

# Testosterone and Mood in Aging Men

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## KEYWORDS

- Testosterone
- Partial androgen deficiency of aging male
- Hypothalamic-pituitary-gonadal axis
- Depression

## KEY POINTS

- Testosterone level is reduced with age.
- Partial androgen deficiency of the aging male (PADAM) is thought to be responsible for a variety of age-associated conditions, such as reduced muscle and bone mass, frailty, sexual dysfunction, and depression.
- Testosterone deficiency is most consistently associated with sexual dysfunction and fatigue, and these are reversed by testosterone replacement.
- There is only limited evidence of a link between hypothalamic-pituitary-gonadal axis hypo-functioning and depressive illness.
- Exogenous testosterone has not been consistently shown to be effective for major depressive disorder in either hypogonadal or eugonadal men; some evidence supports a mood-enhancing effect in men with late-onset dysthymia (which may be considered a PADAM manifestation in some men).

## INTRODUCTION

Male hypothalamic-pituitary-gonadal (HPG) axis function declines progressively after age 40 years, and about one-fourth of middle-aged and older men have testosterone levels below the threshold values used to define testosterone deficiency in younger men.<sup>1,2</sup> Of these, less than half exhibit apparent sequelae of low testosterone levels, meeting the definition of hypogonadism.<sup>1,2</sup> Mild testosterone deficiency in men can be considered physiologic (ie, a para-aging phenomenon) or pathologic (ie, a deficit state). Indeed, whether the age-dependent decline in testosterone levels truly causes health problems in men is being debated vigorously.<sup>3-7</sup> It has been suggested that age-associated testosterone deficiency, termed partial androgen deficiency of the aging male (PADAM), is responsible for many of the typical signs of male aging, such as sexual dysfunction, decreased lean body mass, osteoporosis, and increased

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visceral fat, as well as for neuropsychiatric problems such as fatigue, depression, and irritability.<sup>7–12</sup> Furthermore, it is claimed that the application of a testosterone replacement strategy for older men with low or low to normal testosterone levels will reverse such presumed sequelae.<sup>13</sup>

In contrast to PADAM “enthusiasts,” other investigators have shown that for many, hypogonadism is not a stable health state (eg, in a 15-year longitudinal follow-up of a large population-based sample of men, the majority of those with low testosterone level remit to normal levels in later years<sup>4</sup>); aside from sexual dysfunction and fatigue,<sup>12,14</sup> hormone levels do not correlate with most of the presumed hypogonadal symptoms<sup>8,9,15</sup> although age and illness do<sup>9,10</sup>; and testosterone replacement in elderly men is mostly ineffective in reversing most of these signs and symptoms.<sup>6,10</sup> Finally, the limited data that exist regarding mood effects of endogenous and exogenous testosterone in this population are inconsistent, but broadly unresponsive of a role in major depression or its treatment.<sup>7,16</sup> There is some evidence that testosterone may play a more pivotal role in later-onset, low-grade depressive syndromes, such as dysthymia.<sup>17,18</sup>

### LATE-ONSET MALE HYPOGONADISM

It is controversial whether age should be considered the primary variable linked to “age-related” testosterone decline because there are many influences on HPG-axis functioning, including genetic factors, chronic diseases, medications, obesity, and lifestyle factors.<sup>11</sup> Indeed, poor health is a better predictor than age of decline in testosterone level.<sup>7</sup> Although many men with low testosterone levels are asymptomatic, others may have a partial decline in testosterone associated with various clinical symptoms.<sup>9,12</sup> Of note, there appear to be different thresholds for different hypogonadal symptoms: loss of vigor and libido (<430 ng/dL), obesity (<346 ng/dL), disturbed sleep, depression, poor concentration (<288 ng/dL), and hot flashes (<230 ng/dL).<sup>7</sup> There is also variability in the time course of symptom reversal following testosterone replacement.<sup>19</sup> Based on the linkage of symptoms with androgenic actions, it remains unclear whether PADAM—an age-related hypogonadal syndrome characterized by sexual, somatic, and behavioral symptoms, with insidious onset and slow progression—is a true clinical entity distinguishable from age-related and health-related changes and frailty.

### MALE HPG AXIS AND DEPRESSION

#### *Exogenous Testosterone Administration in Depressed Men*

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Reports from the older psychiatric literature (1935–1960) on the antidepressant effects of testosterone suggested that a substantial number of “depressed” men responded immediately and dramatically to hormone replacement therapy and subsequently relapsed when treatment was discontinued.<sup>20</sup> However, standardized, syndromal, psychiatric diagnoses were not used in these studies, baseline testosterone levels were not assessed, and there was no control group. Anecdotal reports over the past 2 decades have suggested that in some hypogonadal men, comorbid major depressive disorder (MDD) remits with testosterone replacement or testosterone augmentation of a partially effective antidepressant,<sup>21</sup> and that for men infected by the human immunodeficiency virus, testosterone replacement is associated with improved mood, libido, and energy.<sup>22</sup> Yet systematic study has not supported the initial enthusiasm for testosterone as an antidepressant.

In a double-blind, randomized clinical trial of testosterone replacement versus placebo in 30 men with MDD and hypogonadism, Seidman and colleagues<sup>23</sup> found

testosterone replacement to be indistinguishable from placebo in antidepressant efficacy:

- 38% responded to testosterone
- 41% responded to placebo

An influential placebo-controlled trial of testosterone replacement as an augmentation to serotonergic antidepressant partial response suggested that this strategy might be more promising.<sup>24</sup> However, this was not supported by double-blind, placebo-controlled follow-up studies on antidepressant augmentation<sup>25,26</sup> or by a larger replication of the original study.<sup>27</sup>

Among older dysthymic men with low testosterone levels, 2 small placebo-controlled trials demonstrated a mood-enhancing effect of testosterone replacement.<sup>17,18</sup> Such data support the hypothesis that dysthymia is the psychiatric manifestation of PADAM, and that testosterone replacement is an effective treatment, but more systematic study is warranted before such conclusions can be made. At present, available data do not suggest the use of exogenous testosterone in the treatment of depression in PADAM, and clinical guidelines for hypogonadal men stress that testosterone replacement therapy for depression is not supported.<sup>7,28</sup>

### ***Exogenous Testosterone: Clinical Considerations***

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Exogenous testosterone, even at supraphysiologic doses, rarely produces side effects, although there is a remote risk of developing gynecomastia (breast tenderness and breast enlargement), truncal acne (particularly for those with a history of acne), hair loss or hair growth, and/or induction or worsening of obstructive sleep apnea.<sup>29</sup> Because there is always a modest increase in hematocrit, complete blood count should be checked pretreatment and followed.<sup>30</sup> Via the negative feedback mechanism, exogenous testosterone suppresses luteinizing hormone and follicle-stimulating hormone, which leads to reduced testicular sperm production and, consequently, reduced testicular volume. Formulation-specific adverse effects include skin reactions at application site for transdermal patches, skin irritation from transdermal gel, pain at injection site, excessive erythrocytosis (especially in older patients), and coughing episodes immediately after the intramuscular injection of testosterone enanthate, cypionate, or undecanoate.<sup>7</sup>

The primary concern regarding potential adverse effects of testosterone treatment is related to the prostate gland. Androgens play a permissive role in the growth of prostate cancer and benign prostate hyperplasia (BPH); however, there are no data to indicate that testosterone administration can lead to the progression of preclinical prostate cancer or to worsening BPH.<sup>7,29,31</sup> Prostate cancer is an absolute contraindication to treatment with exogenous testosterone, and should be excluded in all men age 50 years and older (or older than 40 if there is a positive family history of prostate cancer) via pretreatment prostate-specific antigen and digital rectal examination of the prostate.<sup>31,32</sup> Finally, although most data support an improvement in cardiovascular health with testosterone replacement,<sup>7</sup> the TOM (Testosterone in Older Men with Sarcopenia) study, in which 209 elderly hypogonadal men were randomized to testosterone gel or placebo, needed to be stopped because of a significant increase in nonfatal cardiovascular adverse events (affecting 23 men in the testosterone group and 5 in the placebo group).<sup>33</sup> Although unique aspects of the trial have been used to explain this unexpected result, the experience has given pause to the testosterone replacement enthusiasts and has encouraged greater precision in defining indications for testosterone replacement in elderly men.

## SUMMARY

In contrast to extensive menopause research, there is no parallel characterization of the psychophysiology of age-related male hypogonadism, despite potential implications for the treatment of psychiatric and sexual problems in this population. Nonetheless, the past decade has seen significant market growth in testosterone therapies for men 40 years and older, with most presumed indications lacking a firm scientific basis.

It is possible that an age-related hypogonadal syndrome, PADAM, is relevant to some men, and may include neuropsychiatric (including depressive) symptoms related to biological and psychosocial changes, and an individual's adaptation to such changes.<sup>34</sup> Although systematic study of the efficacy of exogenous testosterone in the treatment of depression in elderly hypogonadal men has been inconclusive, the great variability of the results suggests that in individual cases testosterone supplementation may be a useful adjunctive therapy in depressed (particularly dysthymic) hypogonadal men<sup>17,18</sup> for sexual dysfunction (including sexual dysfunction caused by antidepressant use<sup>35</sup>) and for frailty.<sup>7,36</sup>

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