LABORATORY EVALUATIONS OF ERECTILE DYSFUNCTION: AN EVIDENCE BASED APPROACH

JOSHUA BODIE, JEAN LEWIS,* DOUG SCHOW† AND MANOJ MONGA‡
From the University of Minnesota and the VA Health Care System, Minneapolis, Minnesota

ABSTRACT

Purpose: We evaluate the prevalence of laboratory abnormalities in men presenting for initial evaluation and therapy of erectile dysfunction.

Materials and Methods: The computerized charts of men receiving treatment for erectile dysfunction from 1987 to 2002 were retrospectively reviewed. We pooled laboratory data for 3,547 men with erectile dysfunction to assess the prevalence of laboratory abnormalities. Values of the common laboratory screening tests for erectile dysfunction were recorded for testosterone, prolactin, luteinizing hormone, thyroid-stimulating hormone, hemoglobin A1c, prostate specific antigen, hemoglobin, cholesterol and creatinine.

Results: Of those patients evaluated 18.7% had low testosterone, 4.6% had increased prolactin, 14.6% had abnormal luteinizing hormone, 4.0% had increased thyroid-stimulating hormone, 8.3% had increased prostate specific antigen, 26.5% had anemia and 11.9% tested had renal insufficiency. A high percentage of patients presenting with a primary complaint of erectile dysfunction had increased hemoglobin A1c and total serum cholesterol levels (52.9% and 48.4%, respectively).

Conclusions: An evidence based approach to standardization of laboratory evaluations for men presenting with erectile dysfunction is recommended. Laboratory screening should be directed to identify those risk factors that may benefit from lifestyle modification and pharmacological intervention.

Key Words: impotence, laboratories, evaluation studies, testosterone

Erectile dysfunction is defined as the inability to achieve and maintain an erection satisfactory for intercourse.1 It affects approximately 10 to 20 million Americans;2 is associated with depression, anxiety and loss of self-worth, and has been shown to compromise overall quality of life.3 There are a variety of etiologies for erectile dysfunction, including psychogenic and/or organic. Organic causes may be vasculogenic, neurogenic or hormonal. Organic and vascular causes comprise the majority of erectile dysfunction, although psychological factors also have a role in most cases.3 Up to 80% of all erectile dysfunction cases have an organic component,2 and it is commonly a sequela of systemic disease, such as hypercholesterolemia or diabetes mellitus.

Medical examination of erectile dysfunction should first include a detailed medical and sexual history, as well as a complete physical examination with attention paid to the cardiovascular, neurological and genitourinary systems. A comprehensive medication history is also essential. There is no consensus on the role of laboratory screening in men presenting with erectile dysfunction. Many advocate a morning serum testosterone determination in most or all patients presenting with erectile dysfunction. Most agree that serum testosterone should be measured if decreased libido is present. Some authors prefer testing bioavailable (free and albumin bound) testosterone rather than total serum testosterone.3, 4 Others have proposed using the clinical signs of decreased libido and small testis volume (less than 19 ml.) as screening guidelines to identify subpopulations of patients with erectile dysfunction who need a more extensive evaluation for endocrinopathy.4

Prolactin, luteinizing hormone (LH) and follicle-stimulating hormone are also often obtained not as primary screening tools for erectile dysfunction, but only if initial serum testosterone is abnormally low or the clinician suspects hypogonadism. One would expect increased gonadotropins in response to gonadal failure, while low gonadotropin levels would indicate a primary pituitary dysfunction. Prolactinomas comprise approximately 60% of pituitary tumors and commonly cause increased prolactin. Disruption of the hypothalamus or pituitary stalk, treatment with dopamine antagonists, and increased thyroid-releasing hormone in hypothyroidism can also cause increased prolactin.

The role of routine testing for thyroid function, anemia, renal function, serum prostate specific antigen (PSA), glycosylated hemoglobin and hypercholesterolemia in men presenting with erectile dysfunction has not been well studied. We evaluate the prevalence of laboratory abnormalities in an unselected Veterans Administration Medical Center male patient population with erectile dysfunction to help establish evidence based screening guidelines.

MATERIALS AND METHODS

The records of all patients referred to the erectile dysfunction specialty clinic at the Veterans Administration Health Care System Minneapolis from 1987 to 2002 were retrospectively evaluated. This clinic serves the primary care population of Minneapolis veterans with complaints of erectile dysfunction. Primary care physicians at the Minneapolis Veterans Administration Medical Center do not treat erectile dysfunction, as the use of pharmacological or other treatment
options is restricted to urologists. No prescriptions were offered to these patients outside of the urology/erectile dysfunction clinic for erectile dysfunction.

A standardized set of routine laboratory tests was ordered by our clerical staff before evaluation of the patient by a physician in the erectile dysfunction clinic. Therefore, laboratory evaluation was performed in an unselected manner, irrespective of medical history or risk factors for abnormalities. Variances in the frequency of each individual test reflect changes in the battery of tests ordered during the defined period.

These tests and their normal values included serum testosterone (280 ng/dl. or greater), prolactin (18 ng/ml. or less), luteinizing hormone (1.3 to 10.1 mIU/ml.), thyroid-stimulating hormone (TSH, 0.3 to 6.0 mIU/ml.), glycosylated hemoglobin (less than 6.4%), prostate specific antigen (4 ng/ml. or less), hemoglobin (14 gm/ml. or greater), cholesterol (200 mg/dl. or less) and creatinine (1.4 mg/dl. or less). The data base was also searched for results of imaging studies in patients with increased prolactin levels.

RESULTS

A total of 3,547 men were evaluated from 1987 to 2002. Patient age distribution is shown in the figure. The frequency of laboratory evaluations and abnormalities within this cohort of patients is presented in the table.

Of 2,623 unselected patients who had testosterone checked on at least 1 occasion it was less than 280 ng/dl. in 528 (18.7%) and less than 220 ng/dl. in 210 (9.2%). Serum prolactin was increased in 4.6% of 2,306 patients, while serum LH was low in 5.7% and high in 8.9%. Serum testosterone levels were low in 50% of men with hyperprolactinemia and in 12% with abnormal LH levels. Imaging studies (computerized tomography or magnetic resonance imaging) were obtained in 47% of patients with increased prolactin levels. Prolactinomas were more likely in patients with prolactin levels greater than 50 ng/ml. (57%) than in those with levels 18 to 49 ng/ml. (10%).

Thyroid abnormalities were identified in 5% of 2,240 unselected men, with 1% having low and 3.9% having high serum TSH levels. Undiagnosed or poorly controlled diabetes mellitus, defined by an increased hemoglobin A\textsubscript{c}, was identified in 53% of 1,739 men, while hypercholesterolemia was identified in 48% of 3,014 men. Serum PSA was increased in 8.3% of 3,055 men. Anemia was detected in 26.5% of 3,420 men, while increased creatinine was detected in 11.9% of 3,423 men.

DISCUSSION

The purpose of our study was to evaluate the usefulness of various routine laboratory screening tests in men with erectile dysfunction. The goal of screening is to identify those patients with significant endocrinopathy or modifiable systemic factors that may be contributing to sexual dysfunction.

Previous studies have shown a relatively low incidence of endocrinopathy among patients with erectile dysfunction. In our study serum testosterone was less than 280 ng/dl. in 18.7% of men and less than 220 ng/dl. in 9.2%. The later value is similar to previous series, in which abnormally low (less than 220 ng/dl.) testosterone was seen in 3.3% to 10.5% of patients.\textsuperscript{4-6} We did not examine repeat testosterone values, which may be important, as up to 40% of patients with an initial testosterone level in the 200 to 300 ng/dl. range may have a normal value on repeat evaluation due to diurnal variation in testosterone secretion.\textsuperscript{4-6} Some investigators propose using pooled serum samples drawn 30 minutes apart to dampen episodic spikes of testosterone and gonadotropin hormone secretion.\textsuperscript{7} Testosterone deficiency is a common and treatable condition, and routine evaluation appears warranted.

Of 2,306 men in whom prolactin was drawn 10 (0.43%) had a serum prolactin level of greater than 50 ng/ml. In a study of 4,803 asymptomatic men by Miyake et al 14 patients (0.29%) had a serum prolactin of greater than 50 ng/ml.\textsuperscript{8} The incidence of prolactinoma in men was estimated to be 1:1,600 in that study. In view of the low prevalence of this abnormality, we do not recommend routine screening of serum prolactin. About 80% of men with prolactin greater than 50 ng/ml. complain of diminished libido and erectile dysfunction because excessive prolactin can suppress secretion of the gonadotropin releasing hormone.\textsuperscript{9} Of the 10 men in our study who had prolactin greater than 50 ng/ml. only 5 had serum testosterone levels less than 280 ng/dl. This finding suggests that serum testosterone may not be a sensitive screening tool for hyperprolactinemia, and the clinician must rely on other signs and symptoms of pituitary dysfunction.

In our study an increased LH level, suggestive of primary testicular dysfunction, was more common than a low level, although only 7 of the 59 patients (11.9%) with increased LH levels had serum testosterone less than 220 ng/dl. The low LH levels demonstrated in 5.7% of men may represent pituitary dysfunction or enhanced feedback inhibition seen in elderly men.\textsuperscript{10}

Of the men in our study with serum TSH determination 3.9% had an abnormally high value (greater than 6.0 mIU/ml.) and were considered to be hypothyroid. In a comparable study by Baskin 6% (38 of 600 men) had hypothyroidism defined by TSH greater than 5 mIU/ml. with or without low thyroxine.\textsuperscript{7} Thyroid hormone replacement with levothyroxine sodium in sufficient doses to lower TSH levels to the normal range has been shown to correct erectile dysfunction in some patients.\textsuperscript{7} Erectile dysfunction may be the presenting complaint or only clinical sign of hypothyroidism. These patients should be identified because thyroid hormone is

### Prevalence of laboratory abnormalities at an erectile dysfunction clinic

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>% Pts. Evaluated</th>
<th>% Pts. With Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>79.6</td>
<td>18.7</td>
</tr>
<tr>
<td>Prolactin</td>
<td>65.0</td>
<td>4.6</td>
</tr>
<tr>
<td>LH</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>Total abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>14.6</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>5.7</td>
</tr>
<tr>
<td>TSH</td>
<td>63.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Total abnormal</td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Hemoglobin A\textsubscript{c} (normal less than 6.4%)</td>
<td>49.0</td>
<td>52.9</td>
</tr>
<tr>
<td>PSA</td>
<td>86.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>96.4</td>
<td>26.5</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>85.0</td>
<td>48.4</td>
</tr>
<tr>
<td>Creatinine</td>
<td>96.5</td>
<td>11.9</td>
</tr>
</tbody>
</table>
easily and safely replaced, and may restore sexual function. It is important to note that we did not identify or exclude from study those men who were receiving thyroid supplementation at the time of presentation.

Of our patients who underwent evaluation of total serum cholesterol approximately half (48.4%) had an abnormal value. Hypercholesterolemia is a significant risk factor for atherosclerotic vascular disease and thus erectile dysfunction. Approximately 25% to 50% of patients who have lived with type I diabetes mellitus for 25 years or more have erectile dysfunction.9 Furthermore, there is evidence that hypercholesterolemia is a modifiable secondary cause of erectile dysfunction. The high prevalence of increased cholesterol in men presenting with erectile dysfunction supports the role for routine screening of total serum cholesterol. Further studies may help establish which cholesterol fractions and lipid levels may correlate with erectile dysfunction.

Hemoglobin A1c was also high in about half (52.9%) of the study group. Diabetes is a well-established risk factor for atherosclerotic vascular disease and thus erectile dysfunction.10 Of 3,547 total veterans, 1,855 had diabetes. Of those, 1,170 had hemoglobin A1c values in the range of 7% to 12%, with an average of 8.9%. Approximately 25% to 50% of patients who have lived with type 1 diabetes mellitus for 25 years or more have erectile dysfunction.11 It is important to note the high prevalence of hypercholesterolemia in this patient population, as undiagnosed or poorly controlled hypercholesterolemia is a modifiable secondary cause of erectile dysfunction. The high prevalence of increased cholesterol in men presenting with erectile dysfunction supports the role for routine screening of total serum cholesterol.

Approximately 25% to 50% of patients who have lived with type 1 diabetes mellitus for 25 years or more have erectile dysfunction.12 These findings support routine screening of hemoglobin A1c in men presenting with erectile dysfunction, as undiagnosed or poorly controlled diabetes is a common and modifiable risk factor for erectile dysfunction. As an index of adequacy of control of diabetes hemoglobin A1c is widely accepted.13 While hemoglobin A1c has been demonstrated to be a highly specific and convenient screening test for diabetes, confirmatory testing with fasting blood glucose or glucose tolerance test is recommended.14

No other studies could be identified in the literature specifically correlating erectile dysfunction and PSA levels, and our study may represent the largest to date. In a prospective study of 127 men with erectile dysfunction Sairam et al. found that the detection rate of prostate cancer using PSA, digital rectal examination and sextant biopsy for men with PSA greater than 4 ng/ml was 5%, which was not significantly higher than that in the general population.15 Of 3,547 total men in our study PSA was greater than 4 ng/ml and serum testosterone was less than 280 ng/dl in 252. These values do not differ significantly from testosterone findings in our study as a whole. However, it is advisable to check PSA before initiating testosterone replacement therapy because androgen therapy may enhance growth of an occult prostate cancer. The percentage of men with increased creatinine values in our study does not suggest that routine screening of serum creatinine is warranted in men presenting with erectile dysfunction.

There was a high prevalence of anemia in our patient population. About 25% of veterans had low hemoglobin. It is not known to what extent the anemia contributed to the erectile dysfunction or if a systemic disease contributed to both. Routine screening of hemoglobin appears warranted.

CONCLUSIONS

The 2 objectives to laboratory screening are to determine the presence and severity of endocrine or systemic disease, and to identify those patients who may respond to various treatments. Our findings indicate that testosterone deficiency is common and routine screening may be warranted. Screening for pituitary dysfunction with a low testosterone level appears to have poor sensitivity. Routine screening of TSH, total serum cholesterol and hemoglobin A1c is warranted in men presenting with erectile dysfunction. Further areas for study include association of cholesterol fractions with erectile dysfunction, and to what degree sexual function may be restored or preserved with normalization of hypercholesterolemia.

REFERENCES