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Epinephrine is associated with both erectile dysfunction and lower urinary tract symptoms

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Abstract

Objective—To determine whether patients with erectile dysfunction (ED) have a higher incidence of insulin resistance (IR) when compared with controls.

Design—Prospective case-control study.

Setting—Academic medical center.

Patient(s)—Twenty-nine nondiabetic men aged 18–66 years were enrolled. Of these, 28 completed the study: 17 had ED, and 11 did not.

Intervention(s)—Validated ED questionnaires, examination, serum hormones evaluation, and oral glucose tolerance testing.

Main Outcome Measure(s)—Association of IR with ED.

Result(s)—The association between worsening degrees of both lower urinary tract symptoms (LUTS) and ED was reaffirmed, as was a potential correlation between the two—epinephrine. There was a negative association between serum levels of epinephrine and scores on the 5-item version of the International Index of Erectile Dysfunction for ED (Spearman correlation coefficient = -0.38). On the other hand, men with ED were not more likely to have IR compared with controls.

Conclusion(s)—Epinephrine may be the common link between ED and LUTS.

Keywords

Erectile dysfunction; lower urinary tract symptoms; epinephrine; insulin resistance; metabolic syndrome

Diabetes is a risk factor for developing erectile dysfunction (ED), such that men with either type I or type II diabetes have a threefold greater risk for developing ED. For this reason, diabetic men should be screened for ED during their 30s and 40s (1, 2). Type II diabetes is

thought to be preceded by and potentially induced by a state of insulin resistance (IR). The effects of IR per se (elevated insulin levels, altered lipids, and down-regulation of nitric oxide [NO] synthetase activity) are likely to worsen erectile function even before the development of frank diabetes. Impaired NO-dependent vascular relaxation is a characteristic feature of the insulin-resistant state. Insulin resistance is also associated with increased levels of insulin—which has been associated with increased sympathetic tone and vascular smooth muscle proliferation (3). Each of these effects would predict worsening erectile function. With IR affecting 25% of U.S. adults (4) and 60% of overweight adults with a body mass index (BMI) $>35 \text{ kg/m}^2$ (5), the potential association between IR and ED merits further investigation. Treating IR, and thereby improving NO-related vasodilation, reducing sympathetic tone, and normalizing cavernosal smooth muscle function, may offer patients with IR-enhanced erectile responses an improved quality of life.

We performed this study to test the hypothesis that men with ED are more likely to have IR. A secondary endpoint looked to confirm the association between ED and worsening lower urinary tract symptoms (LUTS).

MATERIALS AND METHODS

Study Design

This prospective, case-control study recruited volunteers from our urology clinics, from male partners of women being treated at our reproductive endocrinology clinic, and men responding to either print or radio advertisements. All subjects provided written informed consent—approved by the Penn State College of Medicine institutional review board.

Men were enrolled in the study if they were between 18 and 66 years of age and were excluded if they had confounding comorbidities, such as neurologic conditions, spinal cord injury, depression, and use of medications such as nitroglycerine, antidepressants, or β -blockers. Thirty-four men were screened, with 29 consented for the study. Excluded subjects did not meet age requirements, with 1 also reporting use of an oral hypoglycemic agent. A single subject dropped out of the study because of anxiety surrounding venous catheterization. All other subjects completed the study without difficulty or report of side effect. Of the 28 men that completed the study, 27 were Caucasian and 1 control subject was African American. Patients with ED (cases) were required to have ED as defined by a score on the abridged (5-item) International Index of Erectile Function (IIEF-5) (6) of ≤ 21 , subjects were defined as having no ED (controls) when their IIEF-5 score was 22–25. Of those with ED, 4 (14.3%) had mild symptoms (IIEF-5 score of 17–21), 10 (35.7%) had moderate to severe symptoms (IIEF-5 score of 5–16), and 3 (10.7%) had severe symptoms (IIEF-5 score of 0–4).

Study Procedure

The subjects presented to our General Clinical Research Center after a 3-day carbohydrate load and an overnight 10-hour fast in preparation for an oral glucose tolerance test (OGTT). An intake history and physical examination results were recorded, and subjects completed two validated questionnaires: the IIEF-5 (6) and the International Prostate Symptom Score (IPSS) (7). Blood samples were collected in the morning after a 10-hour fast for a lipid profile, catecholamine (epinephrine and norepinephrine), testosterone, glucose, and insulin levels. A nurse inserted an IV catheter into a vein, and a fasting blood sample was drawn into 10-mL syringes and transferred into Vacutainer tubes (VWR Scientific Products, West Chester, PA). An OGTT was then performed with a 75-g oral glucose challenge. Blood samples were taken at 30-minute intervals for 2 hours for measurement of glucose and insulin levels. Serum and plasma were separated by centrifugation for 15 minutes at $1,465 \times$

g (3,200 rpm) and 4°C and aliquoted into 0.5–2-mL cryovials and stored at –80°C until analyzed. Because of rapid deterioration, catecholamine samples (epinephrine and norepinephrine) were drawn into a prechilled Vacutainer tube. Plasma was separated using a refrigerated centrifuge, then transferred into a screw-capped vial and immediately frozen. The frozen specimen was not thawed before processing at the General Clinical Research Center core laboratory (8–10).

Biochemical Analysis

Glucose was measured by the glucose oxidase technique using a YSI 2300 Glucose Analyzer (YSI Life Sciences, Yellow Springs, OH). Insulin was measured by RIA (Linco, St. Charles, MO) (11). Total cholesterol and high-density lipoprotein cholesterol were measured by Quest Diagnostics (Madison, NJ) using an automated chemistry analyzer (Olympus AU-5400, Mshima, Japan). All samples were processed using established assay techniques (12, 13). The assays all have <10% interassay coefficients of variation.

Statistics and Sample Size Justification

The study was designed to detect an absolute mean difference of 1.2 in the insulin sensitivity index (ISI) (14) derived from the OGTT between those men with ED (IIEF-5 <22) and those without ED (IIEF-5 22–25). We assumed an ISI common SD of 0.9 and did not factor in any potential subject dropout. On the basis of these assumptions, to detect an ISI mean difference of 1.2 between the two groups, we needed to enroll 30 men for the study to have a power of 94% for a two-sided test with a type I error of 0.05.

Two-sample *t*-tests with associated 95% confidence intervals were used to estimate the differences in the means between the two groups. Spearman's correlation coefficient was used to assess the association between continuous characteristic variables and the raw IIEF-5 score.

RESULTS

A total of 28 men completed the study, with 11 categorized as controls (without ED) and 17 categorized as having ED. Patient characteristics can be found in Table 1. The mean age was slightly greater for the ED group, but the difference was not statistically significant. This study did not demonstrate any statistically significant difference between the two groups regarding the glycemic and insulin action parameters of fasting glucose, fasting insulin, fasting glucose/insulin ratio, glucose/insulin levels 120 minutes after glucola, area under the curve for insulin and glucose, and ISI. Surprisingly, BMI was greater for the control group, with the difference not reaching statistical significance. The IPSS scores were lower (less bothersome) in men without ED (3.2 ± 3.0) as compared with men with ED (9.7 ± 4.9) (95% confidence interval –9.9, –3.1; $P < .001$).

The association between patient characteristics and the raw IIEF-5 scores for ED is presented in Table 2. There was a relatively strong negative association between the validated (IPSS) survey scores for LUTS and the IIEF-5 scores for ED (Spearman correlation coefficient = –0.61; $P = .001$) (Fig. 1). Furthermore, there was a negative association between serum levels of epinephrine and IIEF-5 scores for ED (Spearman correlation coefficient = –0.38; $P = .04$) (Fig. 2).

DISCUSSION

We did not find that men with ED were more likely to have IR when compared with age- and weight-comparable controls. However, this study did confirm the association between worsening LUTS and ED, with epinephrine as the only tested variable to demonstrate

statistical significance with the IIEFF-5 scores for ED. We will now discuss our findings in light of the current body of literature.

We were surprised not to find an association between IR and ED. A central tenet of IR is the down-regulation of NO production by impaired endothelial NO synthetase activity (15). In addition to decreased levels of vasodilatory NO, hyperinsulinemia is another IR-related cause for erectile dysfunction. Elevated insulin levels have detrimental effects on erectile function due to both increased sympathetic activity and proliferation of vascular smooth muscle cells (3). In addition, NO has been found to inhibit central neural sympathetic outflow—inferring that defective NO synthesis may contribute to a state of elevated sympathetic tone (12). Our findings contrast with those of Bansal et al. (16), who demonstrated that men with ED have a high incidence of both IR and the metabolic syndrome.

The association between ED and various components of the metabolic syndrome, such as hypertension, obesity, and diabetes, has been established (17–19). Several investigators have reported on the high prevalence of metabolic syndrome among patients with ED (16, 20–25). Because signs of the metabolic syndrome predict development of ED (in addition to diabetes, hypertension, and heart disease), Seftel (26) has suggested, “Identification of the metabolic syndrome will now become an essential part of the ED evaluation scheme.

Presumably, a state of IR develops before full-blown diabetes. Insulin resistance affects 25% of U.S. adults (4), with IR affecting approximately 60% of adults with a BMI $>35 \text{ kg/m}^2$ (5). Because the effects of IR correlate with finding of the metabolic syndrome, this study presumed IR would be found in those men with ED. Although higher levels of baseline glucose, baseline insulin, and area under the curve for both glucose and insulin were seen for those men with ED, none of these achieved statistical significance when compared with controls (Table 1). Interestingly, BMI was greater for the non-ED group. Using the Massachusetts Male Aging Study data, Kupelian et al. (27) have provided insight into correlating ED to BMI by reporting that ED predicted the metabolic syndrome—but only in men with a BMI of $<25 \text{ kg/m}^2$. Another study described a “U-shaped” relationship between BMI and ED, such that the odds ratio for having ED was $R = 2.66$ with a BMI of <20 or $>25 \text{ kg/m}^2$. Those with a BMI between 20 and 25 kg/m^2 had an odds ratio of <1.66 (28). Last, Kratzik et al. (29) demonstrated a linear correlation between increasing BMI and worsening erectile function. The average BMI for our study was 29.74 kg/m^2 for non-ED and 27.20 kg/m^2 for men reporting ED. Unfortunately, our study was limited by a small sample size that did not allow subgroup analysis for those men having a BMI of $<25 \text{ kg/m}^2$. Once again, small sample size did not allow subgroup analysis for those subjects with a BMI of $>35 \text{ kg/m}^2$ (60% of whom have findings of IR). That said, another confounding variable may have been that controls had a greater BMI than did those reporting ED.

Although this study did not demonstrate that IR was associated with ED in men with an average BMI of $>25 \text{ kg/m}^2$, two secondary endpoints were found to be significant: [1] the association between ED and LUTS, and [2] epinephrine as a common denominator between ED and LUTS.

Even though an age-related increase in occurrence for each of these conditions was recognized, these prevalent conditions, historically, have been treated and studied independently of each other. More recently, several epidemiologic studies have suggested that the two may be somehow linked. Several studies have demonstrated that men with greater LUTS (higher IPSS score) would also have worse erectile function (lower IIEF score) (30–39). Although a causal link between both of these conditions has not been established, the correlation seems to be independent of age and comorbid conditions, such as

diabetes, coronary heart disease, hypertension, and dyslipidemia. McVary (40) has proposed four pathophysiologic mechanisms that support the relationship between LUTS and ED, one of which is autonomic hyperactivity associated with increased sympathetic tone. This report offers support for the autonomic hyperactivity mechanism as the common denominator between worsening LUTS and ED.

To the best of our knowledge, this is one of the first studies to report epinephrine as a physiologic pathway linking ED and LUTS. Study weaknesses include a small sample size, our relatively crude measures of IR, and the related inability to perform subgroup analysis on different degrees of ED or BMI. An additional weakness of this study was that the potential link between ED and LUTS was a secondary endpoint. Furthermore, serum levels of NO, endothelin, RhoA/kinase, and leptin were not analyzed, and each of these may be affected by epinephrine, thereby further worsening ED and LUTS symptoms. Last, because our analyses were based on defined hypotheses, we have not included corrections for multiple testing. Although the issue of *P* value adjustment for multiple testing has long been a topic of discussion, it is generally accepted that *P* values should not be the sole criterion for assessing clinical relevance. However, findings with marginal statistical significance (e.g., *P*=.005 to *P*=.05) should be interpreted cautiously.

Although ED did not predict IR (in men with an average BMI of >25 kg/m²), the association between ED and worsening LUTS was confirmed. Elevated serum epinephrine levels were found in men with ED and may be the common link between ED and LUTS. It would be important to confirm these findings with additional, larger studies. Other future studies could explore the inverse correlation between epinephrine and NO production (41–46) in addition to smooth muscle proliferation in the face of either elevated sympathetic tone or suppressed NO production (40, 47, 48).

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FIGURE 1.
Correlation between ED and LUTS.

FIGURE 2.
Correlation between epinephrine and ED.

TABLE 1

Characteristics for controls and men with ED.

Characteristic	Control (IIEF-5: 22–25; n = 11)	ED (IIEF-5: 0–21; n = 17)	95% confidence interval for Δ in means	P value
Age (y)	46.8 (15.0)	50.5 (16.1)	(−16.2, 8.8)	.55
Pulse (bpm)	68.6 (7.5)	68.1 (8.9)	(−6.2, 7.2)	.88
Diastolic BP (mm Hg)	75.1 (11.0)	77.5 (11.3)	(−11.3, 6.5)	.59
Systolic BP (mm Hg)	123.5 (18.7)	128.6 (16.5)	(−18.9, 8.7)	.45
BMI (kg/m ²)	29.7 (4.4)	27.2 (5.7)	(−1.7, 6.7)	.22
IPSS	3.2 (3.0)	9.7 (4.9)	(−9.9, −3.1)	<.001
T (ng/dL)	402.7 (114.6)	484.2 (221.6)	(−237.6, 74.5)	.29
Epinephrine (pg/dL)	0.4 (0.3)	0.6 (0.4)	(−0.5, 0.1)	.11
Norepinephrine (pg/dL)	2.9 (1.3)	2.5 (0.8)	(−0.5, 1.2)	.35
Fasting glucose (mg/dL)	90.6 (10.2)	94.7 (10.3)	(−12.2, 4.2)	.32
Fasting insulin (μ U/mL)	15.0 (6.1)	16.1 (8.0)	(−6.9, 4.7)	.70
Fasting glucose/insulin ratio	6.9 (2.5)	7.2 (3.2)	(−2.7, 2.0)	.76
Glucose: 120 min (mg/dL)	111.2 (38.6)	120.7 (42.2)	(−42.0, 23.0)	.55
Insulin: 120 min (μ U/mL)	93.6 (84.1)	80.7 (46.6)	(−46.6, 72.4)	.65
AUC glucose	15,984.06 (3,090.8)	17,636.5 (3,798.0)	(−4,469.8, 1,166.0)	.24
ISI	3.5 (1.7)	3.1 (2.1)	(−1.2, 1.9)	.65

Note: Values are mean (SD) unless otherwise noted. BP = blood pressure; AUC = area under curve.

TABLE 2

Correlation between patient characteristics and IIEF-5 scores for ED.

Characteristic	Spearman correlation coefficient	P value
Age (y)	−0.18	.35
Pulse (bpm)	0.14	.47
Diastolic BP (mm Hg)	−0.03	.90
Systolic BP (mm Hg)	−0.13	.51
BMI (kg/m ²)	−0.02	.92
IPSS	−0.61	.001
T (ng/dL)	−0.13	.52
Epinephrine (pg/dL)	−0.38	.04
Norepinephrine (pg/dL)	0.12	.53
Fasting glucose (mg/dL)	−0.24	.22
Fasting insulin (μ U/mL)	−0.003	.99
Fasting glucose/insulin ratio	−0.09	.67
Glucose: 120 min (mg/dL)	−0.07	.74
Insulin: 120 min (μ U/mL)	−0.003	.99
AUC glucose	−0.21	.28
ISI	0.15	.44

Note: BP = blood pressure; AUC = area under curve.