

TRT - The Best Treatment for Balancing Testosterone in Middle Aged Men

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Abstract

Balance is critical to many aspects of life. Work-life balance ensures that we have time to enjoy the fruits of our labor. Hormones control bodily processes like - metabolism, homeostasis, growth and development, sexual function, reproduction, sleep-wake cycle, and mood. Most men see a gradual and progressive decline of testosterone, the primary male sex hormone, starting around age 30, at a rate of 1–2% per year, though in some men, the decline is faster than the body can adequately compensate. In these cases, the fallout can be felt throughout the body with symptoms that are both disruptive and inconvenient. It is produced in the testicles and the adrenal glands but regulated by the hypothalamic-pituitary-gonadal (HPG) axis, a feedback system that responds to circulating hormone levels.

Hormonal imbalance in men closely parallels the aging process. The most effective way of balancing male hormones is using testosterone replacement therapy (TRT).

Generally, a value < 300 ng/dL is considered low, leading to a condition called hypogonadism. While one-third of Indian men above 40 years of age suffer from hypogonadism, the proportion of them as appropriate candidates for testosterone therapy (TTh) is not clear, not only in India but also in most countries. TTh helps reverse the effects of hypogonadism, but it's unclear if it would benefit otherwise healthy older men.

Primary care physicians encounter clinical conditions of hormonal imbalances in males, such as precocious puberty, delayed puberty, and hypogonadism, in general practice, needing specialists' consultation and guidance for their management.

Quoting half a dozen case reports of hormonal imbalance and their management, this article provides the evidence to prescribe or not to prescribe hormones for men.

Materials and Methods: Sample cases of precocious puberty, delayed puberty, male hypogonadism (MH) (general, diabetic, and intracranial hypertension), and a case of complication of TTh cases in adults and how they were diagnosed and managed. Literature review for current evidence for TTh in men globally and in Indian practices.

Keywords: hormones, testosterone, oestrogen, progesterone, hormonal imbalance, hypogonadism, eligibility criteria for testosterone therapy (TTh) for hypogonadism, sex hormone binding globulin (SHBG) levels

Abbreviations: HPG: hypothalamic-pituitary-gonadal; TRT: testosterone replacement therapy; TTh: testosterone therapy; LH: luteinizing hormone; FSH: follicle-stimulating hormone; MRI: magnetic resonance imaging; IHH: idiopathic intracranial hypertension; CPP: central precocious puberty; SMR: Sexual Maturity Rating; CDGP: constitutional delay of growth and puberty; GnRH: gonadotropin-releasing hormone; MH: male hypogonadism; TT: total testosterone; FT: free testosterone; ESI: Endocrine Society of India; SHBG: sex hormone binding globulin; TD: testosterone deficiency; ED: erectile dysfunction; LOH: late-onset hypogonadism; CK: creatine kinase

Introduction

Hormones are chemicals that coordinate different functions in our body by carrying messages through our blood to our body organs, skin, muscles, and other tissues, what to do and when to do it. Hormones control bodily processes like - metabolism, homeostasis, growth and development, sexual function, reproduction, sleep-wake cycle, and mood.

Most of us, as we age, would say, 'If I just had my hormones back the way they were, it would all work out better.' Hormones are essential for life and our health. A hormonal imbalance happens when we have too much or too little of one or more hormones. It is current day need and urgency for primary care/family physicians to ensure that patients with hormonal imbalances are being heard, their symptoms are recognized appropriately and ascribed to the appropriate problems and managed, and unnecessarily not treated for hormonal problems when they are not [1].

Hormone imbalance therapy medication for men involves i) testosterone replacement which helps with overall oestrogen balance by improving the ratio of testosterone to oestrogen, ii) in cases of increased oestrogen, aromatase inhibitors and antigonadotropins to reduce the production of oestrogen, which keep aromatase from converting androgen hormones into oestrogen, thereby reducing oestrogen levels. Antioestrogens are used to reduce the response to oestrogen.

Men are men! and they wish to remain men! by ending the era of waking up tired and bringing back youthful energy into lives. Sleep is one of the most important components of living an optimized life. Therefore, men must cultivate a sleep schedule that supplements them to sleep deeper and wake up with more energy. Sexual health is an important component of a man's life; everyone must optimize sexual health by solving issues with erectile deficiency or renewing excitement and passion in the bedroom. All must remember that the elderly is never too old to see results in fighting fatigue, weight gain, memory loss, and more, restoring youthful sex drive and performance. They must bring a renewed focus into life through personalized optimization of hormone levels, opting for hormone therapy if required. Testosterone therapy (TTh) can help reverse the effects of hypogonadism, but it's unclear if it would benefit older men who are otherwise healthy [1].

Pathophysiology of hypogonadism in men

Male hypogonadism (MH) is a condition in which the body doesn't produce enough of the testosterone hormone that plays a key role in masculine growth and development during puberty, or enough sperm, or both. An individual can be born with MH, or it can develop later in life, often from injury or infection.

Oestrogen and Progesterone for Men

Don't be surprised, oestrogen and progesterone are not only female hormones! During puberty, oestrogen helps to facilitate physical changes, like chest and facial hair growth, muscle development, and deepening of the voice in men. It is present in low concentrations in blood, but in semen, it can be as high as 250 pg ml(-1) in testis fluids, higher than serum oestradiol in females. Oestradiol is essential for modulating libido, erectile function, and spermatogenesis. Progesterone is a precursor to testosterone, and therefore men need progesterone that counteracts the effects of oestrogen on the male body. It is produced in the adrenal and testicular tissue [2].

Although the male body needs oestrogen to function correctly, high oestrogen levels cause health problems like infertility, erectile dysfunction (ED), and depression. The symptoms of oestrogen dominance in men include ED, migraines, weight gain, depression, pulmonary hypertension, prostate cancer, and gynecomastia. On the other hand, low oestrogen in men gives rise to symptoms of delayed ejaculation, delayed growth during puberty, bone loss, pain, osteoporosis, weight gain, insulin resistance, and depression, in the long run, coronary heart and artery diseases. Falling oestrogens cause the mucus membranes within the inner ear to dry out, which results in blocked ears, tinnitus, earache, hot ears, itchy ears, and hearing loss [2].

This article tries to provide the evidence medical research has on when not to prescribe as well as when to prescribe hormones for men. More importantly, it provides a guideline to family physicians to identify the condition early and refer to appropriate endocrinologists as early as possible. The diagnosis of hypogonadism depends on hypogonadal symptoms and requires laboratory investigation to demonstrate low serum testosterone levels.

Case Reports

1. Precocious puberty in a boy of 7 years

A 6-year 9-month-old Indian male child was brought to Medical College Hospital in January 2022, with complaints of excessive growth of pubic hair and an increase in penile length for 6 months. On local examination of the genitalia, pubic hair was ++, his penile length was 9 cm, and testicular volume was > 4 mL. The Sexual Maturity Rating (SMR) score was Tanner stage T4. Serum testosterone levels - 592.76 mmol/L, serum luteinizing hormone (LH) - 2.18 IU/L, and serum follicle-stimulating hormone (FSH) - 4.69 IU/L. His X-ray of the left wrist showed bone age > 12 years. Magnetic resonance imaging (MRI) of the brain showed an ill-defined T2 hyperintense mass involving the right half of the tuber cinereum. A diagnosis of central precocious puberty (CPP) due to hypothalamic hamartoma was made. He was given an injection leuprodex 3.75 mg intramuscularly once every month. He was discharged with a plan to follow up on an outpatient basis. He is much better as of June 2023, his last visit.

2. A case of delayed puberty

An 18-year-old man was referred by a PHC medical Officer in 2021 for evaluation of delayed puberty. History revealed that he had never grown facial, axillary, or pubic hair, his voice had not changed, and he rarely had acne or body odor. His mother reported that his energy level was quite low, and he rarely mixed with his age cohorts and left the house except for school. He was taken to 3–4 pediatricians at three years of age for speech delay, at 6 years of age for undescended testes, and 14 years of age for cognitive delay. No other concerns were noted at these visits by the pediatricians.

The patient's vitals were normal. His height was within 2 inches of his mid-parental height. His body mass index was in the 85th percentile. He appeared younger than his actual age. His fundi and visual fields were normal. His thyroid gland was not enlarged. He had no axillary or pubic hair. His phallus measured 3 cm and both testes were palpable and approximately 2 mL in volume. He was Tanner stage 2 for pubertal development. Investigations of his serum hormone and imaging helped diagnosis.

Blood reports revealed a testosterone level of < 0.3 nmol/L (prepubertal < 1 nmol/L) with a LH level of < 0.4 IU/L (prepubertal 0 IU/L to 1 IU/L) and a FSH level of 0.80 IU/L (prepubertal 0.5 IU/L to 3 IU/L). There was no response to gonadotropin releasing hormone stimulation testing. His thyroid-stimulating hormone (TSH) was 5.1 mIU/L (0.46 mIU/L to 5.8 mIU/L), free thyroxine (FT4) 4.6 pmol/L (8 pmol/L to 22 pmol/L), prolactin 38 µg/L (6 µg/L to 24 µg/L) and insulin-like growth factor 1 > 25 µg/L (163 µg/L to 584 µg/L). His cortisol level at baseline was 18 nmol/L (150 nmol/L to 690 nmol/L) and only stimulated to 82 nmol/L on an adrenocorticotrophic hormone stimulation test. A complete blood count, electrolytes, and morning serum and urine osmolarities were within normal limits. The patient's bone age was determined by X-ray to be 14 years. MRI of his pituitary gland showed an ectopic posterior pituitary in the hypothalamic location, agenesis of the pituitary infundibulum, and a hypoplastic anterior pituitary gland in the

sella. The optic nerves were unremarkable. There was no evidence of a tumor. A diagnosis of congenital hypopituitarism was made.

The patient was immediately put on hydrocortisone and thyroxine treatment one week later to avoid precipitating an adrenal crisis. After 2 months, he was started on monthly injections of testosterone to initiate puberty. As there was no response, growth hormone therapy was also initiated. After one year of testosterone, he reached appreciable puberty at Tanner stage 5 and now continues to take testosterone once in 2 months.

3. Hypogonadism in men

i) A 34-year-old male presented to the endocrinology clinic in a private medical college in Bengaluru in 2020 with the complaint of the absence of facial, axillary, and pubic hair. He reported absent ejaculations and decreased early-morning erections. The patient had no other history of significance. On physical examination, there were sparse facial, axillary, and pubic hair, bilateral gynecomastia, stretch penile length of 5 cm, and bilateral testicular volume of 10 mL. Laboratory investigations showed low luteinising hormone, FSH, and testosterone with normal prolactin and thyroid profile. MRI of the pituitary gland showed no evidence of pituitary adenomas. The patient was started on monthly testosterone injections, and after 15 months, the patient's testicular size increased to 20 mL bilaterally, and his penile length increased to the mean adult size for his age with normal testosterone and luteinising hormone. He is advised to continue TTh until 60 years of age.

ii) A 40-year-old male patient with morbid obesity, hypertension, and diabetes, with symptoms of absence of facial, axillary, and pubic hair, poor ejaculations, and decreased early morning erections (signs of hypogonadism) in March 2021 to a private medical college hospital in Bengaluru. Ten years ago, he was diagnosed with a low total testosterone (TT) level of 140 ng/dL when he consulted for difficulty in losing weight. He neither took hormone therapy as advised nor further pursued. His testosterone levels were rechecked five years later and again found to be decreased further (TT: 75 ng/dL; free testosterone (FT): 9.0 pg/mL) with elevated gonadotropins (FSH: 15.4 mIU/mL; LH: 12.7 mIU/mL), consistent with primary hypogonadism. He had regained approximately 30 kg weight. Now, he desired to start TTh for weight loss and improved body composition. The scrotal ultrasound revealed bilateral testicles in the inguinal canals, with the left testes measuring 1.5 cc and the right testes measuring 2.5 cc. MRI demonstrated an enlarged sella with significant thinning in the pituitary parenchyma and bilateral tortuosity of the optic nerves, resulting in idiopathic intracranial hypertension (IIH). In consultation with urology and neurology, he was found to have intracranial hypertension. This case report serves to raise awareness of the association between IIH and hypogonadism in men.

4. Use Viagra in a man with erectile dysfunction

Mr. Vinay, the husband of a couple suffering from secondary infertility, was diagnosed diabetic in 2020 and has not been able to manage Hb1Ac well, reported with erectile deficiency for the last one year. The desire for a second child, work pressure, and tension at home led to sexual life disruption. The husband tried Viagra, the male enhancement gummies, from March till recently every month for about a week around ovulation time. Unfortunately, there is no conception so far. Husband and wife are under prolonged investigation.

Discussion

Testosterone is a powerful hormone in men with the ability to control bone density, fat distribution, muscle strength and mass, facial and body hair, red blood cell production, sex drive, and sperm production. It influences human behavior, such as aggression and competitiveness. In men, it is mainly produced by the testes, adrenal, and pituitary glands, and the level of testosterone gradually decreases as a natural part of aging, leading to reduced sex drive. Testosterone levels peak around age 18 or 19 before declining throughout the remainder of adulthood and healthy aging. A testosterone level of at least 300 ng/dL for a man and levels from 15–70 ng/dL for women aged 19 and up is normal [3, 4].

Apart from dropping as we grow older, any cancer of the testicles in men or ovaries in women, hypogonadism, absence of the testicles at birth, thyroid gland disorders, depression, excessive alcohol use, early or delayed puberty, chronic illness like diabetes, kidney disease, severe obesity, chemotherapy, or radiation for cancer treatment, opioid use, genetic conditions - Klinefelter syndrome, Kallmann Syndrome, cause low testosterone levels.

The effects of high and low testosterone levels among men are listed in the table below (Table 1):

| S. No. | Effects of low testosterone | Effects of high testosterone |
|--------|----------------------------------|---|
| 1. | Reduced sexual desire/low libido | More aggressive and irritable behaviour |
| 2. | Fewer spontaneous erections | More acne and oily skin |
| 3. | impotence, infertility | Worse sleep apnoea (if already have it) |
| 4. | Erectile dysfunction (ED) | An increase in muscle mass |
| 5. | Changes in sleep patterns | |
| 6. | Difficulty concentrating | |
| 7. | Lack of motivation | |
| 8. | Reduced muscle bulk and strength | |
| 9. | Decreased bone density | |
| 10. | Gynaecomastia | |
| 11. | Depression | |
| 12. | Fatigue | |

Table 1: Effects of testosterone imbalance in men.

Now let us discuss key clinical conditions of hormonal imbalances encountered in males in general practice, needing specialists' consultation and guidance for their management.

Precocious puberty in male

When puberty begins before age 9 in boys, it is considered precocious puberty. There are two types of precocious puberty: gonadotropin-dependent (CPP) and gonadotropin-independent. CPP is the most common, affecting less boys than girls. It's triggered by the premature secretion of gonadotropins from the brain. Untreated precocious puberty usually leads to short stature and can cause significantly more aggression and develop a sex drive inappropriate for their age. The key signs include i) penis, testicles, and scrotum reaching adult size; ii) pubic hair has filled in and spread to the inner thighs; iii) facial hair will start coming in and some males need shaving; iv) growth in height will slow down, but muscles may still be growing; v) by age 18, most males have reached full growth; vi) adverse psychological outcomes seen are higher rates of depression, anxiety, substance abuse, and criminal behaviors [5].

Tanner staging, {Sexual Maturity Rating (SMR)}, is an objective classification system that providers use to document and track the development and sequence of secondary sex characteristics of children during puberty. The five stages are described as i) Tanner stage 1, when hormones are hard at work behind the scenes; ii) Tanner stage 2, when the first physical signs of puberty occur - pubic hair starts to form; iii) Tanner stage 3, the growth spurt stage - voice begins to change or "crack", muscles get larger; iv) Tanner stage 4, the continuation of development - acne may appear, armpit hair forms; v) Tanner stage 5, the final stage - the testes are greater than 4.5 cm in length, and the penis reaches its mature size by age 16.5 years. Adult pubic hair spreads to the medial thigh. Hair appears on the sides of the face, and a mature male physique is attained [5].

It's perfectly normal for puberty to begin at any point between the ages of 9 and 14 in boys, though it's most common between the ages of 11 and 15. There's no need to worry if puberty does not start around the average age, but it's better to consult a family physician for advice if it starts before 9 or has not started by around 14. The main reason to treat CPP is to ensure that the child reaches full adult height. Such kids grow fast during puberty and seem like a giant compared to other kids, but this growth spurt stops too soon, and the child stays short when compared to his peer friends as they grow. Medication to regulate hormone production may be administered through injections (as was done in our case report) or through an implant under a child's skin that releases medicine over time. Surgery is rarely needed to treat early puberty unless the cause is a tumor [5].

Delayed puberty in male

If puberty does not begin by age 14 years in boys, it is recognized as late puberty. This delay may be due to individual genetic variations, known as constitutional delay of growth and puberty (CDGP), or other causes like undernutrition or chronic illness [6]. Around 60% of boys, delayed puberty is caused by CDGP, which affects twice as many boys as girls. The most common cause of delayed puberty is a functional delay in the production of gonadotropin-releasing hormone (GnRH) from the hypothalamic neuronal networks that initiate the episodic or pulsatile release of the GnRH and activate the hypothalamic-pituitary-gonadal (HPG) axis. Though it is a normal variant of growth but may make a child feel distressed. Late bloomers will catch up on their growth and have standard adult height, a bit late and need patience. The signs include i) testicles are smaller than 1 inch by age 14; ii) penis is small and immature by age 13; iii) there is very little body hair or almost none by age 15; iv) voice remains high-pitched; v) body stays short and thin; vi) fat deposits around the hips, pelvis, abdomen, and breasts. Combined administration of gonadotropins and GnRH induces gonadal development, including fertility, and must be the preferred choice of treatment [6].

The initial investigation of delayed puberty in boys should include measurement of testosterone, LH, and FSH. A low testosterone level in conjunction with high concentrations of LH and FSH is indicative of primary gonadal failure due to gonadal injury/insult, the most common condition of Klinefelter syndrome, which occurs in males with an extra X chromosome. These boys typically present with delayed puberty and abnormally small testes; a karyotype will confirm the diagnosis [6], as was in our case report no 2.

Low or normal levels of LH and FSH suggest either constitutional delay or central gonadotropin deficiency. Central causes include functional gonadotropin deficiency, isolated gonadotropin deficiency, and multiple pituitary hormone deficiencies. Unfortunately, it can be difficult to distinguish between constitutional delay and other more worrisome central causes using LH and FSH levels alone because there is a lot of overlap. However, boys with constitutional delay are typically shorter than their peers and have a positive family history of the same. Their bone age is also delayed by approximately two years, making this an important diagnostic tool. If the diagnosis remains uncertain, extended tests must include i) GnRH stimulation testing, ii) evaluation of other pituitary hormones followed by, iii) cranial imaging if there is evidence of hypopituitarism [7].

Male hypogonadism

The TT and FT concentrations decrease with increasing age in men. Male hypogonadism (MH) is a clinical and biochemical syndrome caused by inadequate synthesis of testosterone due to the failure of the testis to synthesize physiological levels of testosterone and a normal number of spermatozoa due to the disruption of one or more levels of the hypothalamic-pituitary-testicular axis. Pathologically low testosterone levels occur due to some conditions at birth, an illness of testicles in men or ovaries in women, including cancers, thyroid gland disorders, depression, excessive alcohol use, and as a reaction to certain medications. In some failure of the testicles, hypogonadism early or delayed puberty, diabetes, kidney disease, severe obesity, chemotherapy or radiation, opioid use, and genetic condition - Klinefelter syndrome also led to hypogonadism (Table 2).

| Age | Male (ng/dL) | Female (ng/dL) |
|--------------------|---------------|----------------|
| 19 years and older | 265–923 | 15–70 |
| 7–10 years old | 1.80–5.68 | 2.69–10.29 |
| 13–17 years old | 208.08–496.58 | 16.72–31.55 |

Table 2: Typical normal total testosterone levels in Indian adults.

Defining low testosterone levels in men: Men older than age 65 should have a testosterone level of about 300–450 ng/dL. Testosterone levels below 300 affect approximately 40% of men older than age 45, including 20% of men over 60, 30% of men over 70, and men over 80 years old [4]. The Endocrine Society of India (ESI) recommends TTh for men who have either less than 300 ng/dL of testosterone in the blood or symptoms of low testosterone. Measurement of serum FT and/or bioavailable testosterone is considered necessary in individuals suspected of having any disorder accompanied by increased or decreased sex hormone binding globulin (SHBG) levels [8].

MH can occur due to an intrinsic defect of the testes (primary hypogonadism), in which the Leydig, Sertoli, and germ cells are impaired, or at the level of the hypothalamus or pituitary gland (secondary hypogonadism), in which the testes lack gonadotropic stimulation by LH and FSH [1].

Untreated MH can result in long-term effects, including metabolic, musculoskeletal, mood-related, and reproductive dysfunction. The global prevalence of MH varies between 6% and 12% based on the study population and level of diagnostic rigor. Among Indian men above 40 years of age, the prevalence of MH is 20–29%. Among men with type 2 diabetes mellitus, 20.7% are found to have hypogonadism. Surgical comorbidities such as cryptorchidism, testicular trauma, and torsion, as well as radiotherapy to the gonads, are associated with hypogonadism.

- Magnitude of hypogonadism

The proportion of hypogonadal populations that are appropriate candidates for TTh is not clear in most countries. It is hard to know how many men among us have testosterone deficiency (TD), although data suggest that overall, about 2.1% (about 2 men in every 100) may have TD. As few as 1% of younger men may have TD, while as many as 50% of men over 80 years old may have TD.

TD is more common in men who have diabetes or who are overweight. In one research study, 30% of overweight men had low-T, compared to only 6.4% of those with normal weight. The same study found 24.5% of men with diabetes had low-T, compared to 12.6% of those without diabetes.

- A clinical assessment by the family physician must include

Medical history assessment. Case history must elicit-

a) Sexual history:

- (i) Lack of nocturnal erection,
- ii) Absence of premature ejaculation,
- (iii) Lack of libido

b) Medical history:

- (i) Comorbidities of lungs, heart, liver, and kidney disorders,
- (ii) History of gynecomastia

c) Psychological history:

- (i) Anxiety or depression,
- ii) Use of drugs for such conditions

d) Medication history:

- (i) Pre-screening hormonal medication,
- (ii) Use of antihypertensive drugs, - propranolol,
- (iii) Withdrawal of any TTh,
- (iv) Use of dopaminergic drugs

e) Surgical history: injury or testicular surgeries

Diagnosis: The lack of specific symptoms, the role of obesity, metabolic syndrome, and diabetes mellitus are the challenges in the diagnosis of MH.

A serum TT value confirms the diagnosis of MH and serves as a monitoring tool during therapy. When TT levels are equivocal, or elderly people with high SHBG levels, FT are assessed to confirm [4].

Testosterone cutoff values also differ across different guidelines. While most guidelines and ESI suggest that values < 300 ng/dL must be considered low, it is not yet determined whether they are related to loss of libido or ED. Instances of patients with testosterone values < 200 ng/dL and loss of libido being benefitted from treatment are reported.

Our second case of adult hypogonadism with IIH is rare in men, as only 9% of IIH patients are male. Men are twice as likely as women to suffer severe visual loss. Men are less likely to have headaches as their initial symptom and remain asymptomatic until report visual changes as their first symptom compared to women [9, 10].

Diabetic hypogonadism and testosterone replacement therapy

Studies indicate that ~10% of aged men with obesity and T1DM have hypogonadism. A pooled analysis of other observational studies in obese hypogonadal men with T2DM found that testosterone replacement therapy (TRT) significantly reduced- i) fasting blood glucose and HbA1c levels, ii) total cholesterol, iii) low-density lipoprotein cholesterol, iv) triglycerides, thus reducing the risk of CVD, v) levels of inflammatory markers suggesting reduction in the inflammation response, vi) increased high-density lipoprotein cholesterol levels, vii) improved systolic and diastolic blood pressure. These data were validated in a placebo-controlled study over 2 years published in January 2021 [8, 9].

▪ MH management

The use of medicine containing gonadal steroids, GnRH analogues, glucocorticoids, and chronic opiates causes secondary hypogonadism by altering the hypothalamic-pituitary-adrenal (HPA) axis. Recent evidence suggests that TTh is beneficial in the management of hypogonadism and prediabetes despite old beliefs that it increases the risk of CV disease, thromboembolic events, obstructive sleep apnea, benign prostate hypertrophy, and prostate cancer. While caution must continue, evidence suggests that TTh is a reasonable treatment option in many hypogonadal men who were previously excluded.

▪ Testosterone replacement therapy

Testosterone is frequently used for the optimization of mid-life health. For patients with confirmed hypogonadism (either primary or secondary), TRT is recommended [8]. Testosterone injections as hormone replacement treatments are given for sexual dysfunction in males.

The use of TRT for late-onset hypogonadism (LOH) is increasing every year; some of them are even without a clear indication. Multiple professional organizations, such as the International Society for the Study of the Aging Male (ISSAM), the European Association of Urology (EAU), the European Society of Endocrinology (ESE), the European Academy of Andrology (EAA), the American Urological Association (AUA), and the Endocrine Society of India (ESI), have agreed in recent guideline testosterone (TT) of 250–350 ng/dL as the proper threshold value to define low-T. The optimal indication for TRT in LOH is the presence of signs and symptoms of hypogonadism and low-T without contraindications for TRT. LOH is the result of a gradual drop in T levels of about 1% per year, is well documented in men [8], and varies between individuals, with higher rates of decline in men with adiposity and comorbid diseases like diabetes. In LOH, the anabolic effect of T is reduced due to its deficiency [11, 12] (Table 3).

| | | | | | |
|---|----------------------------|----------------------------|-----------------------------------|--|---|
| Symptoms of hypogonadism (physical examination, history, and score) | Measure total testosterone | Low (< 231 ng/dL) | Elevated LH and FSH | Exclude contraindications for testosterone | (i) Trial of testosterone; (ii) Monitor response |
| | | Borderline (231–346 ng/dL) | Calculate free testosterone | Exclude pituitary and other causes | |
| | | | | Low (< 52 pg/mL) | Check for elevated LH and FSH |
| | | Normal (> 346 ng/dL) | Seek other causes of the symptoms | | |

Table 3: Diagnostic algorithm for late-onset hypogonadism.

Although various formulations exist, optimal TRT remains a considerable challenge as patients often need individually tailored therapeutic strategies. The ESI recommends that only an endocrinologist must treat with testosterone if hormone levels are very low. Testosterone can be prescribed in the form of a shot, a skin patch, a skin gel, or a liquid. Primary care doctors must avoid prescribing testosterone as drug safety communication is rigid for prescribing TRT agents. However, TRT for low levels caused by aging alone is not advised.

As of now, only transdermal gel delivery and long-acting injectable testosterone undecanoate provide pharmacokinetic behavior that gives a steady state level within a physiological range. The reference limits are 12.1–33 nmol/L for TT and 70–141 pg/mL for FT for initiating TTh. 1) The use of a short-acting aqueous preparation, an injectable, or an oral preparation should be preferred as the initial dose of therapy, 2) once safety and tolerability have been demonstrated with shorter-acting testosterone, later shift to long-acting preparations if they desire, 3) clinicians must discuss all available options with the patient and allow well informed and shared decision-making. XYOSTED is a prescription medicine used to treat adult men who have low or no testosterone. It is contraindicated in a man who has breast cancer or has, or might have prostate cancer.

TTh personalized optimization requires initial laboratory testing of 60+ biomarkers, supplements and micronutrients, consultation with an andrologist, and follow-up with a physician annually. If deficient, treatment plan includes compounded optimization medications, individual tailored optimization prescriptions, increase energy and lean muscle mass, and reduce the likelihood of chronic disease [11].

The TRAVERSE trial published in the New England Journal of Medicine recently and presented at ENDO 2023, a total of 5246 men, ages ranging from 45–80 years (mean age 63 years), were followed in a multicentre study from May 2018 to February 2022 [11]. After a mean follow-up of 33 months, the primary cardiovascular safety endpoint of the first episode of any component of a composite of cardiac-related mortality, nonfatal myocardial infarction, or nonfatal stroke was comparable between the two groups: 7.0% in the testosterone group vs. 7.3% in the placebo group (hazard ratio 0.96). The secondary endpoints of coronary revascularization were also similar between the two groups. However, the incidence of atrial fibrillation (3.5% vs. 2.4%), acute kidney injury (2.3% vs. 1.5%), and pulmonary embolism (0.9% vs. 0.5%) were higher in patients on testosterone compared to those receiving placebo. The findings of the present study are reassuring, but they do not totally refute the current guidance about exercising caution when prescribing testosterone, but they do enable more informed decision-making after taking into consideration the potential risks and benefits [11].

Sildenafil (Viagra) is used to treat male impotence or ED. In combination with sexual stimulation, sildenafil works by increasing blood flow to the penis to help a man get and keep an erection. Sildenafil, taking at least 30 min, but no more than 4 h, before sexual activity (1 h before most effective) gives good results. Taking more than once daily is not recommended. A high-fat meal may delay how quickly the drug begins to work. The dosage is based on the client's medical condition, response to treatment, and other medications he may be taking [13].

A series of blood tests after a detailed history of symptoms determine a candidate for TRT with weekly intramuscular injections, lowest effective dose (based on clinical experience of the doctor) at the most efficient intervals. Testosterone needs to be injected weekly because it degrades in about 7 days. Once symptoms start to respond and lab values support that observation, a good maintenance dose is determined for everyone based on other hormone levels (Table 4).

| Route | Preparation | Dosage |
|-------------------------|----------------------------------|----------------------|
| Oral capsules | Testosterone undecanoate | 40 mg 2–3 days |
| Percutaneous gel | Testosterone 1% gel | Once daily |
| Intramuscular injection | Testosterone suspension | 25–50 mg q 7–14 days |
| | Testosterone esters 100/250 | Q 21–28 days |
| | Testosterone undecanoate 1000 mg | Q 90 days |

Table 4: Testosterone preparation in the Indian market.

Complications of testosterone therapy: Rhabdomyolysis is a muscle condition resulting from an insult due to overexertion, trauma, medications, or an underlying health condition, as reported in our case no. 4. Common signs and symptoms of rhabdomyolysis are weak muscles, muscle stiffness, muscle pain, and a change in urine colour. The only way to know you have rhabdomyolysis (rhabdo) is through a blood test that checks for the presence of a muscle protein, creatine kinase (CK), in the blood. Symptoms can appear at any time after muscle injury. The laboratory findings that characterize rhabdomyolysis include an acute elevation in the CK and other muscle enzymes and a decline in these values within three to five days of cessation of muscle injury.

▪ Oestradiol therapy

A typical test requires a blood, urine, or saliva sample, tested for levels of oestrogens such as oestradiol and compared against levels of testosterone. If an oestrogen imbalance is confirmed, treating a preexisting medical condition is prioritized first.

If high or low oestrogen is the only issue, lifestyle modifications are suggested, which include:

i) Diet: Weight loss is the “number one” method to balance out oestrogen. Sticking to whole-grain food, low in fat and high in fiber helps. Foods high in oestrogen compounds, such as soybeans, garlic, celery, carrots, potatoes and sweet potatoes, apples, coffee, flaxseed, and foods containing synthetic hormones, be avoided. A plant-based or vegan diet that relies on soy and dairy products as a source of protein must be consumed in moderation.

ii) Exercise: At least 2–3 times a week for 20–30 min of walking, starting slow and steady with easy exercises, like bodyweight moves for beginners, be adapted. The use of simple equipment, such as resistance bands, to enhance workouts facilitates. By lifting heavy weights, we can improve the connection between the muscular system and the central nervous system. This improvement allows for more muscle fibres to be recruited. More muscle fiber recruitment means more micro tears occurring, more muscle tears mean more repairs required, these repairs are done by protein synthesis and protein synthesis is the key. Testosterone binds to receptors on the surface of muscle cells and amplifies the biochemical signals in muscle tissue that result in protein synthesis. With more repairs needed, more testosterone is recruited to allow for more protein synthesis. Being a large muscle group, training legs is important for increasing testosterone levels. This trickle-down effect reflects the importance of testosterone.

iii) Medications are prescribed only when changes in diet and exercise routine do not give desired results.

There are two classes of drugs used to block either the production or the activity of oestrogen. While aromatase inhibitors and antigonadotropins reduce the production of oestrogen, antioestrogens are agents reducing the response to oestrogen. There are three aromatase inhibitors: anastrozole, exemestane, and letrozole. Indian endocrinologists prescribe: i) Chlorotriazine, a synthetic oestrogen, for treating the symptoms of menopause, deficiency in ovary function, and prostate cancer; ii) Dehydroepiandrosterone (DHEA) is also known as androsterone, by trade names of

Coedhea Plus (75mg/500mg) | Depidra (25mg/1.5mg) | Depidra SR (75mg/1.5mg/1000IU) | Dheador (25mg); iii) Ethinyl estradiol and norethindrone contains oestrogen and progestin, prescribed for menopausal symptoms.

Oestradiol, the predominant form of oestrogen, plays a critical role in men as it is essential for modulating libido, erectile function, and spermatogenesis. Viagra contains the drug sildenafil. It belongs to a class of drugs called phosphodiesterase type 5 (PDE5) inhibitors (A class of drugs is a group of medications that act in a similar way). Viagra works by increasing blood flow to your penis, which helps you have and keep an erection.

Oestradiol and SERMs offer new opportunities to achieve improved outcomes in a broad population of individuals with schizophrenia [14].

Conclusion

- Hormones control bodily processes, like metabolism, homeostasis, growth and development, sexual function, reproduction, sleep-wake cycle, and mood.
- A hormonal imbalance happens when we have too much or too little of one or more hormones.
- Hormone imbalance therapy medication for men involves i) Testosterone replacement which helps with overall oestrogen balance by improving the ratio of testosterone to oestrogen; ii) In cases of increased oestrogen, aromatase inhibitors and antigonadotropins are used to reduce the production of oestrogen, which keep aromatase from converting androgen hormones into oestrogen, thereby reducing oestrogen levels. Antioestrogens are used to reduce the response to oestrogen.
- Treatment plan includes compounded optimization medications, individually tailored optimization prescriptions, to increase energy and lean muscle mass, and reduce the likelihood of chronic disease.
- It is current day need and urgency for primary care/family physicians to ensure that patients with hormonal imbalance are being heard, their symptoms are recognized appropriately and ascribed to the appropriate problems and managed, and unnecessarily not treated for hormonal problems when they are not.

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