Testosterone Replacement in Hypogonadic Men

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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: 0.198-0.619 nmol/L
  Men older than 50 years: 0.163-0.473 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,
it's 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 Kliefelter 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
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**

9. Lee DS, Park HJ. Efficacy and safety of Testosterone Therapy


