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ORIGINAL ARTICLE

Impact of the association between elevated oestradiol and low testosterone levels on erectile dysfunction severity

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Our aim was to assess the impact of the association between elevated oestradiol (E_2) and low testosterone (T) levels on erectile dysfunction (ED) severity. A total of 614 male patients with ED and a normal or low T level in association with normal or elevated E_2 levels were enrolled. Patients underwent routine laboratory investigations in addition to measurements of total T, total E_2, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin. We compared the responses to the erectile function domain, Q3 (achieving erection) and Q4 (maintaining erection) of the International Index for Erectile Function (IIEF) score in patients with the following: normal T and E_2 levels; low T level; low T level and elevated E_2 level; and elevated E_2 level. Of the patients included, 449 (73.1%) had normal T and E_2 levels, 110 (17.9%) had a low T level, 36 (5.9%) had a low T level and an elevated E_2 level, and 19 (3.1%) had an elevated E_2 level. Increased ED severity was significantly associated with low T levels, elevated E_2 levels, and both a low T level and an elevated E_2 level. Additionally, the mean values of the EF-domain, Q3 and Q4 were significantly lower in patients with both a low T level and an elevated E_2 level compared to patients with any condition alone. In conclusion, a low T level had the primary effect on erectile function; however, a concomitantly elevated E_2 level had an additive impairment effect.
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INTRODUCTION

A diminution in testicular function with a consequence of testosterone (T) depletion is a common occurrence in older men.[1,2] The multi-factorial mechanisms of this phenomenon, which involve the hypothalamic–pituitary–testicular axis, have been reported.[3]

Several studies have demonstrated that T has substantial effects on cavernosal tissues and that T deficiency impairs the anatomic and physiological substrates of erectile capacity that could be partly reversed upon androgen replacement.[4,5]

Oestradiol (E_2) possesses an opposing functional role of T; therefore, a decline in the T level will affect its physiological balance with E_2 in men.[6] As a consequence, a high E_2 level, which has a strong gonadotropin suppressive effect, may lead to secondary hypogonadism in the ageing male.[7] Despite the concomitant elevation of E_2 in hypogonadal men, the information available on the physiological role of E_2 in erectile function is insufficient to correlate the aetiology of erectile dysfunction (ED) to a high E_2 level.[8] The likelihood of E_2 affecting the T balance and the independent effect of E_2 on erectile function have not been well evaluated.[9] Furthermore, although the association between ED severity and the prospective decrease in testosterone has been investigated,[10] the impact of an elevated E_2 level on ED severity has not been well addressed. The current study was designed to assess the impact of an association between an elevated E_2 level and a low T level on ED severity.

MATERIALS AND METHODS

Research design

This was a prospective office-based study. From January 2009 to December 2010, 614 male patients with a clinical diagnosis of ED associated with normal or low T and/or elevated E_2 levels who visited our andrology clinic were enrolled in this study.

ED assessment

Patients were screened for ED using the International Index for Erectile Function (IIEF).[11] The erectile function domain consists of questions 1–5 and question 15 for assessing the global erectile function. These questions were used to measure items regarding ability to obtain an erection, the hardness of the erection, penetration ability, ability to maintain an erection, difficulty maintaining an erection until the end of intercourse and erection confidence. In the current study, we did not investigate the internal consistency of the IIEF scale or subscales; however, previous studies in different languages have demonstrated that the intraclass correlation coefficients (test–retest reproducibility) of the IIEF scale and subscales are significantly high. Cronbach's alpha coefficient has also indicated a high internal consistency.[12,13] Scoring the IIEF domain of erectile function allowed the classification of each patient as having no (26–30), mild (17–25), moderate (11–16) or severe (0–10) ED. At the same visits during which they were assessed for ED, all patients were also interviewed to gather their sociodemographic characteristics and relevant medical

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history. We compared the responses to the erectile function domain, Q3 (achieving erection), Q4 (maintaining erection) and ED duration in patients with (i) normal T and E_2 levels, (i) a low T level with a normal E_2 level, (iii) a low T level and an elevated E_2 level and (iv) an elevated E_2 level with a normal T level. Patients gave informed consent to be included in the study. The study was approved by the Institutional Review Board.

Laboratory assessment

Patients underwent routine laboratory investigations in addition to evaluations of total T, total E_2, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin.

Total T, total E_2, FSH, LH and prolactin were assessed using electrochemiluminescence immunoassays according to the manufacturer's instructions (Elecsys Systems 20/10; Roche Diagnostics Corporation, Indianapolis, IN, USA). The target values and ranges were determined and obtained using the Elecsys assay reagents and analysers available at the time. The measurement range (0.025–15.0 ng ml^{-1} or 0.087–52.0 nmol l^{-1}) was defined by the limit of detection and the maximum of the master curve. The interassay coefficient of variation for total T at concentrations of 24–700 ng dl^{-1} (0.83–24.31 nmol l^{-1}) was 7.4%–1.7%. Elecsys PreciControl Universal 1 and 2 were used for quality control; these reagents contain lyophilised control serum based on human serum in two concentration ranges. The controls were used to monitor the accuracy and precision of the Elecsys immunoassays.

Definitions

Body mass index (BMI, kg m^{-2}) was rated as follows: normal (<25), overweight (25−<30) and obese (⩾30).

Low T was rated as total testosterone measuring <2.8 (2.8–8.8) ng ml^{-1} on three morning (8:00–11:00 a.m.) occasions (specimens were assayed individually, and the results were averaged).

High E_2 was considered total E_2 >42.6 (7.6–42.6) pg ml^{-1}.

Prolactin (4.1–20 ng ml^{-1}); FSH (1.5–12.4 mIU ml^{-1}); LH (1.7–8.6 mIU ml^{-1})

A normal hormonal pattern was considered to be a normal level of both total testosterone and E_2.

Data analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS.14.0) software programme (SPSS, Inc., Chicago, IL, USA). The chi-square test was used to compare categorical variables, including sociodemographics, medical comorbidities, ED severity and ED duration according to the four categories of T and E_2 patterns (**Tables 1 and 2**). An unpaired *t*-test and one-way ANOVA were used to compare the mean values of the erectile function domain, Q3 and Q4 according to the four categories of T and E_2 patterns (**Tables 2 and 3**).

RESULTS

Sociodemographics and characteristics of the study population

A total of 614 male patients were included in this study. Of the patients, 449 (73.1%) had normal T and E_2 levels, 110 (17.9%) had a low T level, 36 (5.9%) had a low T level and an elevated E_2 level and 19 (3.1%) had an elevated E_2 level. The mean age and standard deviation of the study sample was 56.6±11.4 years, and 36.6% were less than 50 years of age. Additionally, 78.7% were overweight or obese, and 29.5% were current or ex-smokers. The majority of patients (78.8%) had one or more risk factors or medical comorbidities (diabetes, hypertension, dyslipidaemia, ischaemic heart disease) (**Table 1**).

Table 1 Distribution of sociodemographic characteristics and medical co-morbidities in the study population according to hormonal pattern

Sociodemog. and medical comorbidities	*Pattern of hormones (N=614)*				P
	Normal (N=449)	*Low T (N=110)*	*High E_2 (N=19)*	*Low T+high E_2 (N=36)*	
Age groups					
<50 years	196 (43.7%)	16 (14.5%)	8 (42.1%)	5 (13.9%)	[1]*P*=0.001, [2]*P*=0.001
⩾50 years	253 (56.3%)	94 (85.5%)	11 (57.9%)	31 (86.1%)	[3]*P*>0.05, [4]*P*=0.001
					[5]*P*=0.001, [6]*P*>0.05
BMI					
<25	87 (19.4%)	12 (10.9%)	2 (10.5%)	3 (8.3%)	[1]*P*>0.05, [2]*P*=0.001
25−<30	99 (22%)	24 (21.8%)	4 (21%)	4 (11.1%)	[3]*P*>0.05, [4]*P*>0.05
⩾30	263 (58.6%)	74 (67.3%)	13 (68.4%)	29 (80.6%)	[5]*P*>0.05, [6]*P*>0.05
Smoking					
None	323 (72%)	74 (67.3%)	13 (68.4%)	23 (63.9%)	[1]*P*>0.05, [2]*P*=0.02
Ex-smoker	45 (10%)	14 (12.7%)	2 (10.5%)	5 (13.9%)	[3]*P*>0.05, [4]*P*>0.05
Current	81 (18%)	22 (20%)	4 (21%)	8 (22.2%)	[5]*P*>0.05, [6]*P*>0.05
Number of comorbidity					
One or more	337 (75.1%)	98 (89.1%)	16 (84.2%)	33 (91.7%)	[1]*P*=0.01, [2]*P*=0.001,
None	112 (24.9%)	12 (10.9%)	3 (15.8%)	3 (8.3%)	[3]*P*=0.04, [4]*P*=0.02
					[5]*P*=0.008, [6]*P*=0.01

Abbreviations: BMI, body mass index; T, testosterone; E_2, oestradiol; sociodemog., sociodemographic.

The chi-square (χ^2) test was used to compare the non-parametric variables of sociodemographics and medical comorbidities according to the pattern of the testosterone and oestradiol levels at $P<0.05$.

[1] *P*=normal *vs.* low T.

[2] *P*=normal *vs.* low T+high E_2.

[3] *P*=low T *vs.* low T+high E_2.

[4] *P*=low T *vs.* high E_2.

[5] *P*=low T+high E_2 *vs.* high E_2.

[6] *P*=normal *vs.* high E_2.

Table 2 Distribution of ED severity and duration, erectile function domain, Q3 and Q4 according to hormonal pattern

ED variables	*Pattern of hormones (N=614)*				P
	Normal (N=449)	*Low T (N=110)*	*High E_2 (N=19)*	*Low T+high E_2 (N=36)*	
ED severity					
Mild	91 (20.3%)	11 (10%)	3 (15.8%)	2 (5.6%)	[1]*P*=0.001, [2]*P*=0.00
Moderate	247 (55%)	45 (40.9%)	9 (47.4%)	8 (22.2%)	[3]*P*=0.02, [4]*P*>0.05
Severe	111 (24.7%)	54 (49.1%)	7 (36.8%)	26 (72.2%)	[5]*P*=0.001, [6]*P*=0.02
ED duration					[1]*P*>0.05, [2]*P*>0.05,
<5 years	351 (78.2%)	82 (74.5%)	15 (78.9%)	27 (75%)	[3]*P*>0.05, [4]*P*>0.05
⩾5 years	98 (21.8%)	28 (25.5%)	4 (21.1%)	9 (25%)	[5]*P*>0.05, [6]*P*>0.05
EF-domain (mean±s.d.)	15.2±4.1	11.4±4.6	12.2±3.6	7.7±3.2	[1]*P*=0.001, [2]*P*=0.001
					[3]*P*=0.01, [4]*P*>0.05
					[5]*P*=0.001, [6]*P*=0.01
Q3 (mean±s.d.)	2.4±0.88	1.9±0.71	2.1±0.71	1.4±0.61	[1]*P*=0.001, [2]*P*=0.001
					[3]*P*=0.01, [4]*P*>0.05
					[5]*P*=0.001, [6]*P*=0.01
Q4 (mean±s.d.)	2.2±0.81	1.8±0.69	2±0.66	1.4±0.66	[1]*P*=0.001, [2]*P*=0.001
					[3]*P*=0.01, [4]*P*>0.05
					[5]*P*=0.001, [6]*P*=0.03

Abbreviations: BMI, body mass index; E_2, oestradiol; T, testosterone.
The chi-square (χ^2) test was used to compare the non-parametric variables of ED severity and duration according to the pattern of the testosterone and oestradiol levels. An unpaired *t*-test and one-way ANOVA were used to compare the mean values of the EF-domain and Q3 according to the pattern of the testosterone and oestradiol levels. Significance was set at $P<0.05$.
[1] *P*=normal *vs.* low T.
[2] *P*=normal *vs.* low T+high E_2.
[3] *P*=low T *vs.* low T+high E_2.
[4] *P*=low T *vs.* high E_2.
[5] *P*=low T+high E_2 *vs.* high E_2.
[6] *P*=normal *vs.* high E_2.

Risk factors in the study population

A normal hormonal pattern was identified in 87.1% (196/225) of patients less than 50 years of age and 86.2% (112/130) of patients with no risk factors. Patients with a normal hormonal pattern had a significantly lower BMI and were less likely to smoke in comparison to patients with a low T level and high E_2 level ($P<0.05$ for each) (**Table 1**). Age, obesity, smoking and medical comorbidities did not significantly differ among patients with low T alone and patients with both a low T level and an elevated E_2 level ($P>0.05$ for each) (**Table 1**).

Hormonal pattern and ED

Increased ED severity was significantly associated with a low T level, an elevated E_2 level, and both a low T level and an elevated E_2 level ($P<0.05$ for each) (**Tables 2 and 3**). No significant association was observed between hormonal abnormalities and ED duration ($P>0.05$ for each) (**Table 2**). The mean values of the EF-domain, Q3 and Q4 were significantly lower in patients with both a low T level and an elevated E_2 level compared to patients with any of the conditions alone ($P<0.05$ for each) (**Table 2**). Patients with low T only had significantly lower mean values of the EF-domain, Q3 and Q4 compared to patients with a normal hormonal pattern ($P<0.05$ for each) (**Table 2**). No significant differences in the mean values of the EF-domain, Q3 and Q4 were observed between patients with low T and patients with elevated E_2 levels ($P>0.05$ for each) (**Table 2**). ED severity was not significantly associated with high level of FSH, LH, prolactin or the lipid profile in the study population ($P>0.05$ for each) (**Table 3**).

Table 3 Mean hormone levels according to ED severity

Continuously coded variables	*ED severity*		P
	Mild and moderate (mean±s.d.)	*Severe (mean±s.d.)*	
Hormones			
Testosterone	4.6±2.5	3.2±1.9	0.001
Oestradiol	29.8±8.5	38.4±9.3	0.02
Prolactin	10.3±4.3	11.7±5.1	>0.05
FSH	7.7±3.4	8.2±4.1	>0.05
LH	6.5±2.9	6.7±2.8	>0.05
Dyslipidaemia			
Cholesterol	189.4±40.1	191.1±42.6	>0.05
Triglyceride	172.3±86.4	176.5±94.3	>0.05
LDL	117.6±42.9	119.2±45.1	>0.05
HDL	42.1±13.4	41.3±11.4	>0.05

Abbreviations: ED, erectile dysfunction; FSH, follicle-stimulating hormone; HDL, high density lipoprotein; LH, luteinizing hormone; LDL, low density lipoprotein; SHBG, sex hormone binding globulin.
An unpaired *t*-test was used to compare mean values of testosterone, oestradiol, prolactin, FSH, LH and SHBG in patients with mild and moderate ED *versus* severe ED. Significance was set at $P<0.05$.

DISCUSSION

In this study, we assessed the impact of low T level and elevated E_2 level individually and together on ED severity. We demonstrated that both low T level and elevated E_2 level had a negative impact on erectile function and were associated with increased ED severity. No significant associations between hormonal abnormalities and ED duration were observed. The Massachusetts Male Aging Study reported a prevalence of 20% for hypogonadism in men older than 55 years of age when total T levels were lower than normal for young healthy subjects.[14] In the current study, we found that 23.8% of patients had low T only or low T in addition to elevated E_2. The mechanisms behind the ageing-associated decrease in androgen level and the decrease patients with ED have not been fully elucidated. In a previous study, we demonstrated the yearly pattern of T depletion in patients with ED.[10] Furthermore, the possibility of decreased testicular function in older men has been reported to result from several factors, including a disturbance in the hypothalamic–pituitary–testicular axis.[3]

Oestrogens are generally considered as female hormones. However, data obtained from more recent studies have noted the role of oestrogens in male reproduction, which in the past, was a concept confined only to female reproduction.[15] The pathophysiological consequences of elevated E_2 in males have recently gained interest. Oestrogen has been reported to have a significantly negative effect on sexual behaviour and ultimately results in decreased intracavernosal pressure and nitric oxide-mediated cavernosal smooth muscle relaxation.[16,17] In addition, the action of E_2 through a non-genomic mechanism has been reported in which E_2 can modulate the cell surface and influence ionic channels as a part of the tissue response.[18] Although the elevated E_2 levels in ageing males may act as a risk factor for ED,[9] the cause-effect relationship is still unknown.[19]

A recent large population-based study showed that total and free T, but not E_2 or dihydrotestosterone (DHT), was associated with overall sexual function in middle-aged and older men. E_2 was the only hormone associated with sexual function-related distress, such that higher levels were related to greater distress.[20] Although several interesting studies have elucidated the role of E_2 in male reproduction, data on the peripheral levels of sex steroids are lacking. Huhtaniemi *et al.*[21] reported that increased oestrogen activity rather than decreased androgen activity is associated with longer androgen receptor CAG repeats. Furthermore, Saltiki *et al.*[22] investigated the effect of oestrogen levels on endothelial function in males and concluded that endogenous oestrogen levels were associated with flow-mediated dilatation, independent of age and lipid levels, showing a protective effect in middle-aged male subjects.

Although androgen and E_2 are physiological antagonists in many organs, the impact of E_2 on the T balance is unclear; therefore, ED in the elderly may result from a pathophysiological E_2–T imbalance.[23] This hormonal imbalance in the elderly can be attributed, at least in part, to modifiable para-aging phenomena. In the present study, there was a significant increase in BMI in patients with both low T and high E_2. Age, obesity, smoking and medical co-morbidities were not significantly different among patients with low T alone and patients with both a low T level and an elevated E_2 level. This finding is consistent with previous studies showing a complex relationship between ED and hormonal imbalance in obese patients. Furthermore, associations of obesity and its negative correlation with leptin level and androgen insensitivity have been reported.[9,24,25] With increasing BMI, waist circumference and per cent body fat, another study showed that total and free testosterone and sex hormone-binding globulin concentrations decreased, while total and free E_2 increased. The magnitudes of the changes of these hormones were similar, with a one-quartile increase in each body fat measure.[26] In addition to the hormonal imbalance that can occur with ageing, type 2 diabetes, obesity, hypercholesterolaemia and cardiovascular disease, some of these clinical states are known risk factors for ED. A more recent study demonstrated that the calculated free E_2 concentration in men with a subnormal free T concentration was lower than that in men with a normal free T concentration. Directly measured free E_2 concentrations were also lower in men with subnormal free testosterone concentrations.[27] The suppression of the hypothalamic–pituitary–gonadal axis in patients with subnormal free T concentrations and type 2 diabetes has not been associated with increased E_2 concentrations.[27]

In the current study, low T and/or elevated E_2 levels were associated with increased ED severity. A low T level caused the primary effect; however, the existence of a concomitantly elevated E_2 level increased the severity of ED. A previous study has demonstrated that an E_2–T imbalance and relative elevation of E_2 may play a role in the causation and perpetuation of ED. Testosterone supplements improve sexual function in patients with hypogonadism. However, the value of T supplementation, which may be aromatised to E_2 in men with possible hyperoestrogenism, is questionable.[28] A more recent review of the literature demonstrated that the current evidence does not support a role of naturally occurring oestrogen elevations in testosterone deficiency or the treatment of elevated oestrogens during testosterone therapy.[29] Empirical clomiphene citrate (anti-estrogen) was shown to improve sexual function in a group of ED patients with hypogonadism.[30] Although the aromatase inhibitor anastrozole increased both bioavailable and total T and reduced E_2, there was no concurrent improvement in the IIEF scores, indicating the importance of other coexistent factors.[31]

Previous studies have reported the importance of the E_2/T ratio. However, in the current study, we addressed the impacts of the absolute value of each individually and together on ED severity. Extrapolating those findings could raise several clinically relevant issues, including whether an E_2 assay may eventually find a place in the routine clinical investigation of ED. The E_2/T ratio may be a useful diagnostic marker for hormonal abnormalities in ED patients and for hormone follow-up through appropriate therapeutic titration.

Although the Elecsys system and the electrochemiluminescence immunoassay might not currently be the state of the art for measuring steroid levels, they are capable of distinguishing eugonadal males from hypogonadal males if adult male reference ranges have been established in each individual laboratory, and they have been reported to accurately identify low T levels in men.[32]

A potential methodological limitation of our study is the relatively small number of patients in some categories of hormonal abnormalities. Age, obesity, smoking and medical comorbidities did not significantly differ among patients with low T alone and patients with both a low T level and an elevated E_2 level, which suggests that they had little effect on the difference in ED severity between groups. However, the exclusive influence of those possible confounders on each category of hormonal pattern was not addressed in the present study and will be considered in future studies.

The subjects and standard instruments we used indicate that our findings are reliable and certainly signify a good base for further studies. Additional studies with a larger sample size are needed to investigate how much both low T and high E_2 affect the pathogenesis of ED, particularly the vascular, cavernosal smooth muscle and neuronal mechanisms of erection. Future research should also investigate other unclear issues, including how low T and high E_2 influence each other

and whether the normal male ageing process is responsible for the pathophysiology of ED in association with both hormonal abnormalities. Future studies should also examine the presence of concurrent organic conditions and medical comorbidities that predispose individuals to similar hormonal derangements that may ultimately affect successful management outcomes.

Conclusion

Low T and elevated E_2 levels are associated with increase ED severity when present individually or concomitantly. A low T level demonstrated the principal effect; however, the existence of a concomitantly elevated E_2 level increased the severity of ED in patients with a low T level.

COMPETING FINANCIAL INTERESTS

All authors declare that there are no competing financial interests.

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