The Role of Routine Serum Testosterone Testing: Routine Hormone Analysis Is Not Indicated as an Initial Screening Test in the Evaluation of Erectile Dysfunction

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A 60-year-old male physician is self-referred to your office for evaluation of his erectile dysfunction, which has been worsening for 5 years. He reports his erections rarely achieve fullness for penetration, and he is unable to ejaculate. He has tried sildenafil citrate (Viagra®; Pfizer Inc, New York, NY) with mild success in the past. He has a strong libido and feels healthy. He rarely exercises, but is on his feet most of the day at work. He has been healthy his whole life and never seeks a doctor's attention. He has no other medical problems. His only medication is a baby aspirin once a day. His physical examination, including genitalia, is normal. As part of his initial visit, should his serum testosterone level be checked by his urologist?
[Rev Urol. *2004;6(4):203-206*]

Key words: Erectile dysfunction • Testosterone • Hypogonadism

Erectile dysfunction (ED) is rapidly increasing in prevalence as a result of the aging US population. Since the commercial launch of oral phosphodiesterase-5 inhibitors in 1998, treatments for ED have been heavily promoted by the media and aggressively marketed by the pharmaceutical industry. The result is rapidly expanding numbers of patients seeking treatment for ED. Urologists bear part of the burden to diagnose, treat, educate, and attend to this growing patient population. As healthcare costs rise and evidence-based medicine

becomes the standard, we must reconsider what hormonal evaluation, if any, is necessary for the work-up of ED. The rationale for screening testosterone levels in patients with ED is to identify potential comorbid hypogonadal states, as well as to identify any subset of men who could benefit from testosterone replacement therapy. Although it may appear that checking a simple testosterone level is an inexpensive and convenient screening tool, screening the testosterone levels of all patients with ED is very costly and unnecessary. One of patients' and physicians' greatest misconceptions is that hypogonadism is the cause of many cases of ED. Hypogonadism alone is in fact a very rare cause of ED, and serum testosterone must be extremely low in and of itself to cause ED. Still, a majority of physicians and physician references advocate checking the serum testosterone level in men with ED. This is impractical for a variety of reasons.

The Pathophysiology of Hypogonadism

Many authors advocate checking total testosterone levels in new patients with ED as a screening test for occult hypogonadism.[1,2] Testosterone level is chosen because it is the most cost-effective way to screen for the majority of central or gonadal endocrinopathies.[2] If the resultant testosterone level is abnormally low, the test should be repeated and followed-up with analyses of serum leutinizing hormone (LH), follicle-stimulating hormone (FSH), free testosterone, and prolactin levels.[3,4] If the total and/or free testosterone levels are low, and prolactin is elevated, a prolactinoma must be considered. Prolactinomas, although very rare, are treatable causes of ED and are potentially devastating tumors if left untreated. Other organic causes of hypogonadal ED such as hypothalamic-pituitary disease, hormonal irregularity, and testicular atrophy would also be detected in this algorithm.

One of the problems with testosterone screening is that testosterone levels are variable within any given individual at any given time, and there is no immediate cut-off for any individual to determine where the appropriate "normal" range stops and the clinically significant levels set in. To demonstrate the variability of random testosterone levels, consider that within a large ED screening trial of 1022 men, 40% of men initially diagnosed with low testosterone (< 3 ng/mL) had normal testosterone levels upon repeat determination. To put that false positive rate in perspective, only 1.8% of the patients in the same study had markedly low testosterone levels (< 2 ng/mL), and overall, less than 2% of all patients screened went on to benefit from testosterone replacement therapy.

In one study, all patients with laboratory evidence of hypogonadism also had clinically apparent signs and symptoms, including decreased libido and testicular atrophy.

A similar testosterone screening trial by Johnson and Jarow found that of 330 patients presenting for the initial evaluation of ED, only 7 patients (2.1%) had a true endocrinopathy.[4] More importantly, this same study demonstrated that all of the patients with laboratory evidence of hypogonadism actually had clinically apparent signs and symptoms of hypogonadism, including decreased libido and testicular atrophy. Johnson and Jarow concluded that not only is hypogonadism relatively rare in ED, but that the endocrinologic work-up for hypogonadism should be reserved for those patients with decreased libido or clinical signs such as testicular atrophy.[4]

The Incidence of Hypogonadism in ED

Hypogonadism is a relatively rare cause of ED when compared with the alarmingly high prevalence of vascular disease, heart disease, diabetes, and hypertension in impotent men. Across the literature, the reported prevalence of hypogonadism among impotent men ranges anywhere from 1.7% to 35%,[5,6] depending on the study. This huge discrepancy is partly the result of statistical discrepancies and patient selection. For example, in the study by Buvat and Lemaire cited above, 40% of the patients with clinically low testosterone also had significant peripheral vascular disease.[1] Is their ED the result of the vascular disease or low testosterone, and in which category should they be classified?

The proponents of testosterone screening for ED emphasize that a diagnosis of hypogonadism or hyperprolactinemia can uncover important occult diseases such as pituitary tumors.[1,2] In fact, in their article advocating testosterone screening, Buvat and Lemaire[1] uncovered 2 cases of pituitary tumors in the 1022 men they screened (< 0.2% incidence). They did not comment, however, as to whether these 2 patients had decreased libido and/or testicular atrophy as Johnson and Jarow's[4] conclusions would suggest.

To put the 2% prevalence of hypogonadism in ED patients into perspective, compare it with cardiovascular screening of ED patients, which has demonstrated a 50% inci-

dence of atherosclerosis, 24% incidence of diabetes, 17% incidence of uncontrolled hypertension, and 6% incidence of significant angina.[7,8,9] Therefore, our sample patient has a 10- to 20-fold greater chance of having coronary artery or peripheral vascular disease than hypogonadism. Studies show his relative risk of developing an acute myocardial infarction is at least 2-fold greater than that of an identical patient without ED, even after controlling for smoking, obesity, and medications.[7] So if one plans to empirically screen testosterone levels in our patient, then to what extent and cost should his vascular and cardiac risk factors be worked-up?

The Link Between Testosterone and ED

Proponents of testosterone screening often cite the parallel decline in androgen levels and erectile function in aging men as a reason to monitor and restore low testosterone levels. However, there is minimal scientific evidence to suggest that this is anything more than correlation. Androgens are obviously vital for developing and maintaining male secondary sexual characteristics and libido, but the direct role that androgens have on maintaining penile tissue and erection physiology remains very controversial.[10] For example, up to 50% of potent men can retain erectile function after medical or surgical castration.[11]

Outside of its effects on libido, the effects of testosterone on male sexual function are entirely unknown. Penile tumescence involves a complex integration of signals and messengers from the central and peripheral nervous systems, as well as hormonal and vascular systems.[12] At a physiologic level, the erect penis is the product of nitric oxide synthase producing neuronal and endovascular nitric oxide, which, via cyclic guanosine monophosphate, dilates not only the smooth muscle within the cavernosa but also those of the arteries and arterioles that supply the erectile tissue. Exactly how and if testosterone fits into this erectile physiology is undetermined.[10]

Studies show that many patients with severe hypogonadism show significant improvement in their ED following testosterone supplementation.[1,13] A meta-analysis of testosterone supplementation for ED concluded that, overall, 57% of all patients who present with ED and low testosterone will respond to some type of exogenous testosterone therapy.[14] Patients with more severe hypogonadism tend to have a higher incidence of response to testosterone; a majority (63%) of the responders in the study by Buvat and Lemaire had clinical signs or symptoms of hypogonadism, thus reiterating the point by Johnson and Jarow that most of the true cases of hypogonadism can be picked up with routine history and physical examination alone.[1,4]

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Cost/Benefit Analysis

Johnson and Jarow estimated that the cost of screening testosterone levels in all cases of ED is $3624 for every 1 case of hypogonadism detected.[4] If the tests are limited to cases that have clinical signs or symptoms of hypogonadism, the cost can be reduced to $1900 per case of hypogonadism detected. At our institution the laboratory cost of a serum testosterone level is about $50, which is relatively standard and inexpensive at first glance. However, when multiplied by the annual projection of 600,000 new cases of ED per year,[15] the up-front cost to the healthcare system is $30,000,000 per year just to screen testosterone levels. When the costs of the obligatory follow-up levels of total testosterone, free testosterone, LH, FSH, and prolactin are computed for those who screen positive, the screening cost doubles to $60,000,000 per year—of which $12,000,000 is the result of false-positive tests.

Conclusions

In the current era of managed care and sky-rocketing medical costs, it remains the physician's obligation to provide the highest quality of care to one's patients while keeping the costs to society reasonable and appropriate for the disease at hand. A review of the literature supports the following:

1. A thorough history and physical examination remain the most important screening tools for the diagnosis of ED.
2. The overall prevalence of clinically relevant hypogonadism in patients with ED is very low, probably less than 5% and closer to 1% to 2%.
3. Clinically significant hypogonadism in the setting of ED is usually detected from the presence of decreased libido and/or atrophic testes.
4. Clinically significant hypogonadism tends to be more responsive to testosterone supplementation than less severe hypogonadism.
5. The cost of screening all men with ED for hypogonadism cannot be justified by the small per-

centage of additional cases detected and large percentage of false-positive results.

We would recommend the sample patient receive a thorough history and physical examination upon his initial visit without any screening laboratory tests. Focused tests can be performed in the future based on clinical suspicion from the history and physical. ■

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Main Points

- Hypogonadism is a relatively rare cause of erectile dysfunction (ED) when compared with the alarmingly high prevalence of vascular disease, heart disease, diabetes, and hypertension in impotent men. Although checking serum testosterone levels is a relatively simple and inexpensive procedure, routine screening in all patients presenting with ED is unnecessary and ultimately very costly.
- In 1 large trial, 40% of patients with an initial diagnosis of hypogonadism at the time of screening ultimately had a normal hormonal work-up. In another screening trial, all of the patients found to have a true endocrinopathy also had clinically apparent signs and symptoms of hypogonadism.
- It has been estimated that the cost of screening testosterone levels in all cases of ED is $3624 for every 1 case of hypogonadism detected. If the tests are limited to cases that have clinical signs or symptoms of hypogonadism, the cost can be reduced to $1900 per case of hypogonadism detected.
- A thorough history and physical examination remain the most important screening tools for the diagnosis of ED. The cost of screening all men with ED for hypogonadism cannot be justified by the small percentage of additional cases detected and large percentage of false-positive results.