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## ORIGINAL ARTICLE

Erectile Dysfunction

# Estradiol is an independent risk factor for organic erectile dysfunction in eugonadal young men

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Erectile dysfunction attributable to testosterone deficiency is less common in young males, and the effect of estradiol on erectile function in eugonadal young males is unclear. We analyzed data from 195 male participants, including 143 eugonadal patients with erectile dysfunction and 52 healthy men. To distinguish psychogenic and organic erectile dysfunction, penile rigidity was measured using the nocturnal penile tumescence rigidity test. Serum levels of sexual hormones were quantified by electrochemiluminescence, and penile vascular status was assessed by penile color Doppler ultrasound. Both serum estradiol levels and the ratio of estradiol to testosterone were higher in patients with organic erectile dysfunction than in patients with psychogenic erectile dysfunction or healthy controls. Organic erectile dysfunction was negatively associated with estradiol levels and the ratio of estradiol to testosterone, and estradiol was the only significant risk factor for organic erectile dysfunction (odds ratio: 1.094; 95% confidence interval: 1.042–1.149,  $P = 0.000$ ). Moreover, serum estradiol levels were negatively correlated with penile rigidity. Serum estradiol levels were higher and penile rigidity was lower in patients with venous erectile dysfunction than in patients with nonvascular erectile dysfunction. We conclude that elevated serum estradiol levels may impair erectile function and may be involved in the pathogenesis of organic erectile dysfunction in eugonadal young men.

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**Keywords:** erectile dysfunction; estradiol; organic etiology; testosterone; young

## INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a sufficient erection to engage in sexual intercourse. Erectile function is a neurovascular phenomenon modulated by hormonal, local biochemical, and biomechanical/structural factors.<sup>1</sup> Androgens contribute to the physiology of erections. Previous studies had indicated that testosterone levels, as low as 10% of normal physiologic plasma concentrations, are sufficient to maintain erectile function.<sup>2,3</sup> Around 95% of ED patients have normal testosterone levels, suggesting that the role of testosterone in eugonadal patients with ED is limited. Testosterone replacement therapy is frequently recommended for ED.<sup>4–6</sup>

Estradiol is the metabolic transformation product of testosterone through aromatase and exerts an opposite activity. Elevated estradiol inhibits the hypothalamus–pituitary axis, reducing circulating testosterone and potentially causing ED.<sup>7</sup> In addition, damage from elevated estradiol levels has been observed during the onset of ED, and increased ED severity has been associated with low serum testosterone and/or elevated estradiol.<sup>8</sup> Testosterone therapy was not helpful in recovering erections in rat models with ED induced by high estradiol levels.<sup>9</sup> Elevated serum estradiol, but not low testosterone, was independently and negatively associated with penile erection in high-fat-diet rabbits.<sup>10</sup> Although there is evidence of the adverse effect of elevated serum estradiol on erectile function, the connection is unclear.<sup>11</sup>

Estradiol–testosterone imbalance may be involved in the pathogenesis of ED in elderly men.<sup>12,13</sup> The ratio of estradiol to testosterone was reported to be notably higher in subjects with ED, suggesting an association between changes in levels of estradiol and testosterone and sexual dysfunction.<sup>14</sup> Testosterone is involved in erectile function, but testosterone levels below the lower limit of the normal range may be sufficient to retain normal erection in most men. Higher levels of serum testosterone in eugonadal men may not have a determinate impact on erectile function.<sup>5</sup> Among young men, psychogenic ED is more prevalent, but ED in 15%–20% of young men has an organic etiology. In young men, ED resulting from testosterone deficiency is not common (only 4%).<sup>15</sup>

The effect of estradiol on erectile function in eugonadal young men is still unclear. As nocturnal penile tumescence rigidity test is an objective method to assess the erection function, and a useful tool to distinguish psychogenic from organic ED.<sup>16–19</sup> In this study, nocturnal penile tumescence rigidity and penile color duplex Doppler ultrasound were assessed to determine the etiology of patients' ED and the role of estradiol on erectile function.

## PARTICIPANTS AND METHODS

### Participants

Clinical data from 195 men, including 143 eugonadal young patients with ED and 52 healthy men, collected between January 2017 and December 2018, were analyzed retrospectively. Heterosexual men

complaining of sexual dysfunction and admitted to the Department of Andrology of Shanghai General Hospital (Shanghai, China) were surveyed for detailed medical and sexual history and received a physical examination. ED was evaluated using the simplified International Index of Erectile Function (IIEF-5) questionnaire.<sup>20</sup> Patient blood was collected between 7:00 a.m. and 11:00 a.m. Levels of serum sex hormones, including total testosterone, estradiol, prolactin, luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin, were measured using an electrochemiluminescence immunoassay (COBAS 6000, Roche Diagnostics GmbH, Basel, Switzerland). Bioavailable testosterone, including free testosterone, was calculated from the levels of total testosterone, albumin, and sex hormone-binding globulin using the formula provided by the International Society for the Study of the Aging Male. Hypogonadism was defined as total testosterone  $<2.30 \text{ ng ml}^{-1}$  or  $8 \text{ nmol l}^{-1}$ ;<sup>21</sup> samples were assayed individually again if hypogonadism was initially diagnosed, and the results were averaged. Body mass index was calculated as  $\text{weight} \times \text{height}^{-2}$ . Exclusion criteria included hypogonadism, hypertension, hyperlipidemia, diabetes, hyperthyroidism, hypothyroidism, serious liver and kidney dysfunction, severe hyperprolactinemia (prolactin over twice the normal level), serious depression (patient health questionnaire scores  $\geq 20$ ),<sup>22,23</sup> serious anxiety (generalized anxiety disorder scale score  $\geq 15$ ),<sup>24,25</sup> sleep apnea, neurologic disease, pelvic fracture or urethral injury, radiotherapy (pelvis or retroperitoneum), surgery (oncological pelvic surgery, lower urinary and genital tract surgery, penile dorsal nerve resection, and penile dorsal deep vein ligation), and drug therapy (antihypertensives, antidepressants, antipsychotics, antiandrogens, antihistamines, heroin, cocaine, or methadone). The study was approved by the Ethics Committee of Shanghai General Hospital. Written informed consent was obtained from all participants.

#### Penile rigidity measurement

Penile rigidity was measured using RigiScan Plus (Monitor 20212, Timm Medical Technologies, Inc., Dodge City, KS, USA) by the nocturnal penile tumescence rigidity test. The RigiScan Plus device uses loops that are applied to the tip and base of the penis. The loops contract intermittently, applying pressure to the penis and enabling the measurement of rigidity. Nocturnal penile tumescence rigidity tests were performed on two or three consecutive nights, at least 8–10 h per night in the ward. The patients were instructed to avoid alcohol and caffeine-containing beverages in the evening before penile rigidity measurement. Psychogenic ED was considered with an erectile event of at least 60% rigidity recorded on the tip of the penis that lasted 10 min or more time, or else organic ED was considered.<sup>18</sup> Moreover, the following parameters were recorded for analysis: the maximal average penile rigidity (MAPR) at the tip and base of the penis, penile tumescence at the tip and base, and erection duration of the maximal erectile event.

#### Penile color Doppler ultrasound examination

Penile color duplex Doppler ultrasound was performed in patients by a single senior urologist using a penile color Doppler ultrasound scanner (Model 1202, BK Medical, Herlev, Denmark) equipped with an 8-MHz imaging frequency and a pulsed Doppler unit. Ultrasonography was acquired in a quiet and dark room. After  $10 \mu\text{g}$  of prostaglandin E1 was injected into the left corpus cavernosum with simultaneous audiovisual sexual stimulation, hemodynamic responses of the bilateral cavernous arteries were assessed for 30 min. Penile vascular parameters, including peak systolic velocity, end-diastolic velocity, and the resistive index

of both cavernous arteries, were measured and calculated. Here, the resistive index is calculated as  $\text{peak systolic velocity} - \text{end-diastolic velocity} / \text{peak systolic velocity}$ .<sup>26</sup>

#### Statistical analyses

The data are presented as mean  $\pm$  standard deviation (s.d.). SPSS software (version 14.0, IBM SPSS, Armonk, NY, USA) was used for data analysis. The statistical methods included Pearson's correlation coefficients, Bland–Altman plots, linear regression, and one-way ANOVA. The odds ratios and 95% confidence intervals were determined by multivariate logistic regression models.  $P < 0.05$  was considered statistically significant.

## RESULTS

#### Patient information

Of the 178 patients whose data were examined, 35 cases were excluded because of hypogonadism ( $n = 13$ ), serious depression/anxiety ( $n = 6$ ), hyperlipidemia ( $n = 5$ ), diabetes ( $n = 3$ ), hypertension ( $n = 2$ ), notable liver dysfunction ( $n = 1$ ), pelvic fracture or urethral injury ( $n = 1$ ), antidepressant therapy ( $n = 1$ ), penile dorsal nerve resection ( $n = 1$ ), severe hyperprolactinemia ( $n = 1$ ), and sleep apnea ( $n = 1$ ). A total of 143 cases of eugonadal young men with ED met the criteria of the study. The mean patients' age was 30.4 (s.d.: 6.1; range: 20–40) years. Overall, 356 independent nocturnal penile tumescence rigidity tests were conducted (mean  $\pm$  s.d.:  $2.0 \pm 0.2$  per patient). Total number of erection events was 1873 (mean  $\pm$  s.d.:  $9.1 \pm 3.1$ ; range: 1–19 per patient), with a nightly mean of 4.4 (s.d.: 1.8; range: 0.5–9.5) per patient. Seventy-eight patients with ED were examined for penile vascular status using penile color duplex Doppler ultrasound. These patients had a mean age of 30.6 (s.d.: 6.3; range: 21–40) years. Fifty-two eugonadal cases with normal erectile function were used as controls (age: mean  $\pm$  s.d.,  $29.9 \pm 7.9$  years; range: 20–40 years). These controls were selected from patients receiving circumcision for redundant prepuce or phimosis in the Department of Andrology.

#### Clinical characteristics of patients with ED

**Table 1** shows the clinical characteristics of eugonadal young men with organic ED, psychogenic ED, and normal erectile function. There were no significant differences between the three groups in age, height, weight, body mass index, or levels of total testosterone, calculated free testosterone, bioactive testosterone, prolactin, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, and albumin. In addition, no significant differences were observed between the organic and psychogenic ED groups in disease course or simplified IIEF-5, patient health questionnaire-9 (PHQ-9), and generalized anxiety disorder (GAD-7) scores. However, the organic ED group had significantly lower MAPR and penile tumescence than the psychogenic ED group. The organic ED group had significantly higher serum estradiol levels than the psychogenic ED group ( $P = 0.000$ ) or control group ( $P = 0.000$ ), as well as higher estradiol-to-total testosterone ratios ( $P = 0.005$  and  $P = 0.000$ , respectively).

#### Association between MAPR and sexual hormones

To evaluate the effects of sexual hormones on organic ED (MAPR at tip  $<60\%$ ), we performed logistic regression that included the following covariates: age, disease course, IIEF-5 score, PHQ-9 score, GAD-7 score, body mass index, and levels of total testosterone, calculated free testosterone, bioactive testosterone, estradiol, estradiol-to-total testosterone ratio, prolactin, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, and albumin (**Table 2**). Univariate analysis showed that organic ED was associated with

**Table 1: Clinical characteristics of men with erectile dysfunction and normal erectile function (controls)**

Characteristics	Organic ED (n=74)	Psychogenic ED (n=69)	Control (n=52)
Age (year)	30.5±7.0	30.2±6.4	29.9±7.9
Course (month)	25.7±24.6	20.3±24.9	-
IIEF-5 score	10.0±4.2	11.5±5.1	-
PHQ-9 score	9.2±5.8	8.32±5.2	-
GAD-7 score	7.8±5.7	6.37±4.4	-
Height (m)	1.7±0.1	1.73±0	1.7±0.1
Weight (kg)	71.6±11.8	72.6±11.4	70.1±8.7
BMI (kg m <sup>-2</sup> )	23.9±3.1	24.8±3.8	23.9±2.6
TT (ng l <sup>-1</sup> )	5.0±1.4	4.7±1.4	4.3±1.1
CFT (pmol l <sup>-1</sup> )	332.4±96.3	308.4±82.8	297.1±4.9
BAT (ng ml <sup>-1</sup> )	2.5±0.7	2.3±0.5	2.1±0.4
E2 (pg ml <sup>-1</sup> )	36.9±10.2 <sup>#</sup>	25.5±8.7	22.8±8.6
E2/TT (pg ng <sup>-1</sup> )	7.7±3.1 <sup>#</sup>	6.3±2.9	4.9±2.0
PRL (ng ml <sup>-1</sup> )	16.5±7.3	16.7±8.4	15.9±4.0
LH (mIU ml <sup>-1</sup> )	5.3±2.0	5.1±2.0	4.6±1.2
FSH (mIU ml <sup>-1</sup> )	3.8±2.2	4.2±1.8	3.9±1.7
SHBG (nmol l <sup>-1</sup> )	34.8±12.9	36.9±16.0	34.4±16.8
ALB (g l <sup>-1</sup> )	44.9±2.7	45.5±3.3	49.2±2.8
MAPR (tip) (%)	49.7±10.0 <sup>*</sup>	67.0±5.7	-
MAPR (base) (%)	58.1±13.8 <sup>*</sup>	71.6±6.6	-
PTUM (tip) (%)	33.5±11.2 <sup>*</sup>	38.6±13.4	-
PTUM (base) (%)	35.7±9.7 <sup>*</sup>	40.1±10.8	-
Erection duration (min)	24.0±15.6	25.3±13.0	-

Data are presented as mean±s.d. <sup>#</sup>*P*<0.05, organic ED group compared with psychogenic ED group and control group; <sup>\*</sup>*P*<0.05, organic ED group compared with psychogenic ED group. IIEF-5: International Index of Erectile Function 5 questionnaire; PHQ-9: patient health questionnaire; GAD-7: generalized anxiety disorder scale; BMI: body mass index; TT: total testosterone; CFT: calculated free testosterone; BAT: bioactive testosterone; E2: estradiol; E2/TT: estradiol to total testosterone ratio; PRL: prolactin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; SHBG: sex hormone-binding globulin; ALB: albumin; MAPR: maximal average penile rigidity; PTUM: penile tumescence; -: no data was detected. s.d.: standard deviation; ED: erectile dysfunction

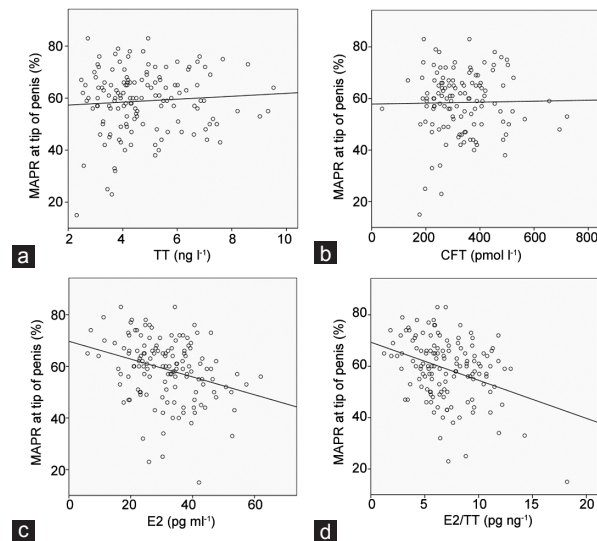
estradiol (*P* = 0.000) and the estradiol-to-total testosterone ratio (*P* = 0.006). Estradiol was the only significant negative factor for organic ED (odds ratio: 1.094; 95% confidence interval: 1.042–1.149, *P* = 0.000). **Table 3** lists the correlations between MAPR and sexual hormone levels. Estradiol and the estradiol-to-total testosterone ratio were negatively correlated with MAPR. **Figure 1** depicts Bland–Altman plots of serum sexual hormone levels and MAPR at the tip of the penis. There were no significant correlations between serum testosterone and MAPR at the tip, while estradiol and the estradiol-to-total testosterone ratio were negatively correlated with MAPR at the tip (*P* = 0.001 and *P* = 0.0000, respectively).

#### Correlations between estradiol and anthropological and gonadal axis parameters

**Table 4** lists Pearson's correlation coefficients between estradiol levels and age, body mass index, and other serum sexual hormones. Estradiol levels were correlated with body mass index (*P* = 0.017), total testosterone (*P* = 0.003), calculated free testosterone (*P* = 0.000), bioactive testosterone (*P* = 0.000), and luteinizing hormone (*P* = 0.003). There were no correlations between estradiol levels and age, prolactin, or follicle-stimulating hormone.

#### Comparison of clinical parameters by penile vascular status

According to penile color duplex Doppler ultrasound, patients were classified as nonvascular ED (peak systolic velocity >30 cm s<sup>-1</sup> and end-diastolic velocity <3 cm s<sup>-1</sup>), arterial ED (peak systolic velocity



**Figure 1:** Bland–Altman plots of serum sexual hormones and MAPR at the tip of the penis. (a) Relationship between TT and MAPR. There was no significant correlation between CFT and MAPR. (b) Relationship between CFT and MAPR. There was no significant correlation between CFT and MAPR. (c) E2 was negatively correlated with MAPR. (d) E2/TT was negatively correlated with MAPR. MAPR: maximal average penile rigidity; TT: total testosterone; CFT: calculated free testosterone; E2: estradiol; E2/TT: estradiol to total testosterone ratio.

<30 cm s<sup>-1</sup> and end-diastolic velocity <3 cm s<sup>-1</sup>), venous ED (peak systolic velocity >30 cm s<sup>-1</sup> and end-diastolic velocity >3 cm s<sup>-1</sup>), and mixed ED (peak systolic velocity <30 cm s<sup>-1</sup> and end-diastolic velocity >3 cm s<sup>-1</sup>).<sup>26</sup> **Table 5** lists the clinical parameters of the four groups. There were no differences in age, disease course, height, weight, body mass index, IIEF-5 score, PHQ-9 score, GAD-7 score, total testosterone, calculated free testosterone, bioactive testosterone, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, or albumin. Serum estradiol levels were higher in the venous ED group than those in the nonvascular ED group (*P* = 0.035). MAPR levels (at both tip and base) were significantly lower in the venous ED group than those in the nonvascular ED group (tip: *P* = 0.028; base: *P* = 0.034). The values were slightly lower in the venous ED group than those in the arterial ED and mixed ED groups. There was no difference in penile tumescence between groups.

#### DISCUSSION

We found higher levels of serum estradiol and a higher estradiol-to-total testosterone ratio in eugonadal young men with organic ED, and estradiol levels were an independent risk factor for organic ED. Previous clinical studies reported that high estradiol and low testosterone were positively correlated with the severity of ED and that an elevated estradiol-to-total testosterone ratio was positively correlated with the incidence of ED.<sup>8,14</sup> Castelló-Porcar and Martínez-Jabaloyas<sup>27</sup> reported that age was the only independent variable for both ED and sexual desire in elderly men (mean age: 66 years). However, these studies did not classify the etiology of ED, and the relationship between estradiol levels and organic ED was unclear. In line with our study, we demonstrated that not only estradiol levels but also testosterone levels should be considered when evaluating young patients with ED. Anti-estradiol approaches (such as aromatase inhibitors) are promising strategies for ED treatment. Previous studies reported that chronic administration of the phosphodiesterase 5 inhibitor tadalafil

**Table 2: Univariate and multivariate logistic regression analysis of organic erectile dysfunction (maximal average penile rigidity at tip <60%)**

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (year)	1.001	0.922–1.087	0.976			
Course (month)	1.012	0.982–1.020	0.943			
IIEF-5 (score)	0.939	0.862–1.023	0.152			
PHQ-9 (score)	0.971	0.882–1.068	0.546			
GAD-7 (score)	0.943	0.849–1.047	0.272			
BMI (kg m <sup>-2</sup> )	1.010	0.884–1.153	0.887			
TT (ng ml <sup>-1</sup> )	1.149	0.929–1.142	0.200			
CFT (pmol l <sup>-1</sup> )	1.002	0.999–1.004	0.277			
BAT (ng ml <sup>-1</sup> )	1.440	0.900–2.305	0.129			
E2 (pg ml <sup>-1</sup> )	1.093	1.050–1.138	0.000 <sup>#</sup>	1.094	1.042–1.149	0.000 <sup>*</sup>
E2/TT (pg ng <sup>-1</sup> )	1.196	1.052–1.360	0.006 <sup>#</sup>	0.994	0.848–1.167	0.945
PRL (ng ml <sup>-1</sup> )	1.001	0.964–1.040	0.964			
LH (mIU ml <sup>-1</sup> )	1.039	0.881–1.224	0.651			
FSH (mIU ml <sup>-1</sup> )	0.879	0.734–1.050	0.154			
SHBG (nmol l <sup>-1</sup> )	0.992	0.971–1.014	0.468			
ALB (g l <sup>-1</sup> )	0.932	0.835–1.041	0.214			

<sup>\*</sup>P<0.05; <sup>#</sup>P<0.01. IIEF-5: International Index of Erectile Function 5 questionnaire; PHQ-9: patient health questionnaire; GAD-7: generalized anxiety disorder scale; BMI: body mass index; TT: total testosterone; CFT: calculated free testosterone; BAT: bioactive testosterone; E2: estradiol; E2/TT: estradiol to total testosterone ratio; PRL: prolactin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; SHBG: sex hormone-binding globulin; ALB: albumin; OR: odds ratio; CI: confidence interval

**Table 3: Correlations between maximal average penile rigidity at the tip and base of the penis and serum sexual hormones**

Variables	MAPR at tip (%)	MAPR at base (%)
TT (ng ml <sup>-1</sup> )	r=0.068, P=0.420	r=0.088, P=0.292
CFT (pmol l <sup>-1</sup> )	r=0.050, P=0.573	r=0.091, P=0.306
BAT (ng ml <sup>-1</sup> )	r=0.041, P=0.684	r=0.066, P=0.462
E2 (pg ml <sup>-1</sup> )	r=-0.272, P=0.001 <sup>#</sup>	r=-0.239, P=0.004 <sup>#</sup>
E2/TT (pg ng <sup>-1</sup> )	r=-0.331, P=0.000 <sup>#</sup>	r=-0.317, P=0.000 <sup>#</sup>
PRL (ng ml <sup>-1</sup> )	r=0.006, P=0.985	r=0.005, P=0.967
LH (mIU ml <sup>-1</sup> )	r=0.067, P=0.428	r=0.042, P=0.614
FSH (mIU ml <sup>-1</sup> )	r=0.181, P=0.086	r=0.205, P=0.074

<sup>#</sup>P<0.01. TT: total testosterone; CFT: calculated free testosterone; BAT: bioactive testosterone; E2: estradiol; E2/TT: estradiol to total testosterone ratio; PRL: prolactin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; MAPR: maximal average penile rigidity

may increase the ratio of testosterone to estradiol, mainly by reducing estradiol.<sup>28,29</sup>

We observed no correlation between serum testosterone (total testosterone, calculated free testosterone, and bioactive testosterone) and the MAPR. Furthermore, there were no significant differences in total testosterone, calculated free testosterone, and bioactive testosterone levels between cases with psychogenic ED or organic ED and controls. A study conducted in elderly men found no differences in total testosterone, calculated free testosterone, and sex hormone-binding globulin levels between cases with psychogenic and organic ED, but levels of calculated free testosterone were related to age and nocturnal erection parameters, including frequent or occasional tumescence.<sup>6</sup> O'Connor *et al.*<sup>30</sup> reported that there was a testosterone threshold (8 nmol l<sup>-1</sup>) for sexual function, which did not increase above 8 nmol l<sup>-1</sup>. ED severity (assessed by the IIEF-5 score) is associated with aging but not with total testosterone.<sup>31</sup> Rajmil *et al.*<sup>32</sup> demonstrated that testosterone levels were weakly associated with penile rigidity and that this association disappeared when ED was influenced by metabolic syndrome.

Another study<sup>33</sup> reported that estradiol levels of young patients with venous ED were higher than those of patients with psychogenic ED or mixed ED, which was consistent with our findings. Furthermore, we

showed that the penile rigidity of patients with venous ED was lower than that of patients with nonvascular ED. Chen *et al.*<sup>34</sup> reported that penile rigidity was positively correlated with the resistive index and negatively with end-diastolic velocity. The end-diastolic velocity was higher in venous ED than that in nonvascular ED in our study. Lower penile rigidity in venous ED may be attributable to venous leakage dysfunction, suggesting that elevated estradiol levels may damage the venous occlusive function of the corpus cavernosum. In consideration of the fact that the corpus cavernosum vasculature and urothelium have extensive classic estradiol receptors,<sup>35,36</sup> the mechanism of elevated estradiol directly impairing erectile function may consist of two aspects: direct impairment of the relaxation function of the corpus cavernosum smooth muscle through the estrogen receptor signaling pathway,<sup>9,10</sup> and the inhibition of cavernous smooth muscle cell differentiation and increase in fibrous connective tissue.<sup>37–39</sup>

We found that estradiol levels were correlated with body mass index, total testosterone, calculated free testosterone, bioactive testosterone, and luteinizing hormone, perhaps because estradiol is converted from testosterone by aromatase metabolism pathways and also associated with lipid metabolism. A limitation of our study is that we could not discern whether elevated estradiol resulted from aromatase dysfunction in these patients. In addition, elevated estradiol may be related to industrial estradiol exposure and phytoestrogen intake, Klinefelter syndrome, a feminizing tumor of the adrenal cortex, noninsulin-dependent diabetes mellitus, hypercholesterolemia, chronic liver disorders, idiopathic hemochromatosis, tumors of male breast or Leydig cells, or chronic hepatitis C virus infection.<sup>12,40–42</sup> These potential risk factors are worth surveying for the purpose of ED prevention.

In conclusion, we showed that both estradiol levels and the ratio of estradiol to testosterone were higher in eugonadal young patients with organic ED than in those with psychogenic ED, and estradiol levels were higher in patients with venous ED than in those with nonvascular ED. Estradiol was an essential risk factor in organic ED in eugonadal young men. The mechanism underlying estradiol upregulation requires further study, and estradiol should be considered in both diagnosis and treatment of ED.



**Table 4: Correlations between estradiol and anthropological and gonadal axis parameters**

Variables	Age (year)	BMI (kg m <sup>-2</sup> )	TT (ng ml <sup>-1</sup> )	CFT (ng ml <sup>-1</sup> )	BAT (ng ml <sup>-1</sup> )	PRL (ng ml <sup>-1</sup> )	LH (mIU ml <sup>-1</sup> )	FSH (mIU ml <sup>-1</sup> )
E2 (ng ml <sup>-1</sup> )	<i>r</i> =0.101, <i>P</i> =0.221	<i>r</i> =0.202, <i>P</i> =0.017*	<i>r</i> =0.241, <i>P</i> =0.003*	<i>r</i> =0.389, <i>P</i> =0.000#	<i>r</i> =0.416, <i>P</i> =0.000#	<i>r</i> =0.157, <i>P</i> =0.068	<i>r</i> =0.248, <i>P</i> =0.003*	<i>r</i> =0.117, <i>P</i> =0.300

\**P*<0.05; #*P*<0.01. BMI: body mass index; TT: total testosterone; CFT: calculated free testosterone; BAT: bioactive testosterone; E2: estradiol; PRL: prolactin; LH: luteinizing hormone; FSH: follicle-stimulating hormone

**Table 5: Comparison of patient clinical parameters by penile vascular status**

Clinical parameters	Nonvascular ED (n=46)	Arterial ED (n=19)	Venous ED (n=6)	Mixed ED (n=7)
Age (year)	30.9±5.6	30.6±4.7	29.7±6.0	31.2±9.6
Course (month)	21.9±21.5	24.2±24.0	39.1±27.3	33.2±22.3
IIEF-5 score	10.7±4.9	10.7±4.5	8.2±4.7	9.3±3.4
PHQ-9 score	7.8±5.4	6.6±4.7	6.6±5.0	8.2±3.2
GAD-7 score	7.2±4.9	4.8±3.3	3.1±1.9	4.4±3.3
Height (m)	1.7±0	1.7±0	1.7±0	1.7±0
Weight (kg)	71.0±11.3	69.5±10.0	71.3±9.2	71.8±12.8
BMI (kg m <sup>-2</sup> )	23.8±3.2	23.2±3.1	24.2±3.3	24.8±4.2
TT (ng ml <sup>-1</sup> )	4.8±1.6	4.8±1.6	4.7±1.2	4.5±1.8
CFT (pmol l <sup>-1</sup> )	326.5±90.7	339.6±153.8	277.6±156.8	293.6±70.3
BAT (ng ml <sup>-1</sup> )	2.3±0.6	2.3±0.9	2.6±0.4	2.2±0.4
E2 (pg ml <sup>-1</sup> )	28.9±9.3	31.5±12.1	39.0±3.4#	30.8±11.1
PRL (ng ml <sup>-1</sup> )	15.3±8.0	17.6±7.5	18.2±10.1	18.1±3.7
LH (mIU ml <sup>-1</sup> )	4.9±2.0	5.0±1.6	5.3±1.6	4.4±2.4
FSH (mIU ml <sup>-1</sup> )	3.8±1.9	3.7±1.7	4.6±3.7	3.5±1.1
SHBG (nmol l <sup>-1</sup> )	37.9±16.6	32.8±12.0	52.6±32.6	30.9±19.1
ALB (g l <sup>-1</sup> )	46.1±3.2	44.5±2.6	43.6±1.5	43.7±3.4
MAPR (tip) (%)	62.7±11.3	58.6±11.8	42.2±3.3#	55.2±8.8
MAPR (base) (%)	65.4±11.8	59.3±13.6	45.7±5.2#	58.0±12.1
PTUM (tip) (%)	35.6±12.6	32.5±10.0	29.0±4.4	37.8±8.2
PTUM (base) (%)	38.6±11.8	34.3±7.2	36.0±8.6	47.4±9.5
Erection duration (min)	27.7±15.7	19.7±8.9	18.2±5.3	26.6±16.7
Left PSV (cm s <sup>-1</sup> )	48.0±13.9	25.4±6.6*	47.5±17.8	27.9±6.0*
Right PSV (cm s <sup>-1</sup> )	52.0±14.6	26.7±7.4*	49.1±17.5	28.3±8.2*
Left EDV (cm s <sup>-1</sup> )	0.1±0.4	0.2±0.6	12.0±4.1§	8.6±6.5§
Right EDV (cm s <sup>-1</sup> )	0.1±0.5	0.2±0.7	11.0±8.5§	10.0±7.4§
Left RI	1.0±0.0	1.0±0.0	0.8±0.0§	0.7±0.2§
Right RI	1.0±0.0	1.0±0.0	0.8±0.0§	0.7±0.1§

Data are presented as mean±s.d. \**P*<0.05, arterial ED group or mixed ED group compared with the nonvascular ED group and venous ED group; §*P*<0.05, venous ED group or mixed ED group compared with the nonvascular ED group and arterial ED group. #*P*<0.05, venous ED group compared with the nonvascular ED group. IIEF-5: International Index of Erectile Function 5 questionnaire; PHQ-9: patient health questionnaire; GAD-7: generalized anxiety disorder scale; BMI: body mass index; TT: total testosterone; CFT: calculated free testosterone; BAT: bioactive testosterone; E2: estradiol; E2/TT: estradiol to total testosterone ratio; PRL: prolactin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; SHBG: sex hormone-binding globulin; ALB: albumin; MAPR: maximal average penile rigidity; PTUM: penile tumescence; PSV: peak systolic velocity; EDV: end-diastolic velocity; RI: resistive index; s.d.: standard deviation; ED: erectile dysfunction

## AUTHOR CONTRIBUTIONS

HRC and RHT conducted RigiScan measurements, completed the statistical analysis, and wrote the manuscript. PL and HXC performed the color duplex Doppler ultrasound examination. SJX assisted statistical analysis and reviewed the paper. ZL conceived and designed the study. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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