Original Research Article

Evaluation of Serum Prolactin and Testosterone in Premature Ejaculation Patients

Abstract

Background: Premature ejaculation is a frequently encountered sexual dysfunction in men. It significantly impairs quality of life of the affected male and his partner. This study investigated the role of hormonal factors (prolactin and testosterone) in patients with premature ejaculation.

Objectives: evaluating the contribution of prolactin and testosterone in the pathogenesis of premature ejaculation.

Methods: A group of 26 patients suffering from premature ejaculation; 15 of them presented with primary type, and 11 of them complained of secondary type. Another group of 10 subjects served as a control group. All the individuals were subjected to clinical evaluation, and venous blood samples for laboratory investigation of serum prolactin and total testosterone.

Results: Comparing the serum prolactin levels between all groups showed no significant statistical differences (p: >0.05). While the levels of total serum testosterone were significantly lower in the primary premature ejaculation patients than in the control group and were more lower in the secondary premature ejaculation patients than both the control and primary type patients (p: <0.05).

Conclusion: It is recommended to routinely investigate testosterone serum levels in secondary premature ejaculation patients especially that is thought to be a high-risk factor in secondary type.

Keywords: premature ejaculation _ prolactin _ testosterone.

INTRODUCTION

"Premature ejaculation (PE) is defined as ejaculation with minimal stimulation and earlier than desired with little or no voluntary control, where ejaculation occurs before or soon after penetration, causing bother or distress for both partners" ***(Shindel et al., 2022).*** "PE is a frequently encountered type of male sexual dysfunction. Although its incidence varies according to the criteria used for its definition, it usually ranges between 22 and 38%" ***(El-Hamd et al., 2019).*** Apart from erectile dysfunction, it is known to affect adult males in all age groups at similar rates ***(Saleh et al., 2021).***

"PE significantly impairs quality of life of the affected male and his partner. Genetic factors are known to have an effect on the lifelong premature ejaculation etiology. However, neurologic, endocrinologic, psychologic and urologic factors might conceivably be involved in the etiology of acquired premature ejaculation" ***(Chen et al., 2022).***

"Prolactin (PRL) is a polypeptide hormone that is synthesized and secreted from specialized cells of the anterior pituitary gland lactotrophs" ***(Ruljancic et al., 2021). "***Prolactin exerts its effects through distinct long and short G-protein-coupled receptors (GPCRs)" ***(Jurek and Neumann, 2018).*** Normal level of prolactin, two hours after waking up, is 20 ng/ml in males and 25 ng/ml in females ***(Osmanova et al., 2019).***

"Eighty–five different biological functions of PRL were reported and subdivided into five broad categories: reproduction, osmoregulation, growth, integument and synergism with steroids" ***(Barrett et al., 2018). "***In men, PRL stimulates testicular functions via its action on Leydig cells and is involved in cellular morphology, increases luteinizing hormone (LH) receptor number, steroidogenesis and androgen production. In Sertoli cells, PRL tends to increase follicle-stimulating hormone (FSH) receptor number. In germ cells, PRL increases total lipids and increases spermatocyte–spermatide conversions" ***(Culpepper et al., 2022).***

"Hyperprolactinemia is associated with erectile dysfunction but it is unclear if its effect is direct or secondary to hypogonadism often seen in men with hyperprolactinemia. Elevated PRL can be found in 16% of patients with erectile dysfunction and 11% of men with oligospermia" ***(Breil et al., 2018; Ribi et al., 2020). "***Patients with drug-induced hyperprolactinemia may experience anorgasmia and decreased libido" ***(Basson and Gilks, 2018).***

"In males, the testes are the major site of testosterone production and the adrenal glands are a minor site" ***(Kische et al., 2018). "***Testosterone synthesis in the Leydig cells of the testis leads to the secretion of the main male androgenic steroid "testosterone". Testosterone production is controlled early in fetal life by placental chorionic gonadotrophin secretion and later by the pituitary luteinizing hormone (LH)" ***(Witchel et al., 2018).***

"Testosterone affects almost every organ in the body and plays a major role in male sexual function. Testosterone promotes spermatogenesis, maintenance of the accessory organs, muscle growth, secondary sexual characters development and feedback to the hypothalamus–pituitary axis" ***(Witchel et al., 2018).***

"Testosterone and prolactin do affect individual's sexuality throughout his life. However, hormonal mechanisms, involving sexual

function and dysfunction, and their degree of impact have not been fully elucidated" ***(Salvio et al., 2021).***

AIM OF THE WORK

The aim of this work is to evaluate the contribution of prolactin and testosterone in the pathogenesis of premature ejaculation.

PATIENTS AND METHODS

I. Patients:

This study was carried out on 36 male individuals. All of them were selected from those attending the Outpatient Clinic of the Dermatology & Venereology Department, Tanta University Hospital. They were divided into groups:

- **Total PE group:** included 26 male patients suffering from PE either primary or secondary type.
- **Control group:** included 10 normal healthy males served as a control group.

Inclusion Criteria:

Patients suffering from primary or secondary premature ejaculation were enrolled in this study. Male participants in both groups were sexually active and engaged in regular sexual activity and received no treatment for PE in the last 6- months.

Exclusion Criteria:

The following patients were excluded from the study:

1- Patients received treatment for PE in the last 6-month.
2- Patients with hepatic and/or renal impairment.
3- Patients suffering from any endocrinal diseases including Diabetes Mellitus.
4- Patients under testosterone or antiprolactin therapy.

II. Methods:

All patients were subjected to the following:

1) Complete history taking.
2) Full clinical examination.
3) Venous blood samples for laboratory investigation of serum total testosterone and prolactin.

1. Full history taking:

It included age, sex, occupation, marital status and special habits. The history of PE was discussed as regard it's onset, course, duration, psychological stress, desire and sense of fatigue and wife reaction toward his PE. Also,

history of previous attacks of PE, drug intake and prostatic affection were included.

2. Full clinical examination:

Complete general examination was done for each patient to identify any underlying medical conditions associated with PE or other sexual dysfunctions.

3. Laboratory investigation:

Since physical or emotional stress may elevate blood levels of prolactin, patients were put under resting basal conditions prior to sampling. Also, PRL levels rise rapidly during sleep, so samples ideally were not taken until 1-2 hours after awakening. Venous blood samples were collected aseptically without additives and put at 37ºC until clot formed (usually 15-45 minutes), then centrifuged to obtain serum specimen for assay. Sera were stored frozen at -20ºC till the time of assay. Repeated freeze-thaw cycles were avoided. Turbid serum samples or samples containing particulate matter were centrifuged prior to testing. Prior to assay, frozen samples were slowly brought to 18-25ºC and mixed gently. The sample required for analysis was 30µL for PRL and 85µL for testosterone.

- ***Principle of prolactin test (Fahie-Wilson et al., 2022; Hu et al., 2021):***

The AIA-PRL was used to measure serum PRL in this assay. The Automated immune assay (AIA)-PRL (prolactin) is two-site immunoenzymometric assay performed entirely in the AIA test cups. PRL present in the test sample was bound with monoclonal antibody immobilized on a magnetic solid phase and enzyme-labeled monoclonal antibody in the AIA test cups. The magnetic beads were washed to remove unbound enzyme-labeled monoclonal antibody and were then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled monoclonal antibody that binds to the beads is directly proportional to the prolactin concentration (Conc) in the test sample. A standard curve was constructed, and unknown sample concentrations were calculated using this curve.

- ***Principle of testosterone test (Barnard et al., 2021; Tng and Tan, 2021):***

The AIA-Testosterone (TES)was used to measure serum testosterone. The AIA-Testosterone is competitive enzyme immunoassay performed entirely in the AIA-Testosterone test cups. Testosterone present in the test sample competed with enzyme- labeled testosterone for a limited number of binding sites on the testosterone specific monoclonal antibody immobilized on a magnetic solid phase. The magnetic beads were washed to remove unbound enzyme-labeled testosterone and were then incubated with a

fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled testosterone that binds to the beads is inversely proportional to the testosterone concentration (Conc) in the test sample. A standard curve was constructed, and unknown sample concentrations were calculated using this curve.

- ***Procedure:***

i. Reagent preparation

a) Substrate solution: all reagents were brought to 18-25ºC before preparing the working reagent. The entire contents of the AIA-PACK SUBSTRATE REAGENT RECONSTITUENT II (100 mL) were added to the lyophilized AIA-PACK SUBSTRATE REAGENT II and mixed thoroughly to dissolve the solid material.

b) Wash solution: the entire contents of the AIA-PACK WASH CONCENTRATE (100 mL) were added to approximately 2.0L of CAP Class I or NCCLS Type I Reagent Grade water, then mixed well, and adjusted to the final volume to 2.5L.

c) Diluent: the entire contents of the AIA-PACK DILUENT CONCENTRATE (100 mL) were added to approximately 4.0L of CAP Class I or NCCLS Type I Reagent Grade water, then mixed well, and adjusted to the final volume to 5.0L.

ii. Calibration procedure

a) Calibration curve:

1. The calibrators used with the AIA-PRL (automated immune assay prolactin) have been standardized on WHO 2nd IS 83/562 (1986).
2. The calibrators used with the AIA-testosterone were compared to the USP reference material. The recovery of this reference material over assay range is 64-133% depending on concentration.
3. The calibration curve for both AIA-PRL and Testosterone is stable for up to 90 days. Calibration stability is monitored by quality control performance and is dependent on proper reagent handling and TOSOH AIA System maintenance according to the manufacturer's instructions. Recalibration may be necessary more frequently if controls are out of the established range for this assay or when certain service procedures are performed e.g. temperature adjustment, sampling mechanism changes, maintenance of the wash probe or detector lamp adjustment or change.

A sample calibration curve from AIA-1800 follows and shows the algorithm used for calculating results **(Figure 1 & 2).**

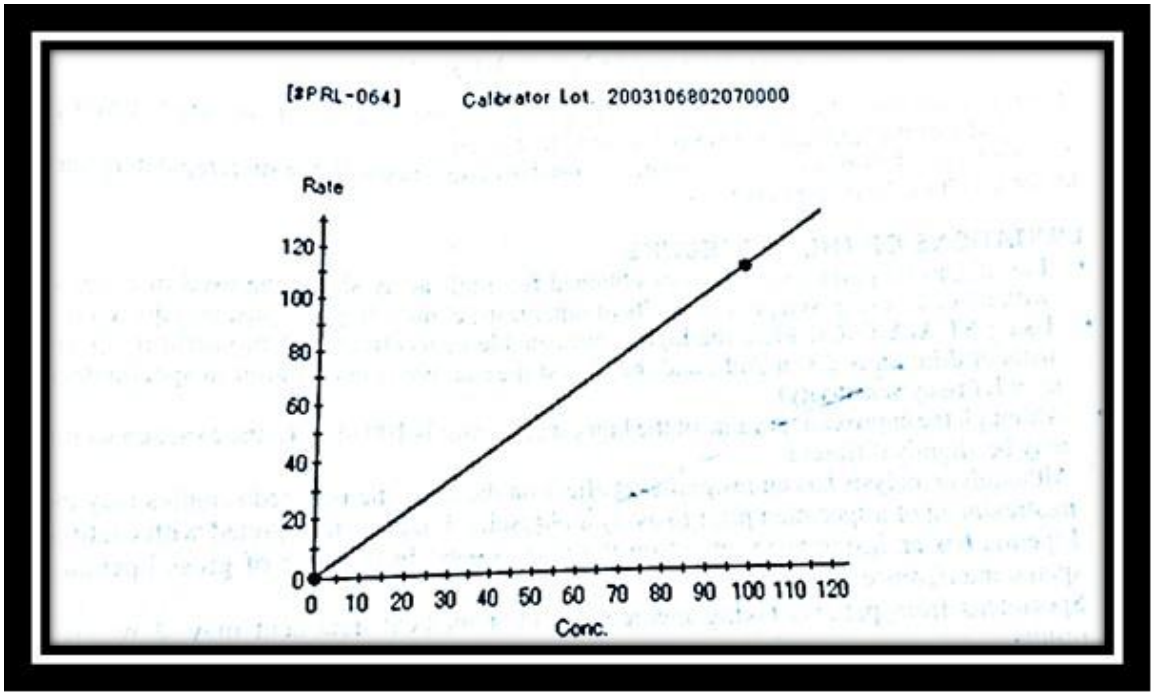

Figure (1): Prolactin calibration curve ***(Fahie-Wilson et al., 2022; Hu et al., 2021).***

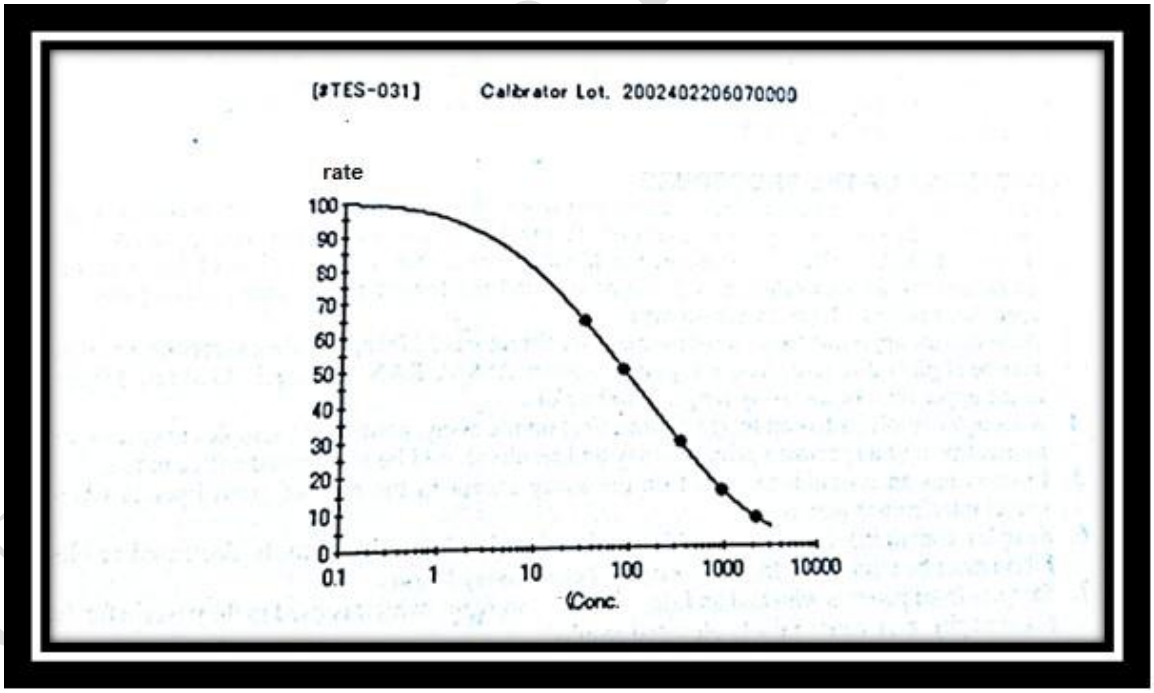

Figure (2): Testosterone calibration curve ***(Barnard et al., 2021; Tng and Tan, 2021).***

b) Calibration procedure

1. Calibration lot and concentration numbers were verified and correctly entered the software

2. ZERO CALIBRATOR for AIA-PRL and Testosterone were provided ready for use. TOSOH recommends that all calibrators be run in triplicate.

iii. <u>POSITIVE CALIBRATOR for AIA-PRL was lyophilized</u>

It was reconstituted with 1.0 mL of CAP Class I or NCCLS Type I Reagent Grade water. Quality control procedure:

a) Commercially available controls were run at least once per day. It was recommended that at least two levels of controls, normal and abnormal, be used. Lot number of control material, acceptable limits, and corrective action to be taken if controls did not meet laboratory criteria will be found in a separate quality control document maintained by the laboratory.
b) Quality control procedure: quality control material to be run with this assay was defined by individual laboratory policy.

- ***Procedural notes:***

1. Lyophilized substrate was completely dissolved.
2. Ligand assays performed by the TOSOH AIA System analyzers require that the laboratory use water designated by the College of American Pathologists as Class I or by NCCLS as Type I. Water was tested at least once per month and was free of particulate matter including bacteria. The pH of the water was routinely tested.
3. If a specimen PRL or testosterone concentration was found to be greater than the upper limit of the assay range, 200 ng/mL or 2,000 ng/dL respectively, the specimen was diluted with the AIA-PRL or Testosterone SAMPLE DILUTING SOLUTION and reassayed according to the Assay Procedure:
    a) The recommended dilution for specimens containing greater than 200 ng/mL for prolactin is 1: 10 or 1: 100 so that the diluted specimen reads between 5 and 200 ng/mL for PRL.
    b) The recommended dilution for specimens containing greater than 2,000 ng/dL for testosterone is 1: 3 so that the diluted specimen reads between 200 and 2,000 ng/dL for testosterone.
    c) The dilution factor was entered into the software.

- ***Calculation of results:***

The TOSOH AIA System Analyzers perform all sample and reagent handling operations automatically. The TOSOH AIA System Analyzers read the rate of fluorescence produced by the reaction and automatically convert the rate to prolactin concentration in ng/mL and testosterone concentration in ng/dL.

For samples requiring dilution, the TOSOH AIA System Analyzers automatically perform dilution and calculate results if the dilution factors

were entered into the software. Dilution factors may be entered into the Test File, or pre-defined dilution factors may be selected in Specimen Processing.

Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation by SPSS V.16.

1- Mean value $\left(\bar{X}\right)$:

The sum of all observations divided by the number of observations:

$$\left(\bar{X}\right) = \frac{\Sigma x}{n}$$

Where $\sum$ = sum & n = number of observations.

2- Standard Deviation [SD]:

It measures the degree of scatter of individual varieties around their mean:

$$SD = \sqrt{\frac{\Sigma \left|x - x\right|^{-2}}{n-1}}$$

3- Standard student "t test":

Test of significance of the difference between two means:

$$t = \frac{\bar{X} - \bar{X}_2}{\sqrt{\frac{(SD_1)^2}{n_1} + \frac{(SD_2)^2}{n_2}}}$$

The calculated "t" was compared with tabulated one at different levels of significance at the degree of freedom (DF):

DF = (d + n_2) -*2* Where:

$\bar{X}$ = The mean value of group L.

$\bar{X}_2$ = The mean value of group II.

SD_1 = the standard deviation of group I.

SD_2 = the standard deviation of group II.

n_1 = the number of observations of group L.

n_2 = the number of observations of group II.

RESULTS

The present study included 36 subjects; 26 patients with premature ejaculation (PE patient group) and 10 healthy persons of matched age served as a control group.

The PE patients were further subdivided, according to the type of PE into, **Group I** suffering from primary PE and **Group II** suffering from secondary PE **(Table 1, Figure 3)**.

Clinical Results:

When the ages of the studied subjects were compared between the total PE patient group and the control group, it showed that; the mean age of patient group was 38.96 ±8.22 compared to 37.52 ±7.14 in the control group with no statistical difference in- between (*p*: 0.552) **(Table 2, Figure 4)**.

When the comparison was made between the groups I (primary PE patients), II (secondary PE patients), and control group, it revealed that:

I. Group I:

This group included 15 patients with primary PE **(Table 1, Figure 3)**. Their ages ranged from 26-53 years with a mean value 37.53 ±8.74 **(Table 3, Figure 5)**.

The patients in this group characterized by experiencing PE from the first coitus. Rapid ejaculations became manifest around the first sexual act encountered during puberty or adolescence, and occurred with nearly every sexual act and remained similar throughout life or might aggravate with aging.

II. Group II:

This group included 11 patients with secondary PE **(Table 1, Figure 3)**. Their ages ranged from 32-50 years with a mean value 40.90±7.39 **(Table 3, Figure 5)**.

The patients in this group characterized by having successful coital relationships in the past, yet began experiencing PE. Acquired PE developed after a period of previously normal control of ejaculation.

In this group, six patients were suffering from PE due to organic causes. Five of them had erectile dysfunction (ED), two patients had hypertension and one of them showed hypercholesterolemia. The other five patients had been found to develop PE secondary to psychogenic stress through their lives.

III. Control group:

This group was consisted of 10 normal healthy persons. Their ages ranged from 28-49 years with a mean value 37.52 ±7.14 **(Table 3, Figure 5)**.

The comparison between the total PE patient (groups I and group and the control group, as regard the age, was statistically non-significant (*P*: 0.417) **(Table 3, Figure 5)**, and when the comparison was made separately between the three groups (group I & control, group II & control, and group I & group II) it also revealed statistically non-significant differences with the *p* values 0.152, 0.969, and 0.142 respectively **(Table 3, Figure 5).**

Laboratory Results of Prolactin and Testosterone:

The levels of serum PRL and testosterone were measured in all PE patients (groups I and II) and also in the control group for comparison.

I. Laboratory Results of Serum Prolactin:

When the levels of serum PRL of the studied subjects were compared between the total PE patient group and the control group, it revealed that the levels of serum prolactin in PE patients ranged from 2.5-34.1 with a mean of 10.02 ±9.31 which was slightly higher than that in the control group, where it ranged between 5.1-14 with a mean of 9.31 ±2.69 but with no statistical difference in-between (*p*: 0.224) **(Table 4, Figure 6)**.

When the comparison was made between the serum PRL levels in the primary PE, secondary PE and control groups, the results revealed that in group I (primary PE patients) the mean level of PRL was 9.84 ±3.88, while in group II (secondary PE patients) the mean level was 10.26 ±4.36, and in the control group it was 9.31 ±2.69 **(Table 5, Figure 7)**.

The mean levels of serum prolactin in total PE patient group (groups I and II) were slightly higher than that in the control group but with no significant statistical difference (*p*: >0.05) **(Table 5, Figure 7)**.

Also, the comparisons between the three groups (group I& control, group II & control, and group I & group II) were statistically non-significant with the *p* values 0.636, 0.257, and 0.856 respectively **(Table 5, Figure 7)**.

II. Laboratory Results of Serum Testosterone:

When the levels of serum testosterone of the studied subjects were compared between the total PE patient group and the control group, it revealed that the levels of serum testosterone in PE patients ranged from 152.1-706.8 with a mean of 419.5 ±160.1 which was lower than that in the control group, where it ranged between 344.2-811.1 with a mean of 610.4 ±158.5 with significant statistical difference in-between (*p*: 0.002) **(Table 6, Figure 8)**.

When the comparison was made between the serum testosterone levels in the primary PE, secondary PE and control groups, the results

revealed that in group I (primary PE patients) the mean level of testosterone was 435.8 ±160.6, while in group II (secondary PE patients) the mean level was 397.4 ±164.3, and in the control group it was 610.4±158.5 **(Table 7, Figure 9)**.

The comparison between serum testosterone levels between total PE patient group (groups I and II) and control group was statistically significant (*p*: 0.005), and when the comparisons between the three groups (group I & control, group II & control, and group I & group II) were made, it revealed a significant statistically difference between group I and the control group (*p*: 0.003) which became highly significant when the comparison was made between group II and the control group (*p*: 0.001) and group I and group II (*p*: 0.001) meaning that the serum testosterone levels were significantly lower in the primary PE patients than in the control group and were more lower in the secondary PE patients than both the control and primary PE patients **(Table 7, Figure 9)**.

Table (1): Comparison between primary (Group I) and secondary (Group II) premature ejaculation patients as regard the number of the patients

Type of premature ejaculation	N	%
Group I (Primary PE)	15	57.7
Group II (Secondary PE)	11	42.3
Total	**26**	**100.0**
X2	**1.325**	
P. Value	**0.156**	

P > 0.05: non-significant.

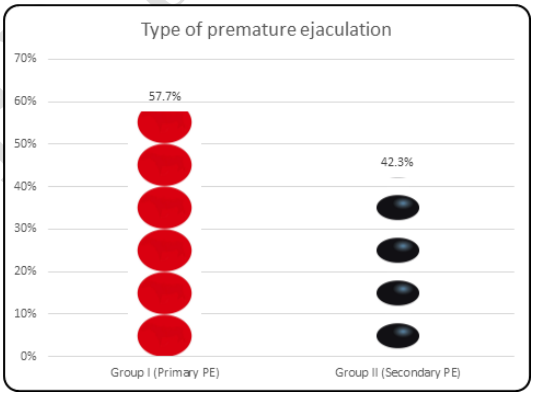

Figure (3): Comparison between primary (Group I) and secondary (Group II) premature ejaculation patients as regard the number of the patients.

Table (2): Comparison between total PE patient group and control group as regard age

	Age	
	PE patient group	**Control group**

Range	26-53	28-49
Mean	38.96	37.52
±SD	8.22	7.14
t. test	**0.639**	
p. value	**0.552**	

PE: premature ejaculation
P > 0.05: non-significant.

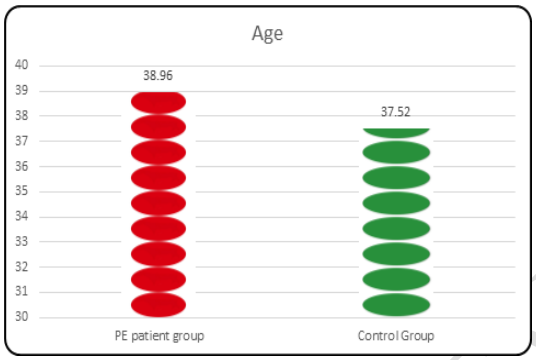

Figure (4): Comparison between total PE patient group and control group as regard age.

Table (3): Comparison between each of primary PE patients (Group I), secondary PE patients (Group II) and the control group as regard age

Age	**PE patient group**		**Control Group**
	Group I (Primary PE)	**Group II (Secondary PE)**	
Range	26-53	32-50	28-49
Mean	37.53	40.90	37.52
±SD	8.74	7.39	7.14
f. test	**1.325**		
p. value	**0.417**		
Group I & Control group	**Group II & Control group**		**Group I & Group II**
0.152	**0.969**		**0.142**

P > 0.05: non-significant.

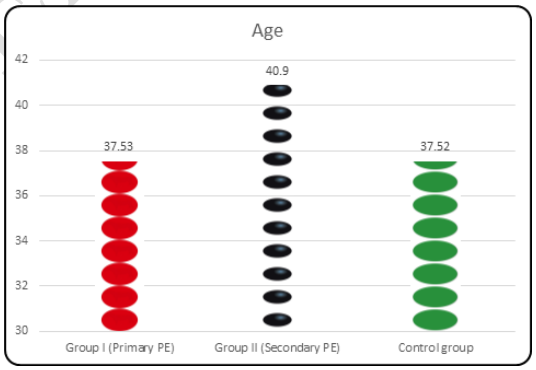

Figure (5): Comparison between each of primary PE patients (Group I), secondary PE patients (Group II) and the control group as regard age.

Table (4): Comparison between total PE patients group and the control group as regard serum prolactin level

	Prolactin level	
	PE patient group	**Control group**
Range	2.5-34.1	5.1-14
Mean	10.02	9.31
±SD	9.31	2.69
t. test	**1.362**	
p. value	**0.224**	

P > 0.05: non-significant.

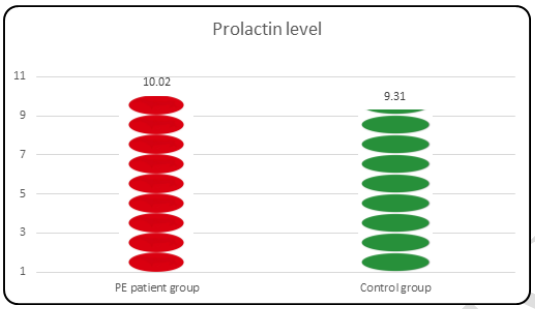

Figure (6): Comparison between total PE patient group and the control group as regard serum prolactin level.

Table (5): Comparison between each of primary PE patients (Group I), secondary PE patients (Group II) and the control group as regard serum prolactin level

Prolactin level	**PE patient group**		**Control Group**
	Group I (Primary PE)	**Group II (Secondary PE)**	
Range	2.5-21.3	3.4-34.1	5.1-14
Mean	9.84	10.26	9.31
±SD	3.88	4.36	2.69
t. test	**2.114**		
p. value	**0.745**		
P value			
Group I & Control group	**Group II & Control group**		**Group I & Group II**
0.636	**0.257**		**0.856**

P > 0.05: non-significant.

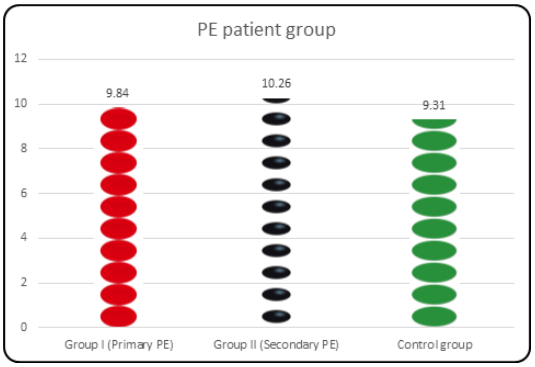

Figure (7): Comparison between each of primary PE patients (Group I), secondary PE patients (Group II) and the control group as regard serum prolactin level.

Table (6): Comparison between total PE patient group and the control group as regard serum testosterone level

	Testosterone level	
	PE patient group	**Control Group**
Range	152.1-706.8	344.2-811.1
Mean	419.5	610.4
±SD	160.1	158.5
t. test	**10.325**	
p. value	**0.002***	

*: significant.

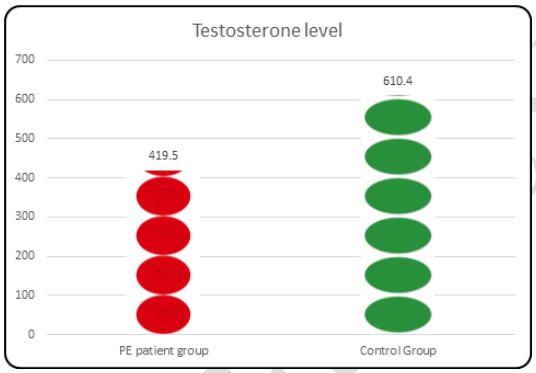

Figure (8): Comparison between total PE patient group and the control group as regard serum testosterone level.

Table (7): Comparison between each of primary PE patients (Group I), secondary PE patients (Group II) and the control group as regard serum testosterone level

Testosterone level	**PE patient group**		**Control group**
	Group I (Primary PE)	**Group II (Secondary PE)**	
Range	152.1-706.8	159-652	344.2-811.1
Mean	435.8	397.4	610.4
±SD	160.6	164.3	158.5
f. test	**3.745**		
p. value	**0.005***		
Group I & Control group	**Group II & Control group**		**Group I & Group II**
0.003*	**0.001****		**0.001****

*: significant.
**: highly significant.

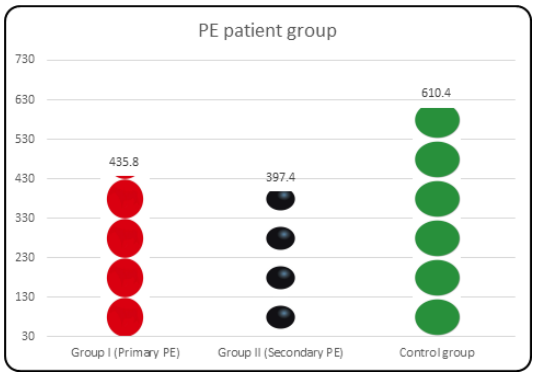

Figure (9): Comparison between each of primary PE patients (Group I), secondary PE patients (Group II) and the control group as regard serum testosterone level.

DISCUSSION

"Premature ejaculation is defined as the ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration with inability to delay ejaculation on all, or nearly all, vaginal penetrations followed by negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy" ***(Ayribas and Toprak, 2021).***

PE is the most common male sexual disorder ***(Corona, 2022).*** **"**It is a frequently encountered type of male sexual dysfunction; although its incidence varies according to the criteria used for its definition. It usually ranges between 20 and 38%, of the male population which is affected by PE at any one time, in different studies" ***(El-Hamd et al., 2019).*** Apart from erectile dysfunction, it is known to affect adult males in all age groups at similar rates ***(Saleh et al., 2021).***

PE has been classified into two types; primary and secondary with different etiological theories and prognosis ***(Schapiro, 1943).*** **"The primary (lifelong) type** is characterized by experiencing PE from the first sexual act encountered during puberty or adolescence. This condition may lead to secondary psychological, sexual or interpersonal relationship problems" ***(El-Hamd et al., 2019).*** **The secondary (acquired) PE** is defined when the patient had successful coital relationships in the past, yet began experiencing PE ***(Althof et al., 2022).***

There are many theories tried to explain the etiology of primary PE. The main big titles are the psychological and the biological theories ***(Gillman and Gillman, 2019).*** On the other hand, many factors may contribute in the occurrence of secondary PE as: prostatitis and urethritis, erectile dysfunction, cardiovascular, endocrinal, neurological diseases and iatrogenic ***(Martin-Tuite and Shindel, 2020).***

"Although many etiologic factors have been blamed for PE occurrence, influential factors have not yet been clearly revealed" ***(Sansone et al., 2021; Tannenbaum et al., 2022).*** Evidence suggesting a potential role of hormonal disorders has been accumulating with increasing frequency.

In ***2020, Ribi et al.*** examined "patients with sexual dysfunction and demonstrated the presence of an association between hyperprolactinemia and PE". In ***2022, Mazzilli et al.*** observed "higher testosterone، and lower PRL and thyroid stimulating hormone (TSH) levels, in men with PE compared with men with other sexual dysfunction". ***Tannenbaum et al. (2022),*** detected "hyperprolactinemia in a significantly higher number of patients with PE relative to the control group".

Although "the mechanisms of sexual dysfunction in cases with hyperprolactinemia have not been fully elucidated, conceivably hypogonadism is frequently seen in those patients, and at least in some of them hypogonadism is responsible for sexual dysfunction" ***(Corona et al., 2023).***

"Hypogonadism was frequently observed in cases with hyperprolactinemia and is generally associated with delayed rather than PE. The reported cases of hyperprolactinaemia in PE patients suggest the presence of another mechanism playing a role in the etiology of PE" ***(Tannenbaum et al., 2022).***

The aim of this work was to evaluate the contribution of PRL and testosterone in the pathogenesis of PE.

To accomplish this aim, 36 subjects were included in this study; 26 patients with PE (total PE patient group) and 10 healthy persons of matched age served as a control group. The PE patients were further subdivided, according to the type of PE into, **Group I** formed of 15 patients suffering from primary PE and **Group II** formed of 11 patients suffering from secondary PE.

As regard the age, the difference between total PE patient group and control group as well as the differences in-between group I (primary PE patients), group II (secondary PE patients) and control group were statistically not significant ($p>0.05$).

These results agree with the reported age of incidence for PE in the literature where it affects adult males in all age groups at similar rates ***(Verze et al., 2018; Abu El-Hamd and Farah, 2018).*** The mean age of group II (secondary PE patients) was higher than that of group I (primary PE patients), and this agrees with ***Culha et al. (2020) & Ayribas and Toprak (2021),*** who reported that men with secondary PE were more often of older age than those of primary PE.

This can be explained relayed on the etiological factors contributing in the occurrence of secondary PE as prostatitis, urethritis, cardiovascular, endocrinal and neurological diseases that are usually occurring in older ages leading to higher mean age for patients suffering from secondary PE than those suffering from primary PE.

Regarding the type of PE in the current study, the reported incidence of primary PE (group I, 15 patients, 57.7%) was higher than that of the secondary PE (group II, 11 patients, 42.3%), but the difference between both of them regarding the number of patients was statistically not significant ($p>0.05$).

These findings go with ***Culha et al. (2020)*** who reported higher incidence of primary PE among patients seeking treatment for PE than those suffering from secondary PE. However, **these findings** go against the studies carried out by ***Culha et al. (2020); Ayribas and Toprak (2021) & Coskuner and Ozkan (2022),*** where they reported higher incidence of secondary PE than primary PE.

The higher incidence of primary PE in the current study can be explained by more awareness and concern about the PE problem in patients with primary PE as it makes more trouble in early marriage than in cases of secondary PE where the couple can find excuses for a while before seeking for medical advice. Also, the small number of the studied group (26 patients) can not give true incidence about the disease.

The mean level of serum prolactin, in the total PE patient group, was slightly higher than that in the control group with no statistical difference in-between (p>0.05). Also, the mean levels of serum PRL in group I (primary PE patients) and group II (secondary PE patients) were slightly higher than that in the control group with no statistical difference in-between (p>0.05).

The mean level of serum PRL in group II (secondary PE patients) was slightly higher than that in group I (primary PE patients) with no statistical difference in-between (p>0.05).

Such observation was similarly reported by ***Abu El-Hamd and Farah (2018) & Abu El-Hamd and Farah (2018)*** who reported no significant difference between PE patients and control subjects as regard the serum PRL levels.

Elevation in serum prolactin in primary PE patients (group I) was reported by ***Lehtimäki et al. (2021)***. They reported increase in serum prolactin among primary PE patients than in control group, but within the normal range, and speculated that these higher prolactin levels might be the result, not the cause, of the loss of ejaculatory control in patients because of the presence of an elevated anxiety trait.

The results obtained in this study are on the contrary of those reported by ***Ribi et al. (2020) & Tannenbaum et al., (2022)*** who reported positive correlation between PE and PRL proposing PRL as a significant predictor for PE. They detected hyperprolactinemia in a significantly higher number of PE patients relative to the control group and referred that the reported hyperprolactinemia associated with hypogonadism, were responsible for this sexual dysfunction. In their studies, the mean testosterone levels in hyperprolactinemic patients were found to be

statistically significantly lower than those with normal PRL levels (control group), although hypogonadism is generally

associated with delayed rather than PE, and speculated that another mechanism may be playing a role in the etiology of PE.

Also, the results of this study are not in agreement with ***Javaroni (2021)*** who reported that serum PRL levels progressively increased from patients with severe PE towards those with anejaculation.

According to ***Waldinger's et al. (1998)*** **"**neurobiological hypothesis, a disturbance in the central serotonin pathway (serotonin-2C receptor hyposensitivity and/or serotonin-1A receptor hypersensitivity) has been advocated as a possible cause of primary PE. The serotonergic system acts, at the hypothalamic level, as a suppressor of the ejaculatory reflex. Accordingly, both selective serotonin reuptake inhibitors (SSRIs) and serotonin agonists determine the extension of ejaculatory latency". Later on, this was confirmed by ***Corona et al. (2006)***, who provided the first clinical finding apparently in consistence with ***Waldinger's et al.*** hypothesis ***(Wu et al., 2021).***

In the present study the same results cannot be detected may be because of the serotonergic central changes, mirrored by low prolactin levels in both primary and secondary PE, that can be a consequence, and not a cause, of the absence of ejaculatory control. "In fact, many psychological disturbances, such as stress and frustration for chronic or acquired inability to enjoy sex, are able to provoke a neuroendocrine imbalance, and this is proved by the therapeutic effectiveness of serotonergic antidepressants demonstrated in both primary and secondary PE" ***(Pai et al., 2021; Lehtimäki et al., 2021).*** Besides, we did not include patients with delayed ejaculation to compare with.

In the current study there was slight increase in the mean level of serum PRL in group II (secondary PE patients) than in group I (primary PE patients) and it could be speculated that even secondary causes of PE would act mainly via influencing the central serotonergic system ***(Pai et al., 2021).***

These variations in the PRL levels among PE patients in different studies can be explained according to ***Javaroni (2021),*** as "PE and delayed ejaculation can be considered as two ends of a single continuum, spanning from severe PE to extreme delayed ejaculation, and the endocrine milieu influences the ejaculatory process, by affecting its overall latency. In particular, three hormones; testosterone, PRL and TSH, significantly and independently contribute to reported intravaginal ejaculation latency time (IELT) variation in subjects complaining of sexual dysfunction. PRL as well

as TSH levels progressively increased from patients with severe PE towards those with anejaculation".

As regard the mean level of serum testosterone, it was significantly lower in the total PE patient group than that in the control group (*p*: 0.002). Also, the mean level of serum testosterone in group I (primary PE patients) was significantly lower than that in the control group (*p*: 0.003).

The data collected from group II (secondary PE patients) revealed that the mean serum testosterone in this group was more lower than that in the control group and group I and the differences in-between them were statistically highly significant (*p*: 0.001) in both comparisons.

These results are in agreement with ***Tannenbaum et al. (2022)*** who reported hypotestosteronemia in some cases of PE with no statistical significant and recommended evaluating levels of bioavailable testosterone for more knowledge, but these results are against that of ***Abu El-Hamd and Farah (2018); Hosseini et al. (2019) & Javaroni (2021);*** who reported no significant difference in serum testosterone levels between PE patients and control group, but reported higher free testosterone levels in PE patients which were not measured in this study.

Also, the results of this study are on the contrary of ***Mazzilli et al. (2022)*** who reported serum testosterone levels progressively decrease from patients with severe PE towards those with anejaculation.

Some hypotheses were speculated to explain association between testosterone levels and ejaculation by both central and peripheral mechanisms ***(Cinislioglu et al., 2023).*** **The first explanation** is **neurological**. According to ***Waldinger's et al. (1998)*** neurobiological hypothesis, a disturbance in the central serotonin pathway **[**5-hydroxytryptamine (5-HT) 2C receptor hyposensitivity and/or 5-HT1A receptor hypersensitivity**]** has been advocated as a possible cause of primary PE ***(Mohd Mutalip et al., 2018; Mazzilli et al., 2022; Cinislioglu et al., 2023).*** It is well known that 5-HT is the most important central neurotransmitter involved in delaying ejaculation and SSRIs are the most used drugs for the treatment of PE ***(Mohd Mutalip et al., 2018).*** Another explanatory option is about a possible **peripheral role of testosterone in regulating male genitalia tract motility** through nitric oxide (NO) synthase activity and type 5 phosphodiesterase (PDE5) expression which are the most important factors involved in the contractility of male genital tract as vas deferens and ejaculatory ducts that, under testosterone control, are critical effectors for semen emission and ejaculation ***(Dimitriadis et al., 2018; Mazzilli et al., 2022; Cinislioglu et al., 2023).***

Another theory through a **"mechanical" mechanism** of testosterone action on the ejaculatory control, asserts that decrease in ejaculate volume

due to lower testosterone levels delays the onset of ejaculatory reflex leading to prolonged ejaculation latency ***(Mazzilli et al., 2022; Cinislioglu et al., 2023).***

These variations in the testosterone levels among PE patients in different studies can be explained as low serum testosterone levels have been inconsistently associated with PE. However, it is a constant finding in cases of delayed ejaculation ***(Mazzilli et al., 2022; Tannenbaum et al., 2022; Cinislioglu et al., 2023).*** Again, according to ***Javaroni (2021),*** **"**PE and delayed ejaculation can be considered as two ends of a single continuum, spanning from severe PE to extreme delayed ejaculation, and the endocrine milieu influences the ejaculatory process, by affecting its overall latency". "In particular, three hormones; testosterone, PRL and TSH, significantly and independently contribute to reported IELT variation in subjects complaining of sexual dysfunction. Testosterone levels progressively decreased from patients with severe PE towards those with anejaculation. Besides that, the possibility of other co-morbid conditions or other sexual dysfunctions might interfere with ejaculatory latency cannot be excluded in this study. However, another theory has been proposed. Accordingly, an aggressive, dominant and irritable way of conduct triggered by higher testosterone levels might lead to PE" ***(Carré and Archer, 2018; Mazzilli et al., 2022).***

As regarding the serum testosterone levels in primary PE patients (group I), the mean level was significantly lower than that in the control group (*p*: 0.003). **These findings** agree with ***Culha et al. (2020)*** who reported significant hormonal disorders among primary PE patients. However, they did not define in their study the type of these hormonal disorders either increased or decreased. **On the contrary, *Lehtimäki et al. (2021)*** reported no significant difference in serum testosterone levels between primary PE patients and control group.

This difference in the results may be attributed to the new concepts in the pathogenesis of primary PE which is currently thought to be primarily of neurobiological, genetic and psychological origin more than endocrinal which is thought to be a high risk factor in secondary PE ***(Rowland et al., 2022; Cinislioglu et al., 2023).***

As regard the serum testosterone levels in secondary PE patients (group II), there were highly significant decrease in serum testosterone than that in group I (primary PE patients) and control group.

These results are going forward with those of ***Colonnello et al. (2021)*** who noticed higher prevalence of hormonal changes among patients with secondary PE. The endocrinal disorders in secondary PE are thought to be a high risk factor ***(Cinislioglu et al., 2023).***

Testosterone has positive effects on erection, mediated not only by central stimulation of libido and sexual activity, but also by direct effects on the penis. Impaired erectile function is a classical symptom of hypogonadism which is corrected by testosterone replacement therapy ***(Onyeji and Clavijo, 2022).*** Also, nearly all chronic diseases, particularly those of the liver, kidneys and cardiovascular system, as well as stress, anesthesia and certain medications (e.g., ketoconazole) can prompt a decrease in testosterone levels ***(Salonia et al., 2021).***

In group II (secondary PE patients), six patients were suffering from PE due to organic causes. Five of them had erectile dysfunction, two patients had hypertension and one of them showed hypercholesterolemia. The other five patients had been found to develop PE secondary to psychogenic stress through their lives. All these causes may contribute to the higher significant decrease in serum testosterone in this group than group I (primary PE patients) and control group.

"Serum testosterone levels, especially free testosterone, decrease with age. It is not clear whether such age-related decrease is physiological or caused by multimorbidity. But when serum testosterone levels are below the lower cutoff of the young adult range, they may be associated with symptoms of hypogonadism requiring clinical attention. For the time being, no separate reference range for the aging men exists. However, evidences are accumulating that there is no one threshold spate between normal and pathological, but that there are symptom-specific thresholds for the various signs of hypogonadism in aging as well as in younger men" ***(Sonnweber et al., 2022; Meyer and Wittert, 2018).***

The mean age of secondary PE patients (group II) was 40.90±7.39, while it was 37.53 ±8.74 in primary PE patients (group I) and 37.52 ±7.14 in control group. This high age in group II may contribute to the higher significant decrease in serum testosterone in this group than group I (primary PE patients) and control group.

"It is important to understand, as far as possible, the etiology in each individual patient to ensure appropriate assessment and treatment. However, identification of an etiological factor does not necessarily mean that the cause of the PE has been completely explained, and the patient may require a combination of treatment approaches. Further studies are warranted to further elucidate the etiology of a primary and secondary PE" ***(Yusof et al., 2018).***

"Endocrinopathy is not rare among patients with sexual dysfunction" ***(Ribi et al., 2020). "***Hormones do affect an individual's sexuality throughout his life (and even in the early phases of fetal life). However, hormonal

mechanisms involving sexual function، and dysfunction, and their degree of impact have not been fully elucidated. Investigation and revealment of hormonal disorders (if any) in patients with sexual dysfunction is important, as among patients with sexual dysfunction، these cases respond to treatment more favorably. In most of the cases, sexual dysfunction also resolves with no further treatment when the hormonal abnormality is corrected" ***(Tannenbaum et al., 2022).***

"Endocrine therapies are widely available and very effective in treating the cognate underlying conditions. It is possible that endocrine therapy of ejaculatory disorders, whenever indicated, ameliorates not only

sexual life but also the overall health of our patients, as could be the case for thyroid or testis disorders" ***(Javaroni, 2021).***

This study through light on that the endocrine system is involved in the control of ejaculatory function and that prolactin and testosterone play an independent role. Although endocrine regulation of the ejaculatory reflex is still in its early stages, this study indicates that it should grow rapidly to help in shedding light on, often-occurring but seldom-studied, conditions like ejaculatory disturbances ***(Javaroni, 2021).***

"There is an increasing, even gradually, body of evidence suggesting hormonal abnormalities as etiologic factors in PE. Pinpointing the place of hormonal causes in PE will enable us to understand its pathophysiology as well as contribute to the development of new treatment modalities. In patients with sexual dysfunction, requirement of routine hormonal evaluation might be decided based on the cost-effectiveness of this evaluation. It is believed that, in consideration of potential detection of other underlying diseases, alleviation of hormonal problems leading to improvement in sexual dysfunction without any additional therapy in many cases might justify the expense incurred" ***(Tannenbaum et al., 2022).***

The results of this study provide support for investigation of hormonal factors in the etiology of PE and the routine laboratory investigation should be directed at identifying treatable endocrine abnormalities such as hypogonadism and hyperprolactinaemia.

SUMMARY

Premature ejaculation is defined as the ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration with inability to delay ejaculation on all, or nearly all, vaginal penetrations followed by negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy ***(Ayribas and***

Toprak, 2021). It is the most common male sexual disorder and usually ranges between 20 and 38% of the male population which is affected by PE at any one time. It is known to affect adult males in all age groups at similar rates ***(Corona, 2022; El-Hamd et al., 2019; Saleh et al., 2021).***

PE has been classified into two types; primary and secondary with different etiological theories and prognosis ***(Schapiro, 1943).*** The primary (lifelong) type is characterized by experiencing PE from the first sexual act encountered during puberty or adolescence ***(El-Hamd et al., 2019).*** The secondary (acquired) PE is defined when the patient had successful coital relationships in the past, yet began experiencing PE ***(Althof et al., 2022).***

There are psychological and biological theories tried to explain the etiology of primary PE ***(Gillman and Gillman, 2019).*** On the other hand, many factors may contribute in the occurrence of secondary PE as prostatitis and urethritis, erectile dysfunction, cardiovascular, endocrinal, neurological diseases and iatrogenic ***(Martin-Tuite and Shindel, 2020).***

Although many etiologic factors have been blamed for the occurrence of PE, influential factors have not yet been clearly revealed. Evidences suggesting a potential role of hormonal disorders have been accumulating with increasing frequency ***(Sansone et al., 2021; Tannenbaum et al., 2022).***

Hyperprolactinemia was detected in a significantly higher number of PE patients. This positive correlation between PE and PRL proposed the PRL as a significant predictor for PE ***(Tannenbaum et al., 2022).***

Testosterone plays a facilitatory role in the control of ejaculatory reflex through both central and peripheral mechanisms. Although hypogonadism can be considered as a possible cause of delayed ejaculation, low testosterone levels have been inconsistently associated with PE ***(Cinislioglu et al., 2023).***

According to ***Waldinger's et al. (1998)*** neurobiological hypothesis through a disturbance in central serotonin pathway, PE and delayed ejaculation can be considered as two ends of a single continuum, spanning from severe PE to extreme delayed ejaculation, and the endocrine milieu influences the ejaculatory process, by affecting its overall latency. In particular, three hormones; testosterone, PRL and TSH, significantly and independently contribute to reported IELT variation in subjects complaining of sexual dysfunction. PRL as well as TSH levels progressively increased from patients with severe PE towards those with anejaculation, while testosterone levels progressively decreased from patients with severe PE towards those with anejaculation ***(Javaroni, 2021,*** Öztürk et al., 2012***).***

The aim of this work was to evaluate the contribution of PRL and testosterone in the pathogenesis of PE.

To accomplish this aim, 36 subjects were included in this study; 26 patients with PE (total PE patient group) and 10 healthy persons of matched age served as a control group. The PE patients were further subdivided, according to the type of PE into, Group I formed of 15 patients suffering from primary PE and Group II formed of 11 patients suffering from secondary PE ejaculation. All of them were subjected to venous blood samples taking for laboratory investigation of serum total testosterone and PRL.

The results of this study showed that:

- The mean level of serum PRL in the total PE patient group was slightly higher than that in the control group with no statistical difference in-between.
- The mean levels of serum PRL in primary PE patients (Group I) and secondary PE patients (Group II) were slightly higher than that in the control group with no statistical difference in-between. The mean level of serum PRL in group II (secondary PE patients) was slightly higher than that in group I (primary PE patients) with no statistical difference in-between.
- The mean level of serum testosterone was significantly lower in the total PE patient group than that in the control group.
- The mean level of serum testosterone in primary PE patients (Group I) was significantly lower than that in the control group, and the mean serum testosterone in secondary PE patients (Group II was more lower than that in both of the control group and primary PE patients (Group I) with statistically highly significant differences in-between them in both comparisons.

Conclusion:

From this study it can be concluded that;

Hormones play central role in the machinery of emission- ejaculation. This implies not only that pathological hormonal levels may directly or indirectly affect the ejaculatory control, but may also be affected or simply modified by the condition of PEs as endocrinopathy is not rare among patients with sexual dysfunction.

The endocrine milieu influences the ejaculatory process, by affecting its overall latency. In particular, PRL and testosterone, significantly and independently contribute to the reported short IELT in subjects complaining of PE.

PRL level seems to progressively increase from patients with severe PE towards those with anejaculation, while testosterone levels progressively decreased from patients with severe PE towards those with anejaculation.

The pathogenesis of primary PE is currently thought to be primarily of neurobiological, genetic and psychological origin more than endocrinal which is thought to be a high-risk factor in secondary PE.

Consent

As per international standard, parental written consent has been collected and preserved by the author(s).

Ethical Approval:

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

RECOMMENDATIONS

This study provides support for investigation of hormonal factors in the etiology of PE and detection of other underlying endocrinal diseases. Routine laboratory investigation should be directed at identifying treatable endocrine abnormalities such as hypogonadism and hyperprolactinaemia as alleviation of the hormonal problems may lead to improvement in sexual dysfunction without any additional therapy.

It is recommended to routinely investigate and evaluate endocrinal condition in secondary PE patients especially testosterone serum levels that is thought to be a high-risk factor in secondary PE.

PRL mirrors the central serotonin tone disturbance that has been advocated as a possible cause of primary PE. Measuring serum PRL can identify those who are at risk of developing PE and may be used as a prognostic factor in measuring efficacy of SSRIs in correcting ejaculatory disturbance by normalizing serum PRL level.

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List of Abbreviations

Abb.	Full term
5-HT	*5-Hydroxytryptamine*
AIA	*Automated immune assay*

FSH**.....** *Follicle-stimulating hormone*
IELT **.....** *Intravaginal ejaculation latency time*
LH**.....** *Luteinizing hormone*
PE **.....** *Premature ejaculation*
PRL**.....** *Prolactin*
SSRI**.....** *Selective serotonin reuptake inhibitor*
TSH**……** *Thyroid stimulating hormone*