

Andropause, testosterone therapy, and quality of life in aging men

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■ ABSTRACT

Testosterone therapy can improve quality of life in aging men because aging is accompanied by declining testosterone levels that may contribute to decreases in muscle mass, bone density, libido, stamina, and cognition. Hypogonadal men can be identified by a test for bioavailable testosterone or by a free testosterone assay that uses dialysis or ultracentrifugation methods.

*"...The sixth age shifts
Into the lean and slippered pantaloons
With spectacles on nose and pouch on side;
His youthful hose, well saved, a world too wide
For his shrunk shank, and his big manly voice,
Turning again toward childish treble, pipes
And whistles in his sound..."*
(William Shakespeare, *As You Like It*)

IF THESE SYMPTOMS—muscle wasting, regression of secondary sexual characteristics, a rising voice pitch—were to develop in a young man, we would have no difficulty in diagnosing hypogonadism. These symptoms may signal hypogonadism in aging men as well.

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The common wisdom that men do not undergo menopause is being replaced: many aging men—perhaps 5 million in the United States—do experience androgen deficiencies that impair quality of life. For these men, testosterone replacement therapy may improve libido, muscle mass, bone mass, cognition, and energy levels.

■ NATURAL HISTORY OF TESTOSTERONE

After age 30, levels of total and bioavailable testosterone in men decrease by 1% to 2% per year.¹ This decrease may be caused in part by decreased testosterone production and in part by slowly rising levels of sex hormone-binding globulin, the protein that binds testosterone and removes it from circulation. Levels of luteinizing hormone, which also affects testosterone bioavailability, do not rise until age 85 to 95.

These subtle changes may be easy to overlook because they develop over a longer period of time than the changes associated with female menopause.

■ IDENTIFYING TESTOSTERONE DEFICIENCY

"Andropause" can be defined as a complex of androgen-related symptoms that occur in the presence of low levels of testosterone.² Symptoms include:

- Decreased muscle mass or strength
- Cognitive changes
- Increased fat mass, particularly visceral fat
- Osteoporosis
- Low sense of well-being
- Decreased sexual desire and impaired sexual function
- Mood changes, including depression, irritability, loss of motivation, and lethargy

**Hypogonadism
may affect
5 million men
in the US**

- Regression of secondary sexual characteristics
- Impaired sperm production.

Because many of these symptoms can be attributed to aging or other medical causes, they may be ignored by both patients and physicians.²⁻⁴ Recently, evidence has accumulated that testosterone also plays an important role in maintaining function with aging.⁵

The Androgen Deficiency in Aging Males (ADAM) Questionnaire, together with a complete history and physical examination, is useful in identifying patients who may benefit from testing for hypogonadism (TABLE 1).⁶

■ OTHER CAUSES OF HYPOGONADISM

Age is not the only cause of hypogonadism, which has an estimated prevalence of 4 to 5 million men.⁷ Other causes include primary testicular failure (either congenital, developmental, or acquired),⁸ obesity, severe systemic illnesses, malnutrition, AIDS, uremia, sickle cell disease, or hepatic cirrhosis.⁴

■ TESTING FOR TESTOSTERONE

Plasma free testosterone tests are a good measure of the amount of bioavailable testosterone because they measure serum testosterone unbound by sex hormone-binding globulin. The traditional free testosterone test is actually an analog assay and is not as informative as a test that uses dialysis or ultracentrifugation (which is cheaper and easier to perform than dialysis). The test that appears to be most useful at present is the **bioavailable or weakly bound testosterone assay**, which measures both free and albumin-bound testosterone.

In contrast, the **plasma total testosterone** level may be less informative because it measures both free testosterone and protein-bound testosterone.³ This test can produce normal readings even when age-related increases in sex hormone-binding globulin lower concentrations of bioavailable testosterone. In addition, the test may have false-positive results in insulin-resistant men, because excess insulin lowers the concentration of sex hormone-binding globulin, which can lower total testosterone levels even when

TABLE 1

The ADAM* questionnaire

1. Has your libido or sex drive decreased?
2. Do you have a lack of energy?
3. Have your strength or endurance decreased?
4. Have you lost weight?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Do you fall asleep after dinner?
10. Has your work performance deteriorated recently?

Consider testosterone testing in any patient who answers "yes" to questions 1 or 7, or to any three others.

*Androgen Deficiency in Aging Males

bioavailable testosterone is adequate.

Another option is the **calculated free testosterone index**. This has been validated in a recent study.⁹

Healthy men experience wide hour-to-hour and day-to-day fluctuations in testosterone levels (up to 20% over the course of a week), so symptomatic men with normal test results should be tested more than once.

If any of these tests confirm testosterone deficiency, tests of gonadotropin levels will help determine whether the cause of the hypogonadism is primary (hypergonadotropic hypogonadism) or secondary to pituitary disease (hypogonadotropic hypogonadism). In the latter condition, gonadotropins fail to rise in response to low testosterone levels.

Serum prolactin levels should also be measured to screen for hyperprolactinemia. This can be caused by heart or renal failure, hypothyroidism, or a number of drugs.

■ TESTOSTERONE THERAPY

The goals of testosterone therapy are to provide and maintain normal levels of testosterone, thus improving libido, psychological disposition, body mass, strength, stamina, and

The bioavailable testosterone assay is the test of choice for older men



bone density.^{2,3,10} Testosterone replacement improves quality of life but probably does not affect length of life.

Testosterone is available in oral capsules, intramuscular injections, transdermal patches, and transdermal gel.⁴ Unfortunately, intramuscular injections can produce widely fluctuating serum testosterone levels.¹¹ The transdermal patch, although it provides more physiologic testosterone levels, may cause rashes.¹²

The latest addition to our armamentarium is a 1% testosterone gel, available at dosages of either 50 mg daily or 100 mg daily. A large randomized trial found that this product provided steadier serum testosterone concentrations than a 5 mg/day transdermal patch.¹³ Using testosterone gel may also minimize skin reactions.

Both testosterone gel and the patch were

associated with improved libido within 30 days and continuing for up to 90 days. Gel therapy was also associated with improved mood and sense of well-being and a higher level of sexual enjoyment.

Other documented effects of testosterone therapy are increased upper body strength, improved lipid balance, better memory, beard growth, and coronary artery vasodilation. In a mouse model of Alzheimer disease, testosterone reversed memory deficits by inhibiting overproduction of amyloid precursor protein.¹⁴ Testosterone may be beneficial for cardiovascular risk factors and for benign prostatic hyperplasia.^{5,15-17}

Testosterone may increase the hematocrit and the risk of strokes. Testosterone therapy is not indicated for men with prostatic cancer, but there is no evidence that testosterone increases the risk of prostate cancer.

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Elevated prolactin can be due to heart or renal failure, hypothyroidism, or a number of drugs