Review Article ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

Testosterone Replacement in Hypogonadic Men

Prof. Dr. Maria Lúcia D'arbo Alves*

Professor of Endocrinology, Ribeirão Preto University, (UNAERP), Ribeirão Preto, São Paulo State, Brazil.

***Correspondence:**
Prof. Dr. Maria Lúcia D'arbo Alves, Professor of Endocrinology, Ribeirão Preto University, (UNAERP), Ribeirão Preto, São Paulo State, Brazil, ORCID: 10000-0001-6817-1357.

Received: 25 Mar 2022; **Accepted:** 22 Apr 2022; **Published:** 27 Apr 2022

Citation: Lúcia D'arbo Alves M. Testosterone Replacement in Hypogonadic Men. J Med - Clin Res & Rev. 2022; 6(4): 1-4.

Keywords
Testosterone, Male hypogonadism, Aging, Sexuality.

Introduction

Male hypogonadism is a diseases involving low serum testosterone levels associated with specific signs and symptoms such as reduced libido, a reduced sensation of vitality, erectile dysfunction, reduction of muscle mass and of bone mineral density, depression, and anemia [1]. This disease has a profound NEGATIVE impact on the physical health and personal satisfaction of both middle-aged and young men [1].

The condition is classified as primary (hypergonadotropic), of testicular origin, secondary (hypogonadotropic), of hypothalamic and/or pituitary origin, and also as a combination of primary and secondary origin, as observed during aging and in various systemic diseases (alcoholism, liver diseases, sickle cell anemia, and others). It may also be due to androgen resistance (a defect in the androgen receptor), to post-receptor abnormalities or to the inability to convert testosterone to its active metabolite (dihydrotestosterone) due to 5α-reductase deficiency.

The prevalence of male hypogonadism increases with age. In the United States, the disease is estimated to affect 2 to 4 million men, with only 5% of them being treated [1]. The estimate is that the prevalence of male hypogonadism is 3.1-70% among men in the 30-to-70 -year age range [1-7].

The testes have a double function, i.e., the production of sexual steroids (testosterone) and of spermatozoa, controlling sexuality and the perpetuation of the species (fertility). They contain two functionally different structural components, i.e., Leydig cells and seminiferous tubules, which are intimately related [5].

Leydig cells or interstitial cells secrete testosterone and are regulated by pituitary luteinizing hormone (LH). Spermatogenesis is regulated by follicle stimulating hormone (FSH) and by testosterone.

The seminiferous tubules represent 80-90% of the testicular mass and are responsible for the daily production of approximately 30 million spermatozoa during the reproductive life of males (from puberty to death). A high testosterone concentration is necessary for the development of germ cells during spermatogenesis.

FSH is necessary for the beginning of spermatogenesis, although full sperm maturation requires the action of testosterone.

Testosterone, the main male hormone secreted by the testes, is produced in quantities of about 7 mg/day. Testosterone levels reach a maximum peak during the second and third decades of life and are gradually reduced with advancing age.

Genetic factors, adiposity and comorbidities affect the course of the age-related decline in testosterone levels. Hypogonadism is the major risk factor for type 2 diabetes mellitus and cardiovascular disease [3,4,7].

Testosterone values (determined by electrochemiluminescence) considered to be adequate for males are:
Total testosterone: 240-816 ng/dl
Free testosterone: Men aged 20-40 years: 0198-0.619 nmol/L
Men older than 50 years: 0163-0.473 nmol/ L

The levels of sex hormone binding globulin (SHBG, determined by electrochemiluminescence) are:
SHBG: Men aged 20-49 years: 18.3-5.41 nmol/L
Men older than 50 years: 206 – 76.7 nmol/L

About 7 to 14% middle-aged and older men have a fasting total testosterone level below 250 mg/dl [3-6]. The proportion of men

with low testosterone levels and sexual symptoms increases from 0.1% among men aged 40 to 49 years to 5.1% among men aged 70 to 79 years [3-6].

The great majority of older men with low testosterone have low or inadequately normal LH levels (secondary hypogonadism) and a smaller fraction of them has high LH levels (primary hypogonadism).

Secondary hypogonadism is more frequently associated with obesity and comorbidities, whereas primary hypogonadism is strongly associated with age [7,8].

Low testosterone levels are associated with reduced sex drive and erectile dysfunction (ED), reduced skeletal muscle mass and strength with impaired physical performance, and reduced bone mineral density (BMD) with an increased risk of osteoporotic fractures, although such fractures are more associated with BMD.

Type 2 diabetes mellitus (DM2) is associated with male hypogonadism, involving low SHBG and testosterone levels. The incidence of male hypogonadism among type 2 diabetic patients is estimated to be 46% in Poland and 3.1% in China. Higher testosterone levels reduce the risk of DM2 in men and improve cardiovascular risk factors including glycemic control, improving insulin sensitivity, dyslipidemia and central obesity. Among women, however, high testosterone levels are associated with worse glycemic control [7,8].

Low testosterone levels are associated with shorter telomere length and increased all-cause mortality [9].

A low testosterone level is considered to be a marker of health problems [9]. A group of seven coordinated placebo-controlled assays has permitted a more encompassing evaluation of the efficacy of increased testosterone levels in men older than 65 years of age determined on two mornings, lower than 275 ng/dl, and of a condition associated with low testosterone levels (low libido, limitation of mobility, and fatigue) [9,10].

The Trials and other randomized clinical trials (RCT) have shown that testosterone treatment for men with low libido improves their general sexual activity and erectile function. However, testosterone treatment does not improve the sexual function of men with normal testosterone levels who have no sex symptoms or the ejaculatory function of men with ejaculatory disorder and low testosterone levels [9,10].

In men with ED and low testosterone levels, treatment with phosphodiesterase 5 inhibitors substantially improves erectile function, while the addition of testosterone does not further improve the erectile function compared to placebo [8].

Testosterone treatment increases in a dose-dependent manner maximum voluntary isometric muscle contraction, leg potency, stair climb power, the distance covered in a 6-minute walk, self-reported mobility and aerobic capacity, and attenuates the age-related reduction of peak oxygen consumption [9-11].
Resisted physical training increases the anabolic effects of androgens on muscle mass and strength [9,10,11]. Testosterone induces a moderate improvement of depressive symptoms in hypogonadic men. None of the available testosterone assays was of sufficient duration or size to determine the effects of the hormone on the risk of fracture. RCT of the effects of testosterone on cognitive function are limited and equivocal.

The administration of testosterone reduces visceral and whole-body fat and is positively associated with improved insulin resistance, but has not shown a consistent improvement of glycemic control [9-12].

In older men, testosterone treatment increases the levels of circulating erythrocytes, platelets, neutrophils, and monocytes, also stimulating erythropoiesis and iron availability [9-12]. It has not been demonstrated that testosterone treatment improves fatigue, memory or cognition.

Although testosterone therapy (TTh) is effective for hypogonadism, its use may potentially involve cardiovascular risks, with the possible occurrence of an up to 20% increase of atheromatous plaque in the coronaries. The preservation of fertility is another reason for seeking viable alternatives to conventional TTh [17].

Available medical therapies include human chorionic gonadotropins, aromatase inhibitors and selective estrogen receptor modulators. Reviewed non-pharmacological therapies include modifications of life style (diet and physical exercise), improved sleep, reduction of stress, and varicocele repair. The high prevalence of metabolic syndrome indicates that its treatment represents a viable approach for affected men These alternatives to TTh can increase the levels of testosterone and should be considered before the use of TTh [9-12].

When available medical therapies do not represent a solution for male hypogonadism, TTh has a role to play.

Potential Risk of Testosterone Treatment

TTh for men with hypogonadism involves a low frequency of adverse side effects such as acne, erythrocytosis (the most frequent adverse effect) [4,5], growth of metastatic prostate cancer, increased risk of detection of subclinical prostate cancer, and reduced sperm production. TTh in patients with Klinefelter syndrome reduces the risk of prostate cancer, suggesting that long-term exposure to testosterone may increase the risk of prostate cancer.

TTh does not cause a worsening of lower urinary tract symptoms or sleep apnea [16]. It is not justified to submit to TTh all older men with low testosterone levels [5,6,8-10,17].

A panel of Endocrine Society specialists has recommended that

"testosterone treatment should be offered in an individualized manner to men older than 65 years with symptoms or conditions suggestive of testosterone deficiency (low libido, unexplained anemia) and consistently low serum testosterone concentrations" [5,6,19,20].

The decision to offer TTh to older men with low testosterone levels should be based on an individualized evaluation of the potential risks and benefits: 1) to determine if the patient shows clear evidence of testosterone deficiency; 2) to estimate the load of symptoms/conditions in relation to the potential benefits and to the uncertainty about long-term damage, and 3) to determine whether the patient has conditions such as prostate cancer, erythrocytosis [19,20], heart failure or a hyper-clotting status that would increase the risk of damage [17,18].

A recent Scottsdale study showed that men with hypogonadism who develop deep venous thrombosis (DVT) were not more likely to have received recent testosterone replacement therapy (TRT). Another study comparing two groups of men with hypogonadism revealed that those with DVT had the same probability of having received TRT (34.9%) or not (33.04%) [13,14].

Older men who consider TRT should be evaluated regarding the risk of prostate cancer and should be monitored [17-20].

There are many divergent opinions about the reference values of testosterone in the main guidelines of the principal international medical societies. Many authors support the indication of TRT in an individualized manner. In Europe, most physicians support the idea that clinical signs and symptoms should be of greater value than laboratory results. This tendency is being observed worldwide: association of symptoms with altered laboratory testosterone tests.

When To Indicate Testosterone Replacement Therapy (TRT)?

There are many divergences regarding the reference values of testosterone in the main guidelines of the principal international medical societies. Many authors defend the indication of TRT in an individualized manner. In Europe, most physicians support the idea that clinical signs and symptoms should be valued more than just the laboratory results. This tendency is being observed all over the world: the association of symptoms with altered testosterone laboratory tests [2,4-6,8,9].

How to Replace Testosterone in Hypogonadic Men?

The prescription of testosterone should be individualized. TRT modalities can be classified as short-lasting esters applied intramuscularly at very short intervals and, for this reason, being subject to oscillating testosterone levels with a higher rate of side effects, and their prescription should be avoided even though the treatment is of lower cost [5,6,8-10].

Long-acting esters such as testosterone undecylenate, also administered intramuscularly but only at 10-14-week intervals, provide adequate bioavailability and stable plasma testosterone levels, representing an effective and safe option.

Formulations of transdermal application (testosterone gel) are still available in Brazil, and should be used daily.

Why Treat Male Hypogonadism?

Testosterone has various functions in male homeostasis which are fundamental for the maintenance of general health, and also participates in the prevention of chronic diseases [4].

The shared decision to start TTH should be accompanied by a standardized monitoring plan for an optimum risk/benefit ratio.

The recommendation is to follow Brazilian and international directives for patients receiving TRT.

Testosterone undecylenate administered intramuscularly at the dose of 100 mg and followed by application of the same dose about six weeks after the first and every 10-14 weeks thereafter has been shown to be a safe and effective option, restoring the physiological levels of testosterone in a rapid and lasting manner, with safe resolution of associated symptoms.

- Medical visits 3, 6 and 12 months after the beginning of treatment with the evaluation of testosterone, hematocrit and PSA. Bone mineral density, digital rectal examination and cardiovascular function should be evaluated case by case.
- Annual monitoring is recommended after the first year of treatment depending on the individual medical assessment of each patient [5,6,8-10,17-20].

References

1. Bembo AS, Carlson HE. Gynecomastia its features and when and how to treat it. Cleve Clin J Med. 2004; 71: 511-517.
2. Terapia de reposição da testosterona na DAEM Deficiência Androgênica do Envelhecimento Masculino. uma revisão de literatura. Tupinambá I, Prazeres TCMM. 2021; 4.
3. Shalender Bhasin, Juan P Brito, Glenn R Cunningham, et al. Testosterone Therapy for Hypogonadism Guideline resources. Guideline Testosterone Therapy in Men with Hypogonadism. An Endocrine Society Clinical Practice Guideline. JCEM. 2018; 103: 1715-1744.
4. Salter CA, Muhall JP. Guideline of guidelines: testosterone therapy for testosterone deficiency. DJUI- International Review. 2019.
5. Burté C, Lejeune H, Faix A, et al. Recommendations pratiques pour la prise in charge du déficit en testosterone. Progrès en Urologie. 2021; 458-476.
6. Burté C. Le Recommendations pour la prise em charge du déficit em testostérone. Sexologies. 2021.
7. Hackett G. Type 2 Diabetes and testosterone therapy. World J Men's Health. 2019; 37: 31-44.
8. Li shu-ying, Zhao Ya-ling, Yang Y, et al. Metabolic effects of testosterone replacement Therapy in Patients With Type 2 Diabetes mellitus or Metabolic Syndrome A Meta-Analasys. Int j Endocrinol. 2020; 2020: 4732021.
9. Lee DS, Park HJ. Efficacy and safety of Testosterone Therapy

based on Guideline Recommendations. Re Clinical practice guideline by American College of Physicians. World j Men's Health. 2020; 38.

10. Morimoto M, Yamaoka M, Hara T. A selective androgen receptor modulator SARM-2f activates androgen receptor increases lean body mass and suppress blood lipid levels in cynomalgus monkeys. Pharmacology Research & Perspectives. 2020; 1.
11. Castle g, Stammers J. testosterone prescribing in UK general practice. Are patients being monitored correctly for associated risks whist ions treatment. Basic& Clinical Pharmacology &Toxicology. 2020; 127: 434-437.
12. Karabay E, Karsuyakali N, Cinier G, et al. change in Frequency and predictors of Erectile Function Domain score in Patients With ST-Elevation Myocardial Function Domain Score in patients longitudinal Study. J Sexual medicine. 2020.
13. Carlos Martinez, Samy Suissa, Stephan Rietbrock, et al. Testosterone treatment and risk of venous thromboembolism population based/case control study. BMJ. 2016; 355: i5963.
14. Walker RF, Zakai Neil A, Macleh Wose, et al. Association of Testosterone Therapy with Risk of Venous Thromboembolism Among Men with and Without Hypogonadism. Jama Intern Med. 2020; 180: 190-197.
15. Kim Sd, Cho KS. Obstructive Sleep Apnea and Testosterone Deficiency. World J Men's Health. 2018.
16. Shalender Bhasin, Juan P Brito, Glenn R Cunningham, et al. Testosterone therapy in men with hypogonadism an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018; 103: 1715-1744.
17. Tong Yu, Zhou RY. Review of the Roles and Interaction of Androgen and Inflammation in Benign Prostatic Hyperplasia Mediators of Inflammation. 2020; 1-7.
18. Hill G, Persad R, Bolomytis S. Reverse intermittent androgen deprivation therapy Prostate Cancer and Hypopituitarism. J Clinical Urology. 2020.
19. Shaline H, Zanaty M, Skakaria A, et al. Oncological safety and functional outcomes of testosterone replacement therapy in symptomatic adult-onset hypogonadal prostate cancer patients following robot- assisted radical prostatectomy. W J UROLOGY. 2020.
20. Xu P, Choi E, White K, et al. Low Testosterone in Male Cancer Patients and Survivors Sexual Medicine Reviews. 2020.