The Role of Serum Testosterone Testing: Routine Hormone Analysis Is an Essential Part of the Initial Screening of Men With Erectile Dysfunction

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As oral phosphodiesterase-5 inhibitor therapy has become the first-line treatment of erectile dysfunction (ED), common approaches in the evaluation of ED have been largely abandoned. Not only is routine hormone analysis no longer widely recommended, but most specialists perform serum testosterone level testing only in the most complex cases of ED. This article explores the rationale for including serum testosterone analysis as part of the initial screening of patients with ED. The use of routine serum testosterone testing is advocated for its efficacy in the diagnosis and treatment of hypogonadism and pituitary disorders associated with ED.
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With the introduction of oral phosphodiesterase-5 (PDE-5) inhibitors in 1998, common algorithms previously employed in the evaluation of erectile dysfunction (ED) have largely been abandoned. Whether neurogenic, vasculogenic, or psychogenic in nature, first-line treatment of impotence today primarily relies on oral PDE-5 inhibitors. While neurophysiologic testing is no longer routinely performed, many but not all investigators continue to recommend a routine hormone profile in the initial evaluation of ED. Standard meas-

urement of at least a serum testosterone level in the evaluation of patients with ED still engenders some controversy, however, with some experts offering the caveat that serum testosterone levels should only be performed in those patients with decreased libido or testicular atrophy on physical examination.[1] Herein, we explore the rationale behind routine endocrine testing in impotent patients, and advocate serum testosterone analysis in the initial evaluation of patients with ED.

Most patients referred to impotence specialists today have already failed PDE-5 inhibitors.

Testosterone and Erectile Function

The role of testosterone in mediating penile erection is largely unknown. Retrospective reviews of impotent patients demonstrate significant improvement in libido with parenteral testosterone therapy,[2] yet only 40% to 60% of these patients have been reported to show improvement in erectile function.[3,4] This disparity suggests the role of testosterone in erection may be limited.

In animal models, castration results in a decrease in cavernosal smooth muscle content, which in turn leads to a decrease in intracavernosal pressure during an electrically induced erectile response[5]; these effects can be reversed with the administration of exogenous testosterone. Furthermore, although nitric oxide is known to be the primary mediator of smooth muscle relaxation within the corporal tissue and the resultant tumescence, its synthesis from neuronal nitric oxide synthase within the nerve terminals of the corpora cavernosa may be regulated by testosterone, and more specifically by its metabolite, dihydrotestosterone.[6] Therefore, although evidence continues to accrue, there is likely a causative relationship between testosterone and erectile function both at the neurogenic and myogenic levels.

Testosterone and Aging

Andropause defines a constellation of symptoms associated with the changing hormonal milieu of aging. This includes decreased lean muscle mass, increased body fat, osteoporosis, decreased libido, ED, and depression. These changes reflect alterations not only in the hypothalamic-pituitary-gonadal axis, but also decreased production of growth hormone, disordered melatonin release, impaired thyroxine production, and elevated levels of leptin.[7] The physical manifestations of andropause likely reflect decreased production of insulin-like growth factor-I, which is under the influence of growth hormone. ED in this syndrome seems to be related only to alterations in serum testosterone levels with aging, despite evidence that adrenal androgens may have a limited role.[8]

Testosterone circulates in the body both free and bound to albumin and sex hormone-binding globulin. Free and albumin-bound testosterone comprise bioavailable testosterone. Data from the Massachusetts Male Aging Study has shown that beyond the age of 40, total serum testosterone declines at an average rate of 0.8% per year.[9] Free testosterone and testosterone bound to albumin decline more steeply, with an average drop of 2% per year. Conversely, levels of testosterone bound to sex hormone–binding globulin increase with age at a rate of 1.6% per year. Thus, a moderate decrease in total serum testosterone belies a much more dramatic decrease in bioavailable testosterone.

With a progressive decline in serum levels of testosterone with age, the prevalence of hypogonadism increases from 7% in males aged 40 to 60 years to 20% in males aged 60 to 80 years.[10] Likewise, the prevalence of ED increases with age, with approximately 50% of men aged 70 years affected.[11] The rates of both hypogonadism and ED are further increased in patients with chronic comorbid conditions, especially obesity and diabetes mellitus.

Hypogonadism and ED

Several large retrospective reviews have examined the importance of hypogonadism in populations of men with ED. The rate of hypogonadism in screening populations of impotent patients varies from 2.1% to 18.7%.[1,3,12-14] Combining these results, approximately 12.2% of patients with ED may have subnormal levels of testosterone.

Symptomatology often reveals patients who may have low serum testosterone values. Typically, these patients report a decreased libido and on physical examination will have atrophic testes. Despite some investigators' assurances that history and physical examination are sufficient screening tools, symptomatology provides only 48% sensitivity and 66% specificity for diagnosing hypogonadism.[3] Buvat and Lemaire[3] described a cohort of 1022 men with ED. Of 533 men with normal sexual desire and a normal physical examination, 32 (6.0%) had documented subnormal values of testosterone. If patients with normal desire and a normal genitourinary examination had not been screened, 40% of the patients that benefited from parenteral testosterone therapy would never have been diagnosed.

Additionally, ED secondary to

hypogonadism can be a presenting complaint of pituitary disorders. Although the prevalence of hyperprolactinemia is low in the entire screening ED population, as many as 30% of patients with low serum testosterone levels have an associated elevation in serum prolactin. In a series reported by Nickel and colleagues, of 5 patients with hypogonadism and hyperprolactinemia, 2 were found to have large pituitary adenomas on imaging studies.[14]

Erectile dysfunction secondary to hypogonadism is reversible, with a significant proportion of men seeing improvement in erectile quality with testosterone therapy.

Finally, the introduction of effective oral therapies for ED has not only altered diagnostic and therapeutic algorithms, but has also changed the population of men seen in ED specialty clinics. Most patients referred to impotence specialists today have already failed PDE-5 inhibitors. Kalinchenko and colleagues demonstrated that a cohort of diabetic men with impotence who failed sildenafil (Viagra®; Pfizer Inc, New York, NY) had significantly lower total serum testosterone than controls.[15] Of 120 men who received combination oral testosterone therapy (testosterone undecanoate) and sildenafil, 84 (70%) were able to achieve satisfactory erections.

Aversa and colleagues have recently shown that the erectile response to sildenafil in men with low normal testosterone levels is improved when exogenous testosterone (Androgel®; Solvay Pharmaceuticals, Inc., Atlanta, GA) is given in tandem with the PDE-5 inhibitor.[16] Scientifically, these clinical observations could be due to the fact that the PDE-5 enzyme appears to be androgen-dependent.[17] This emerging relationship between testosterone and its effect on erectile function in the aged is further supported by the study in animals that long-term androgen therapy by itself will improve the erectile dysfunction seen in aged animals.[18]

Conclusions

The evaluation and management of ED has evolved dramatically following the introduction of oral PDE-5 inhibitors. Most specialists perform directed diagnostic testing only in the most complex cases of ED. Despite the limited role of these tests in the evaluation of the impotent patient, the determination of serum testosterone levels is controversial. Review of the literature reveals the following:

1. Testosterone likely has a physiologic role in the potentiation of erection possibly via its effect at various steps in the nitric oxide-cyclic guanosine monophosphate pathway.
2. Hypogonadism affects a significant proportion of men, especially those suffering from ED.
3. The presence of decreased libido and atrophic testes inaccurately predicts hypogonadism, and screening based solely on symptomatology would fail to diagnose a proportion of patients that would benefit from therapy.
4. ED secondary to hypogonadism is reversible, with a significant proportion of men seeing improvement in erectile quality with testosterone therapy.
5. Hypogonadism can be the presenting complaint of more serious pituitary disorders.

Routine evaluation of serum testosterone should be performed in the initial evaluation of men with ED. ■

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Main Points

- Most specialists perform directed diagnostic testing only in the most complex cases of erectile dysfunction (ED).
- The presence of decreased libido and atrophic testes inaccurately predicts hypogonadism, and screening based solely on symptomatology would fail to diagnose a number of patients that would benefit from therapy.
- ED secondary to hypogonadism can be a presenting complaint of pituitary disorders. Although the prevalence of hyperprolactinemia is low, as many as 30% of patients with low serum testosterone levels have an associated elevation in serum prolactin.

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