

Age-Related Low Testosterone

Male hypogonadism is a syndrome of inadequate production of testosterone due to disease or injury of the hypothalamic-pituitary axis or testes. Clinical manifestations include loss of libido; erectile dysfunction; and systemic effects that may include decreased energy, sleep disturbance, depression, decreased bone mineral density, anemia, decreased muscle mass and strength, and increased body fat. In classic hypogonadism, these manifestations usually respond well to replacement of testosterone to normal levels.

Because testosterone levels tend to decrease with age and many of the manifestations of hypogonadism tend to become more prevalent in aging men, a relation between these 2 phenomena has long been suspected. Even before testosterone was identified as the active agent, animal testicular extracts and transplantation of animal testes had been used in the hope of restoring youthful vigor and potency (1). With the availability of injectable testosterone preparations in the mid-20th century and later development of transdermal testosterone patches and gel, this form of therapy for male hypogonadism has become common.

But doubts exist about the appropriateness of testosterone therapy for what has been called “male menopause” or, more recently, “late-onset hypogonadism” or “age-related low testosterone.” Favorable response to therapy has been less predictable in patients with age-related hypogonadism than in those with established disease or injury of the hypothalamic-pituitary-testicular axis. Age-related decreased testosterone may be related to chronic illness, medications, or obesity, suggesting that low testosterone levels may not be the only cause of a patient's symptoms. One study found an increase in cardiovascular events with testosterone treatment (2), but this was not confirmed in other studies (3, 4).

Direct-to-consumer advertising has familiarized the concept of low testosterone as a cause of symptoms in aging men, and the use of testosterone therapy in older men has increased considerably in recent years, often in men in whom low testosterone levels have not been demonstrated. The U.S. Food and Drug Administration has recommended that labeling of testosterone preparations state that the drug is indicated only in reliably diagnosed classic hypogonadism, in which low testosterone levels have been demonstrated.

The Clinical Guidelines Committee of the American College of Physicians has prepared a set of recommendations for the use of testosterone treatment in men with age-related low testosterone (5). The recommendations are based on a systematic review of 38 randomized trials on the efficacy and safety of testosterone therapy in this setting (6). The review authors found small improvements in global sexual function (moderate certainty) and erectile function (low certainty) but little or no effect on physical function, vitality, depression, or cognitive function. They found little or no dif-

ference in adverse cardiovascular events (low certainty) and no increased risk for serious adverse events (moderate certainty).

The Clinical Guidelines Committee suggests that candidates for testosterone therapy should be men with documented, age-related, low levels of testosterone who want to improve their sexual function. Discussion of the potential benefits, harms, and costs, and consideration of patient preferences, should precede the decision to initiate treatment. Treatment should not be initiated to improve energy, vitality, physical function, or cognitive ability. The guideline recommends considering intramuscular rather than transdermal administration of testosterone because of the considerably lower cost. The effects of testosterone therapy should be evaluated within a year, and periodically after that. If sexual function has not improved, testosterone treatment should be discontinued. The level of certainty of each of these recommendations is considered to be low.

These guidelines agree fairly closely with guidelines recently proposed by the Endocrine Society (7) and the American Urological Association (8). Those organizations agree that treatment should be offered to older men with diminished sexual function and well-documented low testosterone levels but should not be used for the less specific symptoms of fatigue and loss of vitality. They suggest diagnostic studies to differentiate primary hypogonadism (high levels of luteinizing hormone and follicle-stimulating hormone) from secondary hypogonadism (low levels of these hormones), and to rule out hyperprolactinemia and other potentially reversible causes of hypogonadism. They recommend careful discussion of the harms and benefits of treatment, which should include consideration of any comorbid conditions, such as anemia or low bone mineral density, that might improve with testosterone replacement.

The American College of Physicians guideline recommendation to favor intramuscular over transdermal administration will be questioned by many clinicians. The lower cost of intramuscular preparations (\$156 vs. \$2135 annually) is a major consideration. But the need for an intramuscular injection every 1 to 4 weeks is a potential barrier to adherence, and some patients require visits to a health care facility for the injections, which may add to the expense. Also, peak-and-valley blood levels after each injection may cause irregularity of symptom relief and difficulty achieving the desired blood level. Individual preference may vary widely in the choice of testosterone therapy.

This and other current guidelines agree that the recent increase in use of testosterone treatment for nonspecific symptoms of aging, especially in men without confirmed testosterone deficiency, is not indicated. Sexual dysfunction, with documented testosterone levels below normal, should lead to consideration of tes-

tosterone replacement. The decision to initiate testosterone therapy for age-related low testosterone should depend on a discussion between the patient and a well-informed caregiver, with full consideration of the patient's values and wishes.

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