacokinetics and side effects. Oral medication is difficult to comply with as it is required to be taken four times daily. There is doubt over its effectiveness amongst Endocrinologists and with better preparations being available they are not often prescribed.

Intramuscular injections of TRT can be required every one to two weeks. An issue with this route of therapy is the peaks and troughs achieved by the treatment. Attending their physician in this manner is also an inconvenience for many and can affect compliance.

Sub-dermal pellets are available but doubts remain over the serum testosterone levels during treatment as there is only limited data. They can last for 3-6 months and require a minor procedure in order to insert them in to the subcutaneous fat of the buttocks, lower abdominal wall, trocar or thigh.

The transdermal route is preferred. This can be in the form of patches or gels. Any type of patch carries the risk of causing skin irritation and coming loose with exercise and seating. Gels are generally preferred as they don't have the same drawback and fine tuning of the dose is possible. They can have a gooey consistency and men are required to wash their hands after applying.

Intranasal testosterone is a newer delivery method of TRT and may possibly not suppress spermatogenesis. This remains to confirmed by large scale robust trial data.

Monitoring

Risks of TRT

- Marginal increase in PSA
- Testicular atrophy and impaired spermatogenesis
- Sleep Apnoea
- Polycythemia
- Exacerbation of Breast Cancer
- Oily Skin/ Acne

Box 5: Risks of TRT

All patients started on TRT should receive periodic follow up. The response to TRT should be assessed at three, six and twelve months after the commencement of treatment. Thereafter annual review annually is recommended [5]. These assessments should include a serum testosterone level test. The target for treatment is a level in the mid-range. The timing of the tests will vary according to the route of administration. When the Intramuscular route is used, a Testosterone level should be performed around the midpoint between injections. Patches have peak testosterone levels 3- 12 hours after application. With gels, the testosterone level is constant and so the timing of the check is less critical though should be done around one to two weeks after is started or changed.

For men on long term TRT, a prostate examination should be done routinely. A digital rectal examination of the prostate and IPSS score should be done and once yearly a serum PSA should be checked – any abnormality should prompt cessation of therapy and referral to a Urologist. TRT can cause a slight increase in PSA and prostate volume, with this plateauing at twelve months [15]. Failure to respond to TRT should warrant a discussion on compliance as well as a revaluation of whether changes in dose or method of administration are necessary. Persistent failure in response to the TRT should prompt a reevaluation of the diagnosis.

One of the commonest side effects of TRT is a raised Hematocrit [5]. This may be associated with hyperviscosity thrombosis though the significance of this remains unclear [16]. If the Hematocrit is raised to and above 54%, a reduction or cessation in therapy is prudent till levels are normalized. TRT can be restarted at a lower dose if levels fall back to normal.

TRT is known to cause fluid retention in the setting of Chronic Heart Failure (CHF) and so exacerbate the condition [17, 18]. If after careful counseling of the patient a decision is taken to commence TRT, then closer and more frequent follow up will be required, with checks on Hematocrit, testosterone and exacerbation of CHF symptoms necessary.

Counseling patients that the effects of TRT are not immediate and can take time. Some report improvements in symptoms within three to six weeks of starting therapy (such as with libido, erectile function and mood) whereas other changes to muscle mass can take longer show [15].

CONCLUSION

Recent studies have shown that raising testosterone levels of older men with low testosterone has some benefits. Though trials involving a smaller number of patients exist [19], till now no study has enrolled enough men and treated and observed them for long enough to confirm with certainty potential risks of Prostate cancer with TRT. Androgen deficiency in the older male is a relatively common and underdiagnosed problem. Its potential treatment is relatively simple and could have wide ranging benefits at the individual level. Further research and development on different treatment modalities is bringing the day closer where treatment will be routine for older males. This author envisions a future where it will become a more common and acceptable therapy.

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