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## Androgen replacement therapy in men: current evidence and controversy

### *Terapia de reposição hormonal no sexo masculino: evidências e controvérsias*

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**ABSTRACT:** The decline in Testosterone (T) levels in the ageing male - known as andropause or late-onset hypogonadism - may be responsible for several aspects of quality of life decline in older men: erectile dysfunction, impaired libido, decreased strength and energy, sarcopenia, osteopenia, fatigue and even depression in some cases. Many of these signs and symptoms represent the same alterations that are usually attributed to the process of ageing. When some individual presents with such symptoms, hypogonadism should be suspected, and serum T level should be evaluated. Men who are symptomatic and present low levels of serum Testosterone (generally below 300 ng/ml) are candidates for T replacement therapy. Current evidence shows that, when correctly selected, patients receiving T replacement may benefit from improvement in libido, erectile function, overall and sexual related quality of life, bone density and muscle mass. Conversely, patients with physiological circulating levels of T who receive hormone, aiming at supraphysiologic levels, may face severe side effects, including testicular atrophy and behavioral changes. Of note, T replacement, regardless of age and pre-therapy levels, leads to fertility impairment which can be transient or persistent. Direct testosterone replacement should not be indicated in men who wish to conceive children, although other options are available. The effect of Testosterone replacement on prostate cancer and on cardiovascular risk is still controversial; hypogonadal men known to have prostate cancer or high cardiovascular risk should be examined individually to have their risks stratified and mitigated.

**Keywords:** Androgens; Testosterone; Male; Ageing; Hormone replacement therapy.

**RESUMO:** A queda dos níveis séricos de testosterona em homens de idade avançada – conhecida como andropausa ou hipogonadismo tardio – pode ser responsável por vários aspectos no declínio da qualidade de vida de homens idosos: disfunção erétil, diminuição da libido, redução de força física e energia, sarcopenia, osteopenia, fadiga e até depressão. Muitos de tais sinais e sintomas representam as mesmas alterações habitualmente atribuídas ao processo de envelhecimento. Quando um paciente se apresenta com esses sintomas, deve-se suspeitar do diagnóstico de hipogonadismo, sendo recomendada a dosagem de níveis séricos de testosterona. Homens sintomáticos apresentando níveis séricos de Testosterona total abaixo de 300 ng/ml são candidatos a terapia de reposição de testosterona. Evidências atuais indicam que, quando selecionados corretamente, pacientes que recebem reposição de testosterona se beneficiam de melhora na libido, na função erétil, em qualidade de vida nos aspectos gerais e nos quesitos ligados à vida sexual, bem como na densidade óssea e no ganho de massa muscular. No entanto, pacientes com níveis fisiológicos de Testosterona que recebem hormônio exógeno, visando atingir níveis supra-fisiológicos, podem enfrentar efeitos colaterais graves tais como atrofia testicular e alterações comportamentais, como agressividade exacerbada. Deve-se notar que a reposição de testosterona, independentemente da idade e de níveis séricos hormonais pré-tratamento, leva a prejuízo na fertilidade masculina, um fenômeno que pode ser transitório ou persistente. Em pacientes que possuem desejo reprodutivo, a reposição direta de testosterona não deve ser indicada, devendo-se levar em consideração outras opções como o citrato de clomifeno, de ação central. O efeito da reposição de testosterona no risco de câncer de próstata e no risco cardiovascular é ainda controverso; homens com hipogonadismo que sabidamente possuem câncer de próstata ou alto risco vascular devem ser examinados individualmente de modo a terem seus riscos estratificados e mitigados.

**Descritores:** Androgênios; Testosterona; Masculino; Envelhecimento; Terapia de reposição hormonal.

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## INTRODUCTION

Providing higher quality of life to an ever-ageing population is one of the current goals in contemporary Medicine. Maintenance of physical, mental and sexual function are pursued by both patients and practitioners and challenged by several factors in the elderly population. Among these, the decline in Testosterone (T) levels seen in the ageing male - known as andropause, or late-onset hypogonadism - may play a critical role in several domains, from physical to psychological<sup>1,2</sup>. The Hypogonadism in Males Study estimated that up to 39% of men aged 45 years or older may have hypogonadism<sup>3</sup>. Of note, several symptoms of male hypogonadism have significant overlap with those usually attributed to the process of ageing, including sarcopenia, osteopenia, fatigue, decreased libido and sexual function and mental manifestations such as depression<sup>2,4</sup>. Hence, a thorough evaluation is needed when the diagnosis of hypogonadism is suspected: neither isolated symptoms nor isolated low levels of serum testosterone are sufficient to diagnose this condition. Rather, the concomitant presence of testosterone levels below 3.2 ng per milliliter associated with at least three sexual symptoms define the condition of late-onset male hypogonadism<sup>5</sup>. Accordingly, indication for testosterone replace therapy relies on the presence of typical symptoms together with low serum T levels<sup>6</sup>. As per the Endocrine Society guidelines, physicians should measure T levels of patients with signs and symptoms such as reduced libido, reduced muscle mass, depressed mood, decreased energy, osteoporosis, gynecomastia, shrinking testes, infertility, poor concentration, sleep disturbances, increased body fat and anemia<sup>7</sup> (Table 1).

**Table 1.** Signs and symptoms which should raise suspicion for hypogonadism and elicit hormonal investigation

Reduced libido	Erectile Dysfunction
Reduced muscle mass	Osteopenia/osteoporosis
Increased body fat	Anemia
Gynecomastia	Shrinking testes
Decreased energy	Fatigue
Depressed Mood	Poor concentration
Sleep disturbance	Infertility

It has been once unclear, however, if symptoms usually associated with hypogonadism could be correctly attributed to the effect of low circulating hormone levels. It has been speculated that sexual inactivity could lead to reduced testicular function and work as a cause and not consequence of this phenomenon<sup>6</sup>. Evidence for this question has arisen from clinical trials of androgen replacement investigating sexual function of hypogonadal

men after Testosterone Therapy (TTh)<sup>8</sup>. Likewise, the effect of TTh has been studied on several domains including quality of life, mental health and body mass. In this review, we will outline the current evidence of the effect of Androgen Replacement Therapy (ART) on several aspects of male hypogonadism, along with implications of such treatment on concerning events such as Prostate Cancer (PCa) and cardiovascular risk.

### Erectile function

Several prospective placebo-controlled randomized clinical trials have been conducted in order to investigate the role of TTh on sexual function among hypogonadal men. Although results were not entirely homogeneous between studies, it must be noted that several factors - including definition of hypogonadism, baseline serum T among participants and presence of comorbidities may influence the outcomes of trials. Overall, as per demonstrated in a several meta-analyses, ART with Testosterone appears to be effective in improving erectile dysfunction, as measured by the International Index of Erectile Function (IIEF), with greater effect in patients with lower baseline T levels and more modest effect among patients with clinical comorbidities such as diabetes<sup>8-11</sup>. However, when patients receiving TTh include eugonadal men, this therapy does not appear to provide benefit on sexual function<sup>12</sup>.

Allan et al.<sup>13</sup> showed that Testosterone replacement with a transdermal patch increased libido, yet with no effect of erectile function. Conversely, in a trial performed by Chiang et al.<sup>14</sup>, TTh resulted in erectile function improvement with no changes in libido. In accordance with the latter, Giltay et al.<sup>15</sup> demonstrated a 3-point improvement in the IIEF scale in hypogonadal men receiving TTh, with the most effective results in patients with lowest baseline T values. The most recent evidence indicates that, when indicated to men correctly diagnosed with hypogonadism, TTh presents overall positive results on erectile function<sup>8</sup>. However, the improvement on erectile function attributed to TTh alone may be modest. In cases of severe erectile dysfunction, this treatment may not be enough to satisfy an individual's desire for improvement. Likewise, when other factors such as obesity and diabetes are present, vascular and neurogenic mechanisms causing erectile dysfunction are not addressed by TTh. Although ART may be effective in improving erectile function in hypogonadal men, physicians must carefully select patients who may benefit from this therapy and be aware of its limitations.

### Quality of life and mental health

Several randomized controlled trials have been performed to investigate if TTh would lead to Quality of Life (QoL) improvement in hypogonadal men. A

recent meta-analysis of randomized controlled trials has demonstrated that Testosterone replacement in men with late onset hypogonadism can have significant impact on QoL in several domains including psychological, somatic and sexual aspects<sup>16</sup>. However, individual studies have shown different results in select domains and populations. Legros et al.<sup>17</sup> randomized 322 subjects for placebo or an oral dose of 80, 160 or 240 mg of Testosterone undecanoate in a multicentric study. Improvement in overall QoL was significant but similar between placebo and TTh; conversely, in sexual-related QoL, T replacement with 160 mg showed significant improvement over placebo or other doses. Srinivas-Shankar et al.<sup>18</sup>, in a study with 274 patients randomized for placebo or transdermal T replacement of 50 mg per day have demonstrated significant improvement in overall, sexual and somatic QoL. Of note, patients who presented most significant improvement were elder and more fragile individuals. Ho et al randomized 120 for placebo or intramuscular testosterone undecanoate injections of 1000 mg<sup>19</sup>. They have found that patients receiving T injections presented significant improvement on overall QoL, psychological and somatic aspects, with a non-significant improvement in the sexual domain. Taken together, the current evidence accumulated, as analyzed in a meta-analysis, suggests that TTh can in fact lead to QoL improvement in hypogonadal men. Furthermore, it appears that T replacement in men with late onset hypogonadism may have a beneficial effect on reducing depression and enhancing cognitive performance among symptomatic patients<sup>20</sup>. It must be noted, however, that such effects have only been demonstrated for hypogonadal men with document levels of serum T below normality.

### Sarcopenia and osteoporosis

The role of T on muscle anabolism is one of the first documented effects of this hormone. The indiscriminate use of exogenous T in eugonadal men with this purpose often leads to supraphysiologic levels of T and corresponding adverse effects, including mental and behavioral changes<sup>21</sup>. However, in symptomatic individuals with hypogonadism, TTh is indicated to restore skeletal muscle mass. It has

**Table 3.** Treatment options for hypogonadism

Formulation	Dose	Potential adverse effects
Intramuscular injection	75-100 mg weekly or 150-200 mg every 2 weeks	
Transdermal gel	5-10 g applied daily (5-10 mg testosterone systemically absorbed)	Gel transference to partner or children
Transdermal patches (non-scrotal)	2.5-7.5 mg applied nightly	Skin reaction
Long-lasting intramuscular injection	750 mg every 10 weeks	Pulmonary oil microembolization
Buccal tablets	30 mg tablet applied to the buccal mucosa every 12 h	Inflammation of the gums

been consistently demonstrated that T replacement in hypogonadal men can lead to increased muscle mass, increase in bone density, increased strength and a decrease in fat mass<sup>22-24</sup>.

### Diagnosis and treatment

Patients presenting with symptoms suggestive of hypogonadism, in special older men with a suspicion of late onset hypogonadism, should have their hormonal investigation performed. These symptoms include reduced libido, fatigue, sarcopenia, depressed mood, increased body fat among others (Table 1). The diagnosis of hypogonadism consists in the presence of symptoms associated with serum testosterone below a given cut-off, which may vary from 230 ng/dl to 300 ng/dl according to different societies (Table 2). Complementary investigation should also include Follicle stimulating hormone and Luteinizing hormone.

**Table 2.** Diagnostic reference values for hypogonadism, considering the limit below which patients will usually benefit from testosterone therapy

Endocrine Society	Total testosterone below 280-300 ng/dl Free testosterone below 5-9 ng/dl *excluding evaluation during acute or subacute illness
European Association of Urology, American Society of Andrology	Total testosterone below 230 ng/dl

If symptoms are enough to impair patient's quality of life, and after discussion of potential benefits and adverse effects, testosterone replacement therapy may be offered to patients. Options for testosterone therapy include intramuscular, transdermal or buccal presentations (Table 3). Each method is associated with a different profile of adverse effects and has with a particular posology. Intramuscular injections are associated with relatively few adverse effects, and require injections twice a month. By contrast, a transdermal gel will not require injections, but will demand daily applications and is associated with a risk of transmission of hormone to partners and children.

## Potential adverse effects

### Infertility

The use of exogenous T is well known to have negative effects on male fertility. The elevated serum T resulting from exogenous intake leads to a negative feedback inhibition of the hypothalamic pituitary gonadal axis. Such inhibition results in suppression of spermatogenesis, low intratesticular T levels and ultimately oligospermia or azoospermia and testicular atrophy<sup>25</sup>. Although this effect can be reversible in up to 50% of patients after 6 months of therapy cessation, up to 10% of patients may remain persistently azoospermic after TTh<sup>26</sup>. Hence, exogenous T replacement must be discouraged in hypogonadal men with intention to conceive in the future. Instead, such patients should be offered alternative treatments aiming at upregulation of the hypothalamic pituitary axis and ultimately elevating endogenous T production. Among options of such a treatment there is Clomiphene citrate, a selective estrogen receptor modulator, which acts in the hypothalamus and pituitary opposing the inhibitory effect of estrogens on gonadotropin release. As a result, gonadotropin levels rise and T production by the testes is stimulated<sup>27</sup>. Other options include human Chorionic Gonadotropin (hCG) - which stimulates endogenous T production by Leydig cells - and aromatase inhibitors, such as anastrozole, which block peripheral conversion of T to estrogen and are most effective in obese subjects<sup>27</sup>.

### Prostate cancer

Current understanding of the relationship between Testosterone and Prostate Cancer does not follow a linear correlation. Rather, the saturation model proposed by Morgentaler and Traish predicts that changes in serum T concentration below the point of maximal androgen-receptor binding will lead to clinically significant modifications in prostate growth and prostate cancer<sup>28</sup>. This is the case for androgen deprivation therapy, in which levels are aimed at 30 ng/dL or lower. However, in patients with levels of serum T above the point of maximal androgen-receptor binding, oscillations of serum T do not correlate to clinically significant changes in prostate growth or cancer. This theory explains the observation that endogenous levels of T do not increase the risk of Prostate Cancer<sup>29,30</sup>. Current evidence does not show an increased risk for Prostate Cancer in hypogonadal men receiving androgen replacement therapy as compared to age-paired controls or to subjects receiving placebo<sup>31,32</sup>. Furthermore, the previous use of T replacement does not increase Prostate Cancer severity in patients presenting this diagnosis<sup>33</sup>. The use of Testosterone replacement in hypogonadal men with treated prostate cancer may be considered, although this is still a controversial subject<sup>34</sup>. Current evidence suggests that hypogonadal men with low or moderate risk disease receiving T replacement after radical prostatectomy do not

present increased risk of disease recurrence<sup>35</sup>. Yet, series of patients receiving T Therapy after surgery or radiotherapy are small and evidence is limited. Although T therapy may be considered for hypogonadal patients after treatment for Prostate Cancer, it should be restricted to patients with low or moderate risk disease and undetectable or stable Prostate-Specific Antigen (PSA) levels. Patients should be informed that the current level of evidence is insufficient to definitively exclude the risk of disease recurrence, although disease recurrence may or may not be related to this therapy.

### Cardiovascular risk

The potential risks and benefits of T for cardiovascular effects have long been unknown and controversial. Different studies have elicited opposing results regarding the risk of cardiovascular events following testosterone replacement. A recent systematic review investigated such contrasting results<sup>36</sup>. Morgentaler et al demonstrated that, while 4 studies have shown an increased for cardiovascular events after T prescription, several dozen studies have shown, conversely, a beneficial effect of normal testosterone levels on cardiac risk and mortality. These authors have demonstrated, according to their review of the literature, that current evidence suggests that serum T concentration is inversely related to incidence and severity of coronary artery disease, as well as with mortality (level of evidence IIa). Also of note, a recent meta-analysis including 75 randomized controlled trials with over 5,000 patients did not demonstrate an overall increase in cardiovascular risk after T replacement; furthermore, in patients with metabolic derangements, T therapy was associated with a protective effect on cardiovascular risk<sup>37</sup>. As per most recent evidence, it appears that testosterone replacement in older men with hypogonadism could provide cardiovascular protection and carries a lower risk for cardiovascular events<sup>38</sup>. In a retrospective cohort including over 40,000 men, Cheetham et al.<sup>38</sup> showed that hypogonadal men who received testosterone presented lower risk of stroke and myocardial infarction as compared to those who never received T reposition. However, this effect may be significant only when hormone levels reach normality. It appears that T replacement could potentially provide cardiovascular benefit for selected patients; however, this statement is yet to be confirmed. Currently, evidence for the use of T in men at high cardiovascular risk is not considered to be enough to safely indicate hormone reposition in such patients<sup>38</sup>. Men at low or intermediate risk are considered safe candidates for T therapy; however, this should not be indicated in men with a recent myocardial infarction, revascularization, poorly controlled heart failure, and stroke within the previous 6 months<sup>39</sup>.

## CONCLUSIONS

Testosterone replacement in hypogonadal men

can lead to several benefits, including recovery of sexual function, libido, muscle mass and overall quality of life. However, diagnosis of this condition and indication for therapy must be strict and follow guidelines. The use of Testosterone in asymptomatic men or in subjects with normal levels of serum Testosterone should not be encouraged by physicians.

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