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Is There A Role for Dihydrotestosterone/ Estradiol Ratio in Premature Ejaculation?

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ABSTRACT

Background: The association between endocrine control and ejaculatory reflex is still not completely elucidated. Serum dihydrotestosterone (DHT) concentrations have been reported to be lower in premature ejaculation (PE) patients. We hypothesized that homeostasis between testosterone (T) and their metabolites; dihydrotestosterone (DHT) and estradiol (E2); could be involved in orchestration of the ejaculatory process.

Aim: To test this hypothesis, we aimed to investigate any possible relationship between DHT/ E2 ratio and T/E2 ratio in a cohort of patients consulting for premature ejaculation (PE).

Methods: This prospective hospital-based cross-sectional case-control study has been carried on 104 PE patients (30 patients with primary lifelong PE and 74 patients with acquired PE) compared to 90 healthy men as controls.

Results: DHT levels were significantly higher in secondary PE compared to primary PE group (p = 0.011). Besides, serum E2 showed significant higher level among both primary and secondary PE groups compared to the control group **(**p=0.001). Moreover, both total testosterone (TT)/E2 and DHT/E2 ratios were significantly lower in both primary and secondary PE compared to the control group (p=0.001 for both). Furthermore, DHT/E2 ratio showed fair discriminating ability between PE and healthy controls (AUC = 0.749, p=0.001).

Conclusions: Both TT/E2 and DHT/E2 ratios were significantly lower in both primary and secondary PE subjects suggesting a role of hormonal imbalance in this context. Although this link seems likely, large-scale studies are needed to confirm these findings.

Keywords: Dihydrotestosterone, Dihydrotestosterone/estradiol ratio, Estradiol, Premature Ejaculation, Testosterone/estradiol ratio.

Short running title: DHT/E2 ratio in premature ejaculation

INTRODUCTION

Premature ejaculation (PE) is one of the most common male sexual dysfunctions and has been estimated to occur in 4-64.7% of men in the general community [(1)]. Over the past 2 decades, increasingly assertive efforts have been proposed to explain the etiology of PE. Psychological, genetic, neurobiological and organic etiologies including both local and systemic factors have been hypothesized for the PE etiology [(2,3)]. Although it is well designated that sexual function is hormonally regulated, the association between the endocrine control and ejaculatory reflex is still not completely elucidated. It has been demonstrated that sex steroids may be potential candidates in the regulation of the ejaculatory process, but the exact mechanisms are not exactly known [(4,5)].

Therefore, a putative imbalance of sex steroid concentrations might contribute to the physiology of the ejaculatory performance. For instance, dihydrotestosterone (DHT) as the most potent androgen might play a pivotal role in the hormone profile of PE. In this context, serum DHT concentrations have been reported to be lower in PE patients [(6)]. Furthermore, it has been shown that that the estradiol (E_2) / testosterone (T) ratio was reduced in PE patients, which was primarily associated with high T levels [(7)]. Additionally, rats with high E2 levels showed prolonged ejaculation latency [(8)]. We hypothesized that homeostasis between T and their metabolites; DHT and E2; could be involved in orchestration of the ejaculatory process. To test this hypothesis, we aimed to investigate any possible relationship between DHT/ E2 ratio and T/E2 ratio in a cohort of patients consulting for PE.

PATIENTS AND METHODS

This prospective hospital-based cross-sectional case-control study was carried on 104 PE patients (30 patients with primary lifelong PE and 74 patients with acquired PE) compared to 90 healthy men as controls. These patients were recruited from the andrology outpatient clinic of Mansoura University hospital during the period between July 2019 and July 2020.

Ethical approval:

This research was carried out in accordance with the declaration of Helsinki for experiments involving humans. The institutional review board of Mansoura university approved the study protocol (MS#.19.05.618) where all participants provided written informed consent.

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The inclusion criteria were; PE patients who fulfilled the unified criteria of International Society for Sexual Medicine (ISSM) [9], and heterosexual married men with trials of sexual relationship during the last 6 months. On the other hand, the exclusion criteria were; unmarried men, patients received medications for PE over the last 3 months prior to the enrolment in the study, smokers, alcohol consumers, history of sexual desire disorders, problems of sexual orientations, paraphilias, major psychiatric disorders, and primary hypogonadism. Control persons were selected from healthcare workers and patients' accompanying persons**.** Sampling was carried out by the non-probability purposive technique. Consecutive eligible men who followed both inclusion and exclusion criteria were included in this study.

All participants included in this study were subjected to the following:

i) Detailed history taking with special focusing on age, marital status, history of surgery, drug intake or medical disorders, type and duration of PE, presence or absence of erectile dysfunction (ED); symptoms suggestive of prostatitis/urinary troubles; pain in the pelvis, perineum or genital organs.

ii) Careful clinical examination including general and local genital examination to identify the possible underlying medical conditions that could be associated with acquired PE including ED, endocrine causes (e.g., thyroid dysfunction) and urological disorders (e.g., prostatitis). The weight and height were measured using a standardized stadiometer as subjects wore light clothes without shoes. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1 cm. The body mass index (BMI) was calculated by dividing the individual's weight by the square of height (kg/m^2).

iii) Laboratory investigations including: urine analysis, hormonal levels of serum prolactin (PRL), serum total testosterone (TT), and E2 using the enzyme-linked immunosorbent assay (ELISA) method (Bioassay Technology Laboratory, Shanghai, China). Serum DHT levels were measured using chemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). All hormones were measured in a venous blood sample after an overnight fasting. Calculation of TT/E2 and DHT/ E2 ratios was performed.

Measures:

The intravaginal ejaculation latency time (IELT) was assessed by a stopwatch for three consecutive episodes of sexual intercourse (the mean was used). The patients were evaluated with the Arabic Index of Premature Ejaculation (AIPE) questionnaire[10]. PE severity was classified into the following five categories based on AIPE scores; severe (7 – 13), moderate (14 – 19), mild to moderate (20 – 25), mild (26 – 30), and no PE (31 – 35). Besides, the Arabic validated version of international index of ED (IIEF5) was utilized to evaluate the presence and severity of ED [11].

Statistical analysis

Kolmogorov-Smirnov test was used as a test of normality. The collected data were summarized in terms of mean ±SD or median and range for quantitative data as appropriate. Qualitative data were presented as frequency and percentage. Comparisons between the different study groups were carried out using Fisher's exact test to compare proportions as appropriate. One way ANOVA and Kruskal–Wallis tests were used to compare parametric and nonparametric qualitative data respectively. Correlations were assessed using Spearman's or Pearson's method whenever appropriate. The ROC curve (Receiver operating characteristics) of different diagnostic variables was conducted for discrimination between different study groups. The area under the ROC curve (AUC) was assessed [12]. After logarithmic transformation of variables, logistic regression analysis was used to evaluate the association, given as an odds ratio (OR) and a 95 % confidence interval (CI), between hormonal levels, DHT/E2 ratio, and TT/E2 ratio as the primary predictor variables and PE. This association was tested in both unadjusted and adjusted models accounting for age. The software SPSS® (version 23.0; SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. P values of <0.05 (two-sided) were considered to be statistically significant.

RESULTS

PE patients and controls were matched for age however primary PE patients were significantly younger and showed slightly lower BMI than secondary PE. The characteristics in the 3 groups were summarized in table 1.

Table (1): Comparison of demographic and clinical variables between studied groups

	Primary PE n=30	**Secondary PE n=74**	**Controls n=90**	**P[1]**	**Post hoc tests**

Age (years)	Mean ±SD (range)	32.1± 6.6 (23-45)	45.6± 12.1 (26-68)	39.7 ± 9.4 (28-55)		<0.001	P2=0.214 P3=0.232 P4<0.001
IIEF5	Mean ±SD	27.4 ± 1.3	22.1 ± 5.1	28 ± 1.3		<0.001	P2=0.363 P3<0.001 P4<0.001
AIPE	Mean ±SD	17.7 ± 4.3	17.6 ± 4.2	32.5 ± 1.3		<0.001	P2<0.001 P3<0.001 P4=0.873
BMI (kg/m^2)	Mean ±SD	25.4± 2.9	27.1±3.8	25.7±2.9		0.010	P2=0.662 P3=0.007 P4=0.017
Prostatitis	Absent (n,%)	30 (100%)	56 (75.7%)	0 (0%)		0.003	
	Present (n,%)	0 (0%)	18 (24.3%)				
ED	n,%)	0 (0%)	48 (64.9%)	0 (0%)		<0.001	
IELT	<30 sec (n,%)	0 (0%)	3 (4.1%)	-	-	<0.001	
	<1 min (n,%)	14 (46.7%)	4 (5.4%)	-	-		
	min (n,%)	0 (0%)	20 (27%)	-	-		
	-2 min (n,%)	12 (40%)	24 (32.4%)	-	-		
	min (n,%)	4 (13.3%)	3 (4.1%)	-	-		
	-3 min (n,%)	0 (0%)	18 (24.3%)	-	-		
	>3 min (n,%)	0 (0%)	2 (2.8%)	-	-		

P1=comparison between all groups; P **2**= comparison between controls and primary PE; P **3=**, comparison between controls and secondary PE; P **4**= comparison between 1ry and 2ry PE. Abbreviations: AIPE= Arabic Index of Premature Ejaculation, BMI=body mass index, ED= erectile dysfunction, IIEF5= international index of erectile function 5, IELT=intravaginal ejaculation latency time.

DHT levels were significantly higher in secondary PE compared to the primary PE group. The mean levels of serum E2 were significantly higher among both primary and secondary PE compared to the control group. Both TT/E2 and DHT/E2 ratios were significantly lower in both primary and secondary PE compared to the control group (Table 2).

Table (2): Differences between laboratory data among groups (median, range)

	Controls n=90	**1ry PE n=30**	**2ry PE n=74**	**P[1]**	**Post hoc tests**
TT (ng/dl)	498.5 (300-770)	590 (310-750)	580 (60-840)	0.075	-
E2 (ng/dl)	2.5 (1.1-3.3)	3.1 (1.9-4.8)	3.6 (1.6-11.1)	<0.001	P2<0.001 P3<0.001 P4=0.234
TT/E2 ratio	20.5 (10.2-65.5)	15.4 (9.8-33.9)	15.9 (4.2-60)	<0.001	P2=0.009 P3<0.001 P4=0.873
DHT (ng/dl)	105.3 (82.8-456.6)	104 (53.4-148.9)	106.1 (53.9-205.4)	0.035	P2=0.140 P3=0.131 P4=0.011
PRL (ng/dl)	8.1 (3.2-11.5)	7 (3.4-14)	9.3 (4.7-30.4)	0.004	P2=0.892 P3=0.001 P4=0.029
DHT/E2	44.9 (28.6-87.8)	30.7 (18.2-59.9)	31.3 (9.5-93.3)	<0.001	P2<0.001 P3<0.001 P4=0.189

P1= comparison between all groups; P **2**=comparison between control and primary PE; P **3**= comparison between control and secondary PE; P **4**= comparison between 1ry and 2y PE. Abbreviations: DHT= serum dihydrotestosterone, E2= estradiol, DHT/E2 = serum dihydrotestosterone/estradiol ratio, PRL= serum prolactin, TT= serum total testosterone, TT/E2 ratio= serum total testosterone/estradiol ratio.

DHT levels were significantly higher in secondary PE compared to the primary PE group. The mean levels of serum E2 were significantly higher among both primary and secondary PE compared to the control group. Both

TT/E2 and DHT/E2 ratios were significantly lower in both primary and secondary PE compared to the control group (Table 2).

Furthermore, both TT/E2 and DHT/E2 ratios were significantly lower in men with ED, prostatitis plus ED compared with those without (p=0.01; p=0.003 respectively). Moreover, there was a significant negative correlation between DHT/E2 ratio and IELT (r=-0.313, p=0.001) with a lack of significant correlation between serum DHT and IELT (r=-0.147, p=0.136). Additionally; there was a significant positive correlation between BMI and serum E2 in our patients (r=0.549, p=0.001).

Table (3): ROC curve (AUC) results of different hormones and sex steroids ratios for discrimination between PE and control groups

Biomarker	AUC	CI 95%	p	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TT	0.593	0.511-0.675	0.026	565	60.2	73.3	72.3	61.4	66.3
E2	0.802	0.738-0.866	<0.001	2.9	67	90	88.6	70.2	77.7
TT/E2	0.666	0.588-0.745	<0.001	<17.9	67	76.7	76.9	66.8	71.5
DHT	0.524	0.441-0.606	0.572	97	75.7	40	59.3	58.8	59.1
PRL	0.609	0.529-0.688	0.009	6.6	69.9	44.4	59.2	56.1	58.1
DHT/E2	0.766	0.680-0.818	<0.001	<31.9	55.3	93.3	90.4	63.9	72.4

Abbreviations DHT= serum dihydrotestosterone, E2= estradiol, DHT/E2 = serum dihydrotestosterone/estradiol ratio, PRL= serum prolactin, TT= serum total testosterone, TT/E2 ratio= serum total testosterone/estradiol ratio.

Table (4): ROC curve (AUC) results of different hormones and sex steroids ratios for discrimination between 1ry and 2ry PE groups

Biomarker	AUC	CI 95%	p	Cut off	Sensitivity (%)	Specificity (%)	PPV %)	NPV (%)	Accuracy (%)
TT	0.510	0.377-0.642	0.876	<614.9	69.9	43.3	8.8	55.5	57.6
E2	0.618	0.505-0.732	0.060	3.4	60.3	70	9.9	60.4	64.8
TT/E2	0.505	0.387-0.624	0.931	15.9	52.1	60	0.1	52.0	55.8
DHT	0.640	0.511-0.769	0.026	105.4	54.8	63.3	3.3	54.8	58.7
PRL	0.637	0.517-0.757	0.029	8.75	56.2	70	8.4	58.0	62.6
DHT/E2	0.589	0.463-0.715	0.157	26.3	75.3	40	9.2	58.4	58.9

Abbreviations DHT= serum dihydrotestosterone, E2= estradiol, DHT/E2 = serum dihydrotestosterone/estradiol ratio, PRL= serum prolactin, TT= serum total testosterone, TT/E2 ratio= serum total testosterone/estradiol ratio.

Although serum DHT failed to discriminate between PE and healthy subjects (Table 4), serum E2 level showed a good AUC suggesting its ability to discriminate between PE and healthy subjects at a cutoff value of 2.9 ng/dl. Furthermore, DHT/E2 ratio showed fair discriminating ability between PE and normal controls (Figure 1). In contrast, TT/E2 showed poor AUC in discrimination between PE and healthy controls (Table 3). On the other hand, TT/E2 and DHT/E2 ratios failed to discriminate between primary and secondary PE (Table 4).

Table (5): Logistic regression analysis for laboratory variables as predictors for PE

Predictor variable	P value	OR	95% CI for OR
Age (years)	0.977	1.001	0.962 – 1.041
BMI (kg/m^2)	0.374	0.941	0.823 – 1.076
TT	0.601	1.001	0.998 – 1.004
E2	**<0.001**	8.315	2.936 – 23.548
TT/E2	**0.005**	1.094	1.028 – 1.164
DHT	0.870	1.001	0.992 – 1.010
PRL	**0.002**	1.301	1.101 – 1.537
DHT/E2:			
>31.68	**<0.001**	R	R
≤31.68		16.81	4.04 – 69.96

OR=Odds ratio, CI=Confidence interval. R=reference category. OR, odds ratio; CI, confidence interval; Abbreviations DHT= serum dihydrotestosterone, E2= estradiol, DHT/E2 = serum dihydrotestosterone/estradiol ratio, PRL= serum prolactin, TT= serum total testosterone, TT/E2 ratio= serum total testosterone/estradiol ratio.

The logistic regression analysis showed that DHT/E2 ratio ≤31.68, as well as higher serum E2 and PRL, may be suggested to be independent predictors of PE (Table 5).

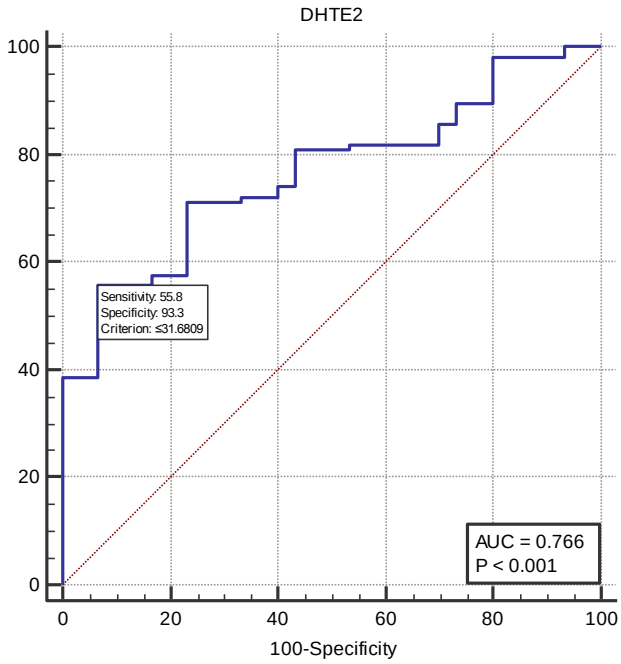

Figure (1): ROC curve for DHTE2 in discriminating PE from control

DISCUSSION

It has been demonstrated that androgens are known to be important for ejaculatory performance in men [4,5]. Furthermore, T and T's primary metabolites, DHT and E_2 appear to interact differentially with their respectable androgen and estrogen receptors; not only for the maintenance of accessory sex organs but also may participate in the regulation of the ejaculatory reflexes [13,14]. However, the possible role of T in PE has been controversial. While subjects with PE reported higher total T, and free testosterone (FT) levels compared to the control and delayed ejaculation groups [15,16] suggesting that elevated serum T is an independent risk factor for PE; on the other hand; other studies have concluded that there was no disturbance in serum total T [17-19] and FT [17,18] in PE patients. Moreover, **Tahtali *et al.*** [20] showed significantly lower T in secondary PE compared to the other types of PE (primary PE, variable PE, and subjective PE). Additionally, it was noted that T replacement therapy is effective in the treatment of secondary PE showing T deficiency. Likewise, numerous animal studies [13,21-24] have shown conflicting results regarding the effects of DHT and E2 on ejaculation latency. Whether DHT, E2, or DHT/ratio acts synergistically or antagonistically to influence the PE is not exactly known and has received little clinical research attention. **Mousa *et al.*** [6] demonstrated that PE patients exhibit a differential sex steroid profile compared to age-matched controls, pointing both towards higher aromatization (higher serum E2) and less 5-alpha-reduction of testosterone (higher serum T and lower serum DHT).

In the current study, the serum levels of DHT did not differ significantly between both primary PE and secondary PE and the control group. However, DHT levels were significantly higher in secondary PE compared to primary PE groups in contradiction with those reported by **Mousa *et al.*** [6]**.** This difference could be attributed to the differences in the patients and methods. **Mousa *et al.*** study [6] was a retrospective study that has enrolled 47 PE patients without being classified into either primary or secondary PE. Additionally, there was evidence of variation of 5α-reductase activity among different races that may be reflected on the serum DHT levels [7,25]. This lack of association between PE and serum DHT does not completely nullify the androgen hypothesis in the pathogenesis of PE; rather, it may underscore the importance of the better understanding the mechanism of androgen action within the vas deferens, seminal vesicles, prostate, and the related brain regions including the relationship between tissue and serum androgen (T and DHT) levels. For example, local prostatic production of DHT results in concentrations that are ~10-fold higher than serum concentrations [26, 27].

Although DHT acts as a paracrine independently of circulating DHT concentrations for the target organs in adults; it remains possible, however, that DHT might have specific effects as a classic hormone because DHT has physiologically different effects than testosterone due to differences in receptor binding avidity and differences in interaction with the androgen receptor and its function and turnover rate[28]. In this context, one should mention the ability of DHT to cause non-genomic relaxation of different smooth muscles including the rat vas deferens possibly through partial blockade of Ca^{2+} influx [29]. This finding may suggest that lower DHT may be

associated with lack of this relaxant effect and hence short ejaculation latency. However, support for this hypothesis has not been strong due to conflicting results of the effects of DHT on ejaculation latency [23, 30-32]. Thus, though DHT was the most effective androgen to restore penile growth and maintain sex glands, it is a weaker modulator of male sexual behavior [23,32]. For all these reasons, there was a lack of correlation between serum DHT and IELT and serum DHT failed to discriminate between PE and healthy subjects in our study.

The role of Es in PE pathogenesis is more complex. **Mousa *et al.*[6]** reported higher E2 concentrations among PE patients, whereas others have observed low [16] or similar levels [7,33] of E2 compared to the controls. Significantly higher level of E2 were observed among both primary and secondary PE compared with the control group. Additionally, E2 was significantly higher in those with ED, prostatitis plus ED compared to those without. Moreover, the serum E2 level showed good AUC suggesting the ability of this hormone to discriminate between PE and healthy subjects at a cutoff value of 2.9 ng/dl. In contrast to the current findings, **Chen *et al.*[33]** observed that E2 levels were unlikely to distinguish PE patients from healthy cases. This discrepancy could be illustrated by various populations (Egyptian versus Chinese) and different eligibility criteria (primary versus secondary PE). However, serum E2 level failed to discriminate between primary and secondary PE or to correlate significantly with IELT in the current study. Therefore, our results and the findings of **Mousa *et al.*[6]** may suggest a role for E2 in PE. In this context, the increased level of E2 seems to be related to the increased activity of the aromatase, a cytochrome P-450 enzyme responsible for the aromatization of T to E2. Increased aromatase activity secondary to the accumulation of adipose tissue may be a plausible explanation because of the significant positive correlation between BMI and E2 in our patients. However, secondary PE showed significantly higher BMI compared to primary PE and the control group that could be explained by the fact that primary PE has been viewed as a neurobiological defect rather than a hormonal dysfunction [34]; nevertheless; the condition appears to be more complex and may include other significant biological components [35].

The current study has a number of strengths. It is the first work to explore the relationship between DHT/E2 ratio and PE. The data were collected prospectively to examine the relationship between DHT/E2 and PE. Besides, the study included the 2 major types of PE. On the other hand, the study does have limitations. First, the major limitation is the small number of patients included in this study. The small sample size due to economic issues may be problematic especially in cases of secondary PE, where the patients are heterogeneous with one or more different etiologies are concomitantly participating in the pathogenesis. Second, our investigation is a single center study; although this might hinder generalizability to other populations, the need for a larger multicenter study is warranted. Third, it is observational and descriptive, which means that causation cannot be attributed to the hormonal imbalance associated with PE.

CONCLUSIONS

Both TT/E2 and DHT/E2 ratios were significantly lower in both primary and secondary PE suggesting a role of hormonal imbalance in PE. Although this link seems likely, large-scale studies are needed to confirm these findings.

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