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Original Article

Estradiol-to-testosterone ratio and erectile dysfunction in men aged 35-45

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Abstract

Aim: This study investigated the relationship between erectile dysfunction and the estradiol-to-testosterone ratio in men aged 35 to 45.

Materials and methods: Screening procedures were designed to select eugonadal men between 35 and 45 years of age to evaluate the impact of the estradiol-to-testosterone ratio on the development of erectile dysfunction. Out of 1,521 patients examined in the andrology office for erectile dysfunction between January 2013 and December 2019, a total of 73 men were included for evaluation. Erectile dysfunction was evaluated using the International Index of Erectile Function (IIEF). Twenty age-matched men without erectile dysfunction were randomly selected to form the control group. We measured the total serum testosterone level three times, every 45 days, for three months, and measured estradiol once at the third blood collection.

Results: Among the patients with erectile dysfunction, we observed the estradiol-to-testosterone ratio values ranging from 0.0042 to 0.0110. These values were significantly higher than those of the control group (0.0015–0.0020) ($p<0.001$). There were significant differences in the questionnaire score between the patients and the control group ($p<0.001$). We did not observe fluctuations in the blood flow to the artery profunda of the penis bilaterally during color Doppler ultrasound.

Conclusion: Our study suggests that erectile dysfunction in men aged 35 to 45 years may be associated with an estradiol-to-testosterone ratio of 0.0041–0.0110. In the clinical examination of these patients, it is necessary to test for estradiol in addition to testosterone.

Keywords

erectile dysfunction, estradiol/testosterone ratio, testosterone, young men

Introduction

Erectile dysfunction (ED) and low sexual desire are multifactorial diseases that affect 5% to 10% of men under the age of 40.[1] Many authors have reported that the majority of these patients were diagnosed with psychogenic ED.[2,3] Along with the psychological origin of ED in young patients, other causes should be considered, including metabolic, endocrine, vasculogenic, neurological, and psychiatric diseases.[1] Androgens have long been thought to play an important role in male erections as serum total testosterone (TT) levels decline with age and the incidence of ED increases.[4] The decrease in TT levels is one cause, but the effect of estradiol (E2) remains unclear. Previous studies have found that an elevated E2/T ratio negatively affects penile erection, yet the relationship between the two still remains unclear.[5] Furthermore, studies have shown that the E2/T ratio is a more significant factor in assessing sexuality than E2 alone.[5] Some authors have not found a relationship between E2/T imbalance and changes in erectile function and sexual desire. They conclude that, in the clinical examination of these patients, it is unnecessary to include E2 in laboratory tests.[6] Neto et al. have found that low testosterone levels and low T/E2 ratios are significantly

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associated with decreased perceived libido in men seeking treatment for sexual dysfunction. They recommend further studies to confirm these data and understand how treatment affects these parameters.[7]

Aim

The aim of this study was to investigate the relationship between erectile dysfunction and the estradiol-to-testosterone (E2/T) ratio in men aged 35-45 years.

Materials and methods

Study site, design, and population

From January 2013 to December 2019, we selected 73 Bulgarian men aged 35-45 years with ED and varying body mass indexes (BMIs), with no congenital or acquired reproductive diseases, and no mental disorders from a total of 1521 patients examined in the andrological office of St Sofia Hospital in Obstetrics and Gynecology. Twenty clinically healthy age-matched men with a normal BMI and without ED who visited the andrology office for a preventive examination served as our control group.

Institutional review board statement

The analysis of patient data was performed by extracting data from our electronic database.

All patients gave written informed consent for the use of their data for scientific evaluation, in accordance with the Declaration of Helsinki for studies involving humans. The protocol was approved by the Ethics Committee of the Hospital (IC code: No. 3 / 28.11.2022)

Interview

In our study, we used the short form of the International Index of Erectile Function (IIEF) questionnaire.[8] Subjects completed the IIEF questionnaire at the end of the third month, after the final blood draw to measure total testosterone (TT) and estradiol (E2) levels.

Clinical and laboratory evaluation

We determined the BMI of all men.[9] Over a period of 3 months, we tested the serum levels of testosterone and estradiol in each man three times at equal intervals. Blood was drawn in the morning after an overnight fast, while the subjects were resting. The determination of TT and E2 was performed using an automated immunoanalyzer Mini Vidas, Biomerio with ELFA method. The samples were subjected to an analytical cycle under standard conditions to ensure high analytical reliability.

The E2/T ratio was calculated from the results obtained for TT and E2 for each sample taken separately for each patient.

Ultrasonographic technique

Following the third blood collection for serum testosterone and estradiol levels, an ultrasound scan of the penis was performed using a Mindray NS2 device with a 7.5 MHz sector converter for surface organs in all men. The deep penile artery (DPA) could be found easily along the length of the corpus cavernosum. Due to the symmetry of the changes in the two arteries, we deemed it sufficient to measure only the right artery. Analysis of blood flow in the deep penile artery included peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI).[9] RI was calculated using the following formula:

RI = PSV – EDV/PSV [9]

Statistical analysis

The age, BMI, serum TT level, E2, E2/T ratio, International Index of Erectile Function (IIEF) scores, diameter of the DPA, PSV, EDV, and RI values for all patients were entered into IBM SPSS Statistics (version 25). The data were analyzed using means and standard deviations, an independent samples t-test, and correlation analysis. A significance level of $p \leq 0.05$ was used.

Distribution of men according to clinical and laboratory results

According to clinical and laboratory results, the men we studied were divided into five groups based on BMI[10] and E2/T ratio values, as shown below:

1. Group 1: healthy controls, men without ED, BMI 19.71–24.68, E2/T ratio 0.0015–0.0020 (n=20);
2. Group 2: men with ED, BMI 19.44–23.80, E2/T ratio 0.0041–0.0088 (n=18);
3. Group 3: men with ED, BMI 25.34–28.84, E2/T ratio 0.0042–0.0081 (n=27);
4. Group 4: men with ED, BMI 31.26–34.81, E2/T ratio 0.0055–0.0090 (n=16);
5. Group 5: men with ED, BMI 35.91–38.94, E2/T ratio 0.0061–0.0110 (n=12);

Results

All parameters except IIEF scores **(Table 1)** have also been thoroughly presented by us[11], and the correlation dependencies are summarized in **Table 2**. Parameters of the ultrasound examination of the DPA are presented in **Table 3.** The comparative curves obtained from the E2/T ratio and IIEF scores are presented in **Fig. 1**.

Table 1. IIEF scores: the average number of points with the standard deviation and range from the answers to the questionnaire

Parameter	Mean ± SD[1]	Range
IIEF score		
Group 1	1.000±0.000	1–1
Group 2	9.389±1.975	7–13
Group 3	9.074±1.639	6–13
Group 4	10.250±1.571	8–13
Group 5	8.750±2.006	6–12

Table 2. Correlation dependencies - some dependent variables

	IIEF score	BMI	E2/T
IIEF score	1,000		
BMI	0.393**	1,000	
E2/T	0.524**	0.517**	1,000

IIEF score: the average number of points from the answers to the questionnaire; BMI: body mass index; E2/T: estradiol/testosterone ratio; **$p<0.01$

Discussion

Publications on this topic in the relevant literature have used both the testosterone-to-estradiol ratio (T/E2)[5,7] and the estradiol-to-testosterone ratio (E2/T)[6]. Since the E2/T ratio is more commonly used, it was adopted in this study.

At the start of the study, we selected men aged between 35 and 45 years old. Upon completion of the study, no cases of erectile dysfunction (ED) were found in men aged 35 or 36; ED was observed only in men aged 37 to 45. Most authors associate ED onset in this age group with below-normal serum testosterone levels.[6,7] Our clinical study doc-

Table 3. Parameters of the ultrasound examination of DPA

Parameter	Mean ± SD[1]	Range
Diameter of DPA (cm)		
Group 1	0.505±0.128	0.3–0.7
Group 2	0.439±0.114	0.3–07
Group 3	0.430±0.091	0.3–0.7
Group 4	0.481±0.122	0.3–0.7
Group 5	0.442±0.108	0.3–0.7
PSV (cm/sec)		
Group 1	47.114±6.953	37.56–59.43
Group 2	44.941±6.299	36.44–58.63
Group 3	45.679±6.838	37.58–58.35
Group 4	44.510±12.059	27.81–51.67
Group 5	45.434±10.158	27.61–56.61
EDV (cm/sec)		
Group 1	7.792±0.815	6.69–9.71
Group 2	8.102±1.065	6.58–10.35
Group 3	8.426±1.257	6.64–11.39
Group 4	8.118±2.055	5.28–9.44
Group 5	7.636±2.066	5.42–10.63
RI		
Group 1	0.832±0.022	0.79–0.88
Group 2	0.820±0.008	0.80–0.84
Group 3	0.816±0.009	0.80–0.83
Group 4	0.823±0.023	0.80–0.84
Group 5	0.823±0.017	0.80–0.85

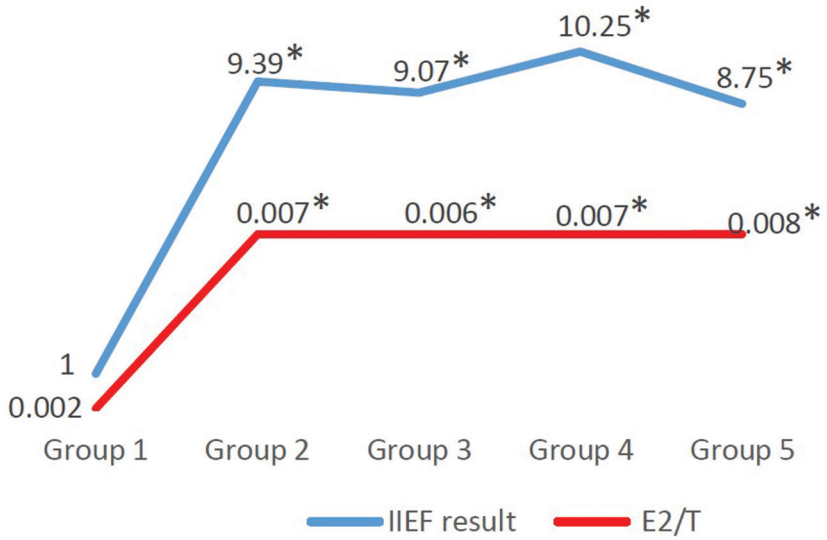

Figure 1. The E2/T ratio and IEFI result.

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umented significant differences in the E2/T ratio between young men with and without ED. While serum androgen levels decline with age in adult men, estradiol levels remain constant, increasing the E2/T ratio.[12] In the present study, however, as serum TT levels decreased in men with ED, we observed an increased estradiol levels within reference limits, resulting in a significantly higher E2/T ratio (p<0.001) compared to controls.

The positive correlation we found between BMI and E2/T (r=0.517, p<0.001) confirms the view of many other authors who have demonstrated the importance of increased BMI for higher E2/T ratios.[13] Of interest is the ED of men in the second group who have normal BMIs. It is possible that an E2/T ratio, either independently or in conjunction with other factors besides an elevated BMI, is a prerequisite for ED. These observations, alongside with the moderate correlation obtained between the IIEF score and BMI (r=0.393, p<0.001), indicate that a greater BMI may be less important than E2/T ratio in ED occurrence among young men.

For the appearance of reproductive disorders and lower urinary tract symptoms, as well as the increase in the volume of the prostate gland, the change of the E2/T ratio is relatively clearer, due to the presence of receptors for testosterone and estradiol in the organs of the male reproductive system.[12,14] Unlike the above disorders, the relationship between E2/T and ED is still a debatable matter and not fully clarified. Previous studies have found that the increased E2/T ratio has a negative effect on sexual function, but the relationship between the E2/T ratio and the erection of the penis is not clarified.[5] Some studies indicate a link between altered levels of TT and E2 and brain function. Quantity is not quality, and at present, from the limited number of publications in the literature, it is very difficult to conclude exactly how TT and E2 levels may affect cognition and emotion. It is generally accepted that testosterone is an anxiolytic, antidepressant, and improves spatial abilities. But this picture is oversimplified. Many variables contribute to the complex interactions between TT and the brain.[15] Another study demonstrated that the E2/T ratio has a greater impact on libido than E2 alone and a negative relationship between the E2/T ratio and penile erection, especially at its root.[6] Neto RP et al. consider that a low TT level and a low T/E2 ratio are significantly associated with perceived decreased libido.[7]

Most studies on the relationship between E2/T and erectile dysfunction have focused on men over 50 years of age with testosterone values below 300 ng/dL (10.4 nmol/L).[4-6] Our study examined a younger group of men and demonstrated that ED can occur when total testosterone levels are below 14.28 nmol/L for an extended period of time, with estradiol (E2) levels above 0.072 nmol/L and an E2/T ratio above 0.0041. In this study, a higher E2/T ratio was significantly correlated with ED in our sample of men seeking treatment for ED (r=0.524, p<0.001). Recognizing an imbalance in the E2/T ratio can help clinicians identify men with ED and determine the best course of treatment. Further studies are necessary to confirm these findings and to understand how treatment affects these parameters and whether this should be addressed in clinical practice.

The average diameter of the DPA and blood flow parameters in our study were close to those of Jung et al.[10,16] There were no significant differences in the blood flow parameters between the individual groups, thereby rejecting the vascular factor as the cause of ED in our study.

Limitations

1. The E2/T ratio values were only observed once, so we cannot say how ED would develop in the future. Based on our preliminary data, we can conclude that if these values remain above 0.041 for an extended period of time, ED will occur in this group of young men.

2. The number of patients included in this pilot study is relatively small, and we are considering expanding it.

Conclusion

Our findings suggest that erectile dysfunction in men aged 35 to 45 years may be associated with estradiol-to-testosterone ratio values ranging from 0.0041 to 0.0110, and that estradiol should be tested alongside testosterone during clinical examinations of these patients.

Funding

This research did not receive any specific grant.

Conflicts of interest

The author declares he has no conflict of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author. They are not publicly available due to legal restrictions on publishing personal patient data.

Ethical statement

All patients gave written informed consent for the use of their data for scientific evaluation, in accordance with the Declaration of Helsinki for studies involving humans. The protocol was approved by the Ethics Committee of the Hospital (IC code: No. 3/28.11.2022).

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