

# Testosterone replacement in male hypogonadism

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**Abstract:** This article contains a review of the clinical aspects of testosterone replacement in androgen deficiency of the aging male.

**Keywords:** testosterone, supplementation, hypogonadism, ADAM

As men age, there is a gradual decline in testosterone of 1.0% and 1.2% (total and free levels, respectively), annually, after age 40. Free testosterone levels decline faster because of the associated increase in sex hormone-binding globulin.<sup>1,2</sup>

This phenomenon is known as andropause, or as (partial) androgen deficiency of the aging male [(P) ADAM], when it is associated with signs and symptoms of androgen deficiency.<sup>3</sup>

ADAM can be defined biochemically, or clinically. Biochemically, a total testosterone cut off of 325 ng% (11.3 nmol/L) leads to a diagnosis of androgen deficiency in 20% of men >60 years, 30% of men >70 years, and 50% of men >80 years.<sup>4</sup> Many of these men, however, have no clinical features of testosterone deficiency, and risk being overtreated.

The clinical approach utilizes symptoms and signs of androgen deficiency. These, however, are nonspecific, and may be due to other illnesses. Lethargy, asthenia, lack of concentration, disturbed sleep, irritability, and depression are the common symptoms which have multiple etiologies.

Both clinical and biochemical parameters, therefore, must be used to define ADAM, before it is treated.

## Symptoms and signs

The signs and symptoms of androgen deficiency may be nonspecific. In general, the features can be classified as physical, psychological, and sexual symptoms and signs, and laboratory abnormalities. These are listed below:

### Physical symptoms/signs

- decreased muscle bulk
- increased adiposity
- loss of secondary body hair
- loss of vigor

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## Psychological symptoms/signs

- low mood
- poor cognition
- irritability

## Sexual symptoms/signs

- declining sexual desire
- erectile dysfunction

## Laboratory abnormalities

- loss of bone mineral density
- atherosclerosis

## Effects of treatment

Physiologic androgen replacement can be differentiated from pharmacological androgen therapy. Physiologic androgen replacement, which is the focus of this review, aims to achieve normal androgen levels in serum and tissue, so that the signs and symptoms of androgen deficiency are alleviated in a hypogonadal male. It does not target a specific organ system, and does not try to reach supraphysiological levels. On the other hand, pharmacological androgen therapy, such as for anemia due to bone marrow failure, or for endometriosis, is aimed at producing specific effects on specific tissues.

A long term (3 years long) trial has demonstrated increase in lean mass, with reduction in fat mass in 96 men aged 73 years who wore a scrotal testosterone patch delivering 6 mg testosterone every 24 hours.<sup>5,6</sup>

No change was noted in muscle strength and function, bone density, or subjective perception of energy or sexual functions with testosterone.

Though the prostatic specific antigen concentration increased slightly over the first six months, it remained stable for the remainder of the study.<sup>5</sup> Urodynamic parameters and number of clinically significant prostate events were similar in the testosterone and placebo groups. Hemoglobin and hematocrit increased significantly in the testosterone group over the first 6 months.

Libido and sexual function improved with transdermal testosterone replacement in clear cut cases of hypogonadism.<sup>7</sup>

Other randomized, placebo controlled trials in older healthy men have shown beneficial effects of sublingual testosterone in functional performance, hand grip strength, lean body mass (+3.8 kg), bone mineral density at lumbar spine (+10.2 ± 1.4%), and hip (+2.7 ± 0.7%) at 36 months, along with a decrease in low density lipoprotein (LDL) cholesterol.<sup>8</sup>

Simultaneous use of finasteride<sup>9</sup> in one study was shown to reduce the increase in prostate volume seen with exogenous testosterone in hypogonadal men. Testosterone replacement, either injectable or noninjectable, in elderly men leads to only modest or no decrease in plasma HDL.<sup>10-12</sup> The levels of LDL are inversely proportional to testosterone concentration.<sup>13,14</sup>

Testosterone supplementation of middle aged men reduces visceral fat, serum glucose, blood pressure, and improves insulin sensitivity.<sup>15,16</sup> One trial with oral testosterone has shown reduction in symptoms of angina in men with coronary heart disease.<sup>17</sup> A recent study, however, has been stopped prematurely<sup>18</sup> because of excess cardiovascular events noted in the testosterone gel-treated arm of a study involving elderly community-dwelling men (mean age 73 years) with low testosterone levels.

Studies have shown improved spatial and verbal memory with supraphysiological testosterone levels,<sup>19</sup> and improved spatial and working memory with high normal levels in healthy older men.<sup>20</sup>

Results related to major depression have been conflicting, with one study suggesting a benefit,<sup>21</sup> but another reporting no effect of supraphysiological testosterone therapy in this condition.<sup>22</sup>

## To treat or not to treat

Treatment should be decided based on both clinical and biochemical parameters.<sup>23</sup> Biochemical confirmation is carried out if patients present with signs and symptoms suggestive of androgen deficiency. Diagnosis should not be made during an acute or subacute illness.

An arbitrary cut off of 200 mg% (7.0 nmol/L) has been suggested.<sup>24,25</sup> This cut off is lower than that suggested by earlier population-based studies.<sup>4</sup> The discrepancy may be a reflection of the greater understanding of need for optimal androgen levels by endocrinologists.

The clinical features which demonstrate highest association with low testosterone levels are decreased morning erections, decreased sexual desire, erectile dysfunction, and low physical activity.<sup>26</sup> Physical and sexual symptoms are likely to provide more specificity than psychological symptoms.<sup>26</sup>

Laboratory evaluation is ideally carried out by measuring early morning total or free testosterone levels. One should be aware that total testosterone can be affected by changes in sex hormone binding globulin (SHBG) concentration. SHBG concentrations are reduced in obesity, nephrotic syndrome, hypothyroidism, and use of glucocorticoids,

progesterins, and androgenic steroids.<sup>27</sup> SHBG cause increases in aging, cirrhosis, hyperthyroidism, HIV infection, and estrogen use.

The aim of treatment is to return testosterone value to 'physiologic' age-matched levels. Titration of dose is carried out according to serum testosterone levels.

The duration of testosterone therapy is uncertain, and may depend on changes in prostate size, PSA levels, and hematocrit.

## Choosing a testosterone preparation

Various testosterone preparations are available for use.<sup>3</sup>

Oral testosterone undecanoate, formulated in oleic acid, is absorbed through the lymphatics into systemic circulation, bypassing the liver. Doses of 40 to 80 mg two to three times a day with meals are used, but clinically responses are variable.

Oral testosterone should be used initially for all patients requiring androgen replacement, because it has the advantage of being easy to discontinue in case of an adverse clinical reaction.

Injectable and transdermal preparations are also available. Esterification of testosterone at the 17- $\beta$  hydroxyl position makes it hydrophobic and increase the duration of action, in a manner directly proportional to the length of the side chain.

Testosterone undecanoate<sup>28</sup> has the longest duration of action, and is injected in a dose of 1,000 mg, followed by a similar dose at 6 weeks, and then every 12 weeks. Stable levels of testosterone are achieved, but the large volume (4 mL) may cause some discomfort. Dose titration can be done by varying the dose (1–4 mL) or frequency (6 to 8 to 12 weekly) of injections.

A mixture of testosterone enanthate, cypionate, and propionate is also available as a total dose of 100 mg and 250 mg, to be administered IM every 14 to 21 days. It is easy to use, and is effective, but leads to peaks or supraphysiological concentrations, and lows or hypogonadal ranges of testosterone, during the mid-phase and late phase of the dosing interval.

Transdermal preparations are available for nongenital use and scrotal use as well. The gel is applied in a dose of 5 to 20 g on scrotal skin, and it achieves uniform concentrations over 24 hours. It is easy to use, invisible, and allows for flexibility of dosing, but can be transferred through skin to skin contact.

Nongenital 5 mg patches also available. Controlled release, bioadhesive 30 mg testosterone tablets can be applied every 24 hours to the buccal mucosa. Implant of crystalline testosterone can be inserted into the subcutaneous tissue, and maintain adequate serum testosterone levels for up to 6 months, if used in a dose of 4 to 6 200 mg implants.

Oral 17- $\alpha$  alkylated testosterone derivatives are no longer used, because of potential hepatotoxicity.

Choice of the testosterone preparation depends on various factors. In general, injectable preparations are more economical than others. Oral and transdermal preparations are easier to administer, while some patients prefer the occasional injectable therapy. Oral testosterone has a quicker onset and shorter duration of action, while transdermal testosterone leads to less increase in PSA than oral preparations.<sup>29</sup>

## Contraindications

The contraindications to testosterone therapy are listed below:

1. Metastatic prostate cancer
2. Breast cancer
3. Undiagnosed prostate nodule or induration
4. Unexplained PSA elevation >3 ng/mL
5. Erythrocytosis (hematocrit >50%)
6. Severe BPH symptoms (AUA/IPSS >19)
7. Unstable severe congestive heart failure (class III or IV)

## Adverse events

Testosterone-related adverse events are usually uncommon. However, frequently seen side effects include acne, oily skin, breast tenderness, erythropoiesis, detection of subclinical prostate cancer, increase in prostate volume, and growth of metastatic prostate cancer. None of the randomized clinical trials on testosterone has been powered for long-term prostate safety. Most studies, however, have shown no change in prostate size or urine flow prostate symptom score with testosterone.<sup>30</sup>

There is only weak evidence of an association of testosterone replacement with gynaecomastia, male pattern baldness, worsening of BPH symptoms, growth of breast cancer, and induction or worsening of obstructive sleep apnea.<sup>3</sup>

## Monitoring of testosterone therapy

Men should be followed up for 3 months after starting therapy, and annually thereafter. The aim should be to maintain serum testosterone levels in the mid normal range. Serum LH and FSH are not used to monitor therapy.<sup>9</sup>

Hemoglobin, hematocrit, digital prostate examinations, and PSA should be checked regularly.

Patients on injectable testosterone mixtures should have their testosterone levels assessed midway between injections, aiming for a level 350–700 ng/mL. Those on the injectable testosterone undecanoate should have a serum testosterone assessment prior to the injection. Levels should be assessed 3 to 12 hours after applying transdermal patch, 3 to 5 hours after ingesting oral testosterone undecanoate, at any time while on a testosterone gel, and just prior to inserting a buccal tablet.

Hematocrit should be checked at baseline, at 3 months, then annually. Testosterone should be stopped if hematocrit rises to >54% and reinitiated slowly when it falls to below 50%.

Digital rectal examination and PSA should be carried out at baseline, at 3 months, and then as clinically indicated.<sup>9</sup>

A urology consultation should be sought if serum PSA rises above 4.0 ng/mL, increases by 1.4 ng/mL or more over 12 months, or >0.4 ng/mL/year for 2 years. A urology consultation is also indicated if a prostate abnormality is noted or the AUA/IPSS symptoms score rises above 19.

## Conclusion

Testosterone replacement is an effective method of treating hypogonadism in elder men, if used judiciously. An understanding of possible benefits and risks, judicious choice of the testosterone preparation, combined with regular monitoring, makes testosterone replacement a beneficial choice for older men with both biochemical and clinical evidence of androgen deficiency. Both physicians and patients must be aware of the possible side effects and complications of testosterone therapy.

## Disclosure

The authors report no conflicts of interest in the work.

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