Andropause
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Abstract
Age-related decline in serum testosterone level may present as a constellation of signs and symptoms of hypogonadism known as andropause. However, low testosterone can also be indicative of an underlying pituitary disorder; therefore, careful workup should be performed to distinguish between benign and pathologic conditions in individual men. This article presents an overview of the etiology and pathophysiology of hypogonadism, and offers guidelines for the evaluation of men who should have further testing. The pros and cons of various testosterone formulations are discussed.

Keywords: Andropause; Androgen deficiency; Hypogonadism; Testosterone; Male aging; Pituitary

1. Introduction
Andropause is defined as an age-related decline in serum testosterone levels to below the normal range for young men that results in a clinical syndrome of androgen deficiency. The signs and symptoms of low testosterone in adult men include diminished libido, erectile dysfunction, decreased muscle mass and muscle strength, and decreased bone mass. Other symptoms may include decreased cognitive function and memory, depression, irritability, sleep disturbance, fatigue and hot flashes. This constellation of symptoms and signs may be present to a variable degree in individual men. There is controversy as to whether or not this is a physiologic adaptation to aging or a pathologic event. Andropause should not be viewed as a disease, but as a clinical syndrome.

2. Incidence and etiology of age-related hypogonadism
Serum testosterone levels begin to decline at approximately 30 years of age, with an approximate 1% decline yearly thereafter. In addition to the progressive decline in serum testosterone concentrations, the sex hormone binding globulin (SHBG) level progressively increases with age, resulting in a more pronounced decrease in free and bioavailable testosterone compared with total testosterone concentrations. The Baltimore Longitudinal Study of Aging conducted in 890 men 26–96 years of age revealed that 30% of the men in their 70s had a subnormal testosterone level, and the free testosterone index (total testosterone divided by the SHBG level) in men in their 70s was below normal in 65% [1]. The prevalence of hypogonadism in other studies was similar. Wishart et al. [2] found that 25% of men over age 65 had serum testosterone levels below 300 ng/dl. Vermeulen [3] found that 7% of men between the ages of 40 and 60 had a subnormal testosterone level whereas, 35% of men 80 years of age had a low value. In another study, a decrease in bioavailable testosterone was observed in 7% of men between the ages of 40 and 49; this progressively increased to a prevalence of 70% in men 70–79 years of age [4].

Factors contributing to the age-related decline in serum testosterone concentrations include lifestyle issues (e.g., alcohol abuse), comorbid illness (e.g., Type 2 diabetes, obesity) and medication use. The precise etiology of this decline is not known, but studies suggest both peripheral and central defects may play a role. Leydig cell dysfunction is implicated by a decreased testosterone response to exogenous human chorionic gonadotropin (hCG) administration. A hypothalamic–pituitary defect is implicated by a decrease in the amplitude of luteinizing hormone (LH) secretion and a change in the
normal rhythmic pattern of LH release, thus diminishing stimulation of the testes.

3. Evaluation of hypogonadism

An Andropause Consensus Conference was held in April 2000, which was sponsored by the Endocrine Society. Subsequently, recommendations for the evaluation of possible hypogonadism in adult men were published [5]. The recommendations included obtaining morning serum testosterone, LH and prolactin levels. A diagnosis of andropause may be considered if the serum testosterone level is below normal and the LH and prolactin levels are normal. However, in the instance of a patient with a normal or low LH level or a raised serum prolactin level and a testosterone level below 150 ng/dl, magnetic resonance imaging (MRI) of the pituitary is recommended to exclude a hypothalamic or pituitary lesion (e.g., pituitary adenoma, craniopharyngioma).

The selection of a serum testosterone level below 150 ng/dl as a criterion for diagnosing andropause is somewhat arbitrary and cannot definitively exclude the presence of a pituitary lesion. A substantial number of men with pituitary lesions may have serum testosterone levels above 150 ng/dl. While an MRI study in most men with a subnormal testosterone will not demonstrate a pituitary lesion, the failure to identify such a lesion may have serious consequences and delay treatment of an unrecognized pituitary lesion.

4. Testosterone therapy

Testosterone replacement may be beneficial in ameliorating the symptoms and signs of hypogonadism, and replacement therapy should be considered after a thorough evaluation to determine if there are any contraindications to treatment. Risks of testosterone replacement include exacerbation of benign prostatic hyperplasia (BPH), which is present in approximately 80% of men by the age of 80. Additional adverse consequences of testosterone therapy include worsening of sleep apnea, promotion of polycythemia and worsening of high-density lipoprotein (HDL) cholesterol concentrations.

The presence of prostate carcinoma and promotion of tumor growth is also an important consideration with testosterone therapy. In one study the prevalence of occult prostate cancer was 20% in men over the age of 50; these men had normal prostate-specific antigen (PSA) concentrations and results of digital rectal examinations were also normal [6]. The occurrence of prostate cancer varies according to ethnic groups. Between 1990 and 1996, new cases of prostate cancer per 100,000 men in the US were reported for 222 African-American, 147 white and 82 Asian men. The death rate per 100,000 men also varied according to ethnic group; 55 African-American, 24 white and 11 Asian men died in that time period [7].

If testosterone replacement therapy is indicated, there are various preparations available. Oral testosterone tablets (testosterone undecanoate) must be ingested 2–3 times per day, which may not be convenient for some men. This formulation is not available in the US. The 17-alkylated testosterone formulations should be avoided because of potential hepatotoxicity and promotion of increased low-density lipoprotein (LDL) and decreased HDL cholesterol concentrations. Intramuscular testosterone is usually administered every 2–3 weeks using testosterone enanthate or testosterone cypionate. However, this may result in large variations in serum concentrations, with supraphysiologic levels occurring during the first week and subphysiologic levels occurring before the next injection. Variations in serum concentrations may cause mood swings, hot flashes and variable sexual function. Administration of testosterone via the transdermal route is the most physiologic method of replacing this hormone. Serum concentrations achieve a steady state within the normal range, and peaks and nadirs do not occur if the preparation is used daily.

There is no doubt that testosterone replacement in hypogonadal men is beneficial, resulting in improvements in libido, sexual function and sense of well being. Additionally, increased muscle mass (and potentially increased muscle strength) and increased bone mass as well as decreased fat mass are frequently observed with testosterone therapy. However, it is not known if the increased bone mass results in a decrease in the overall risk of bone fracture. Men receiving testosterone replacement should be monitored regularly with measurements of serum PSA and lipid levels, hematocrit and digital rectal examinations. If results of these assessments become abnormal, then dose adjustment or discontinuation of treatment should be undertaken, and a thorough evaluation should be conducted.

5. Conclusions

The questions of how much evaluation of age-related hypogonadism is required and whom to treat are controversial. If the demographic information on the prevalence of hypogonadism in aging men is considered, then up to 70% of men over the age of 70 may be candidates for treatment. Only after careful evaluation and consideration of the risks and benefits should testosterone replacement be administered to older men. Gonadal steroid replacement in older men, as occurs in women, has some inherent risk of adverse consequences, thus requiring careful medical evaluation and monitoring.
References


