# ORIGINAL ARTICLE

## Role of tadalafil in erectile dysfunction

**Ali Mohamed Younis [1], Mohamed Amer Ahmed Abdellatif [1,] Mohammed Abu El-Hamd [2], Abdallah Mahmoud El-Ebidi [3], Salah Mohamed Ali Maklad [4], Essam El-Din Abdel-Aziz Nada [2], Moustafa Adam Ali El Taieb [1]**

[1] Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Aswan University

[2] Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Sohag University

[3] Department of Biochemistry, Faculty of Medicine, Aswan University

[4] Department of Radiology, Faculty of Medicine, Aswan University

### ABSTRACT

Keywords: Tadalafil; erectile dysfunction (ED).

*Corresponding author: Mohamed Amer Ahmed Abdellatif

Mobile. 01060394083

e-mail: mohammed.abdellatif@med.aswu.edu.eg

**Background:** tadalafil is PDE-5 inhibitor which helps to maintain the erection by enhancing the vasodilatory effects of endogenous nitric oxide. Tadalafil has a long half-life, which gives men the option of taking it up to 12 hours before sex. **Aim**: To assess the effect of daily oral tadalafil 5mg for 3 months on erectile dysfunction. **Patients and Methods:** A case controle study involved 30 patients ED and 30 age matched controle persons. Appropriate clinical history and relevant laboratory findings (total testosterone), answering practical questionnaires that is administered in the international Index of Erectile Function (IIEF)-5 and intracorboreal injection (ICI) of 5 to 20 mg of alprostadil to asses degree of erection. **Results** We found that patients had significantly ($p < 0.001$) lower levels of testosterone (4.7 ± 0.4 ng/dl) compared with controls (5.9 ± 0.2 ng/dl) with significant ($p = 0.002$) increase in the levels of testosterone after treatment (8.3 ± 1.0 ng/dl) compared with before treatment (4.7 ± 0.4 ng/dl), significant increase in degree of erection by ICI after treatment( p value < 0.001) and significant increase of IIEF-5 from 12.67 ± 4.2 to20.53 ± 2.2 after treatment ( p value < 0.001). **Conclusion:** Oral daily tadalafil 5mg for 3 months is considered an effective treatment for ED.

### INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to obtain or maintain penile erection sufficient for a satisfactory sexual performance. In ED etiology, the vascular component is dominant in favour of psychogenic factors. [1]

**Incidence**: The incidence of ED increases with age, and data from the International Consultation Committee showed the prevalence of ED were 1–10% in men younger than 40 years and 2%–9% in men between the ages of 40 and 49 years. It increases to 20–40% in men aged 60–69 years and 50%–100% in men older than 70 years**.** [2]

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

ED can be a manifestation of peripheral atherosclerosis and a potential early sign of coronary disease, with which it shares common risk factors such as obesity, smoking, dyslipidemia, and metabolic syndrome .[3]

Several pathological conditions that affect the blood vessels, such as atherosclerosis, can lead to vasculogenic ED through the important role that endothelial cells play in vascular homeostasis. [3]

Deregulated release of vasodilatation stimulating factors from endothelium is referred as to endothelial dysfunction which can increase the risk of vascular events. Next to the traditional risk factors of age, BMI, and smoking, emerging risk factors have been proposed as predictors for cardiovascular disease as well as ED .[4]

Diabetes mellitus (DM) is a complex disease characterized by chronic hyperglycemia, metabolic abnormalities, and long-term macro- and micro- vascular complications involving the blood vessels, eyes, kidneys and nerves. [5]

ED is a frequent comorbidity in men with DM and it is frequently overlooked in the routine clinical evaluation. The prevalence of ED among diabetic men varies from 35% to 90%.[6]

Oral Phosphodiesterase inhibitors-5 (PDE-5) inhibitors are first-line treatments for ED.[7]

Sexual stimulation is needed to produce an erection; the PDE-5 inhibitor helps to maintain the erection by enhancing the vasodilatory effects of endogenous nitric oxide. Four PDE-5 inhibitors with similar effectiveness and safety profiles are currently approved by the U.S. Food and Drug Administration (FDA) for treatment of ED: avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) .[8]

All are effective within about one hour of dosing and are typically used on an as-needed basis. The effects may be delayed or decreased if the patient has recently eaten a fatty meal, particularly for sildenafil and vardenafil .[9]

PDE-5 inhibitors are ineffective in some men, particularly those with severe ED. Headache, flushing, and dyspepsia is common adverse effects. PDE-5 inhibitors are contraindicated in men using nitroglycerin or other nitrates because of the risk of catastrophic low blood pressure. Tadalafil has a longer half-life, which gives men the option of taking it up to 12 hours before sex or as a lower-dose, once-daily medication; however, adverse effects also last longer. Vardenafil is available as a 10-mg oral disintegrating tablet. Insurance coverage for these medications is limited, and prescriptions may require prior authorization.[10]

## PATIENTS AND METHODS

After the approval of our ethical committee and written informed consent from all participants, the study included 30 patients complaining from ED and 30 age matching healthy control males; who attending the Outpatient clinic of Dermatology, Venereology and Andrology, Aswan University Hospital, Aswan University, during the period from April 2018 and Marsh 2021. After taking detailed history from each participant in our study, complete clinical examination was done.

Laboratory assessment: Total testosterone level.

Inclusion criteria:

- Patients with ED

Exclusion criteria:

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

- Patients with history of pelvic trauma.
- Patients with major pelvic surgical intervention.
- Patients with hypogonadism and hyperprolactinemia.
- Patients with chronic liver disease.
- Patients with cardiovascular system diseases**.**
- History of chronic intake of central nervous system, anti androgen drugs or other drugs as tramadol.
- Smokers.
- Patients with non-vasculogenic ED.
- Any blood diseases as hemophilia, purpura and anemia.

**All patients were assessed by:**

- Detailed history of medical diseases as renal, hepatic and cardiac diseases and history of previous surgical operations, family history and sexual history.
- Consent from the patient.
- Answer practical questionnaires that is administered in the international Index of Erectile Function (IIEF)-5 . [11]
- Medical examination included general and local examination.
- Total testosterone estimation before and after treatment.

**Statistical analysis:**

The statistical analysis was done via statistical package for social sciences (SPSS) version 22 (SPSS Inc, Chicago, USA). For qualitative data, frequency and percent distributions was calculated.

**RESULTS**

The current study included 60 participants (30 diabetic patients with ED and 30 age-matched healthy men). **Table 1** described the baseline demographic/laboratory characteristics of the studied participants.

Patients had significantly ($p < 0.001$) lower levels of testosterone ($4.7 \pm 0.4$ ng/dl) compared with controls ($5.9 \pm 0.2$ ng/dl). **(Table 1) (Figure 1)**.

**Table 2** shows the effects of treatment on total testosterone level there was significant ($p = 0.002$) increase in the levels of testosterone after treatment ($8.3 \pm 1.0$ ng/dl) compared with before treatment ($4.7 \pm 0.4$ ng/dl) **(Fig. 2)**.

Notable increase in the level of testosterone was observed after treatment (3.3 ng/dl), this represented 104% improvement in the testosterone level.

There was significant ($p < 0.001$) improvement in the level of erection after treatment. The rate of E1 and E2 was decreased from 53.3% to 3.3%. Likewise, the rate of E3-E5 was increased from 46.7% to 96.7% **(Table 3).**

Using IIEF-5 Categories; there was significant improvement after treatment ($p < 0.001$) i.e., about 43% converted to normal vs. 0% before treatment, 0% became severe ED vs 23% before treatment and those

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

with mild to moderate represented only 57% after treatment compared with 77% before treatment **(Table 4)** and **(Fig 3).**

In our study there was a significant increase in penile erection degree after ICI with 1ml psotaglandin E2. The rate of E1 and E2 was decreased from 53.3% to 3.3%. Likewise, the rate of E3-E5 was increased from 46.7% to 96.7%. There was a singnificant increase in duration of erection after treatment.

**Fig. 1: Mean testosterone level in patients vs. controls.**

**Fig 2: Effect of treatment on the level of testosterone among patients**

**Fig. 3: Effect of treatment on the IIEF-5 score among patients.**

## DISCUSSION

The current study aimed to assess effect of treatment with daily tadalafil 5mg for 3 months on ED and total testosterone level.

This study showed a significant decrease in serum total testosterone level in diabetic patients with ED than healthy controls subjects with a significant increase in serum total testosterone level after treatment, this represented 104% improvement**.**

It has been recorded that erection is clearly androgen-dependent, as evidenced by the observation that men with marked hypogonadism have a marked reduction in the frequency, amplitude, and rigidity of erections. However, the level of hypogonadism required to induce this ED is debatable**.** [12]

**Nelson et al.**[13] founded a high prevalence of low serum testosterone in men with diabetes.

In agreement with our study, **Dhindsa et al.** [14] founded a significant decrease in serum testosterone level in diabetic men.

In agreement with our study, **Ozcan et al.** [15] founded a significant increase in total testosterone levels after treatment of patients with ED and metabolic syndrome with oral tadalafil 5mg daily for three months.

While **Matsukawa et al.** [16] showed insignificant increase in total testosterone levels after daily oral tadalafil supplementation for 12 months.

The difference in results in this study from our study may be attributed to the difference in treatment duration as in **Matsukawa et al.**[16] study the treatment duration was 12 months compared to 3 months in our study, also different mean age with 69.8 ± 7.5 years in **Matsukawa et al.**[16] study compared to 53.17 ± 7.8 years in our study, in our study all patients are diabetic but in **Matsukawa et al.**[16] study diabetes mellitus is not inclusion criteria and number of cases is 69 in **Matsukawa et al.**[16] study compared to 30 cases in our study.

PDE5 is abundantly expressed in the rat Leydig and peritubular cells, and administration of sildenafil to rats stimulates the expression of steroidogenic mechanisms behind this increase in serum testosterone levels**.** [17]

Similarly, **Spitzer et al.** [18] determined the effects of sildenafil administration on the hypothalamic-pituitary-gonadal axis in men with ED and low testosterone levels. According to this study, sildenafil administration was associated with increased TT levels likely attributable to a direct effect on the testis**.**

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

In another study, **Carosa et al.** [19] showed that men with ED who reported improvement in erectile function with PDE5i therapy found similar increases in TT levels.

**Zhang Xi et al.** [20] indicated that surgical castration induced a significant reduction of PDE5 gene of the rat corpus cavernosum and that tadalafil treatment was ineffective in ameliorating the electro-stimulation response in castrated rats.

They concluded that testosterone positively regulated PDE5 expression and in vivo responsiveness to tadalafil in the rat corpus cavernosum. Additionally, some articles reported that the expression of PDE5 appeared androgen- dependent in human and testosterone deficiency predicted a poor response to sildenafil, one of the PDE5 inhibitors, in the improvement of erectile function.[21]

In our study there was a significant increase in penile erection degree after ICI with 1ml psotaglandin E2. The rate of E1 and E2 was decreased from 53.3% to 3.3%. Likewise, the rate of E3-E5 was increased from 46.7% to 96.7%. There was a singnificant increase in duration of erection after treatment.

Using IIEF-5 Categories; there was significant improvement after treatment, about 43% converted to normal vs. 0% before treatment, 0% became severe ED vs 23% before treatment and those with mild to moderate represented only 57% after treatment compared with 77% before treatment.

In agreement with our study **Ozcan et al.** [15] showed a significant increase in IIEF after treatment of ED patients with metabolic syndrome with oral tadalafil 5mg daily for three months.

Also in agreement with our results **Porst et al.** [22] founded that treatment with tadalafil vs placebo were significant for the International Index of Erectile Function (IIEF) Erectile Function domain, Intercourse Satisfaction domain, Overall Satisfaction domain, and Question 15 (confidence in the ability to get and keep an erection), and for the Sexual Encounter Profile Questions. Analysis of covariance modeling identified significant treatment for the IIEF-Overall Satisfaction domain and erection confidence question and Sexual Encounter Profile.

## CONCLUSION

serum total testosterone and IIEF-5 significantly decreased in ED patients compared with controls, which are significantly increased after daily treatment with oral tadalafil 5mg for 3 months.

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

## REFERENCES


1. **Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M and Dimitriadis K (2020).** Microvascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol;18(2):117-124.
2. **Lewis RW, Fugl-Meyer KS and Corona G (2010).** Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med. 2010;7(4 Pt 2):1598–1607.
3. **Zamorano-Leon JJ, Segura A, Lahera V, Rodriguez-Pardo JM, Prieto R, Puigvert A and Lopez-Farre AJ (2018).** Relationship Between Erectile Dysfunction, Diabetes and Dyslipidemia in Hypertensive-Treated Men. Urol J;15(6):370-375.
4. **Verze, P, Margreiter M, Esposito K, Montorsi P and Mulhall J (2015).** The Link Between Cigarette Smoking and Erectile Dysfunction: A Systematic Review. European urology focus; 1(1), 39–46.
5. **Kodiatte TA, Manikyam UK, Rao SB, Jagadish TM, Reddy M, Lingaiah HK and Lakshmaiah V (2012):** Mean Platelet Volume in Type 2 Diabetes Mellitus. Lab Physicians ;29(3):659-663.
6. **Malavige LS and Levy JC (2009):** Erectile dysfunction in diabetes mellitus. J Sex Med;6(5):1232–1247.
7. **Yuan J, Zhang R, Yang Z, Lee J, Liu Y, Tian J, Qin X, Ren Z, Ding H, Chen Q, Mao C and Tang J (2013).** Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. European urology; 63(5), 902–912.
8. **Ückert S, Kuczyk MA and Oelke M (2013).** Phosphodiesterase inhibitors in clinical urology. Expert review of clinical pharmacology;6(3):323-32.
9. **Hawksworth D and Burnett A (2015).** Pharmacotherapeutic management of erectile dysfunction. Clinical Pharmacology & Therapeutics ;98(6):602**.**
10. **Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J and Mishra A (1997).** The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology, 49(6), 822–830.
11. **Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J and Mishra A (1997).** The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology, 49(6), 822–830.
12. **Buena F, Swerdloff, RS, Steiner, BS, Lutchmansingh, Peterson, MA, Pandian, MR, Galmarini M & Bhasin S (1993).** Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. Fertility and sterility, 59(5), 1118–1123.
13. **Nelson Cunha, Leonor Gomes, Diana Martins, Diana Oliveira, Adriana Lages, Mara Ventura, Lúcia Fadiga, Diana Catarino & Francisco Carrilho (2017).** Testosterone levels in men with diabetes mellitus. What relation? Endocrine Abstracts; 49 EP44.
14. **Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A and Dandona P (2004).** Frequent occurrence of hypogonadtropic hypogonadism in type 2 diabetes. J Clin Endocrin Metab; 89: 5462–5468.
15. **Ozcan LE, Polat C, Kocaaslan R, Onen E, Otunctemur A and Ozbek E (2017).** Effects of taking tadalafil 5 mg once daily on erectile function and total testosterone levels in patients with metabolic syndrome. Andrologia;49(9).
16. **Matsukawa Y, Kanada Y, Takai S, Inoue S, Majima T, Funahashi Y, Kato M, Yamamoto T and Gotoh M (2020).** Pre-treatment serum testosterone level can be a useful factor to predict the improvement in bladder outlet obstruction by tadalafil for male patients with lower urinary tract symptoms induced by benign prostatic obstruction. The aging male : the official journal of the International Society for the Study of the Aging Male; 23(5), 641–647.


Submission date: (17/3/2023) - acceptance date: (5/4/2023)

17. **Andric SA, Janjic MM, Stojkov NJ, and Kostic TS (2010).** Sildenafil treatment in vivo stimulates Leydig cell steroidogenesis via the cAMP/ cGMP signaling pathway. Am J Physiol Endocrinol Metab;299(4):E544-50.

**18. Spitzer M, Bhasin S, Travison TG, Davda MN, Stroh H and Basaria S (2013).** Sildenafil increases serum testosterone levels by a direct action on the testes. Andrology;1(6), 913–918.

**19. Carosa, E, Martini, P, Brandetti, F, Di Stasi S M, Lombardo F and Lenzi A (2004).** Type V phosphodiesterase inhibitor treatments for erectile dysfunction increase testosterone levels. Clinical Endocrinology (Oxford) ;61(3):382-6.

**20. Zhang XH, Morelli A, Luconi M, Vignozzi L, Filippi S, Marini M, Vannelli GB, Mancina R, Forti G and Maggi M (2005).** Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. European urology; 47(3), 409–416.

**21. Hwang TI, Chen HE, Tsai TF and Lin Y C (2006).** Combined use of androgen and sildenafil for hypogonadal patients unresponsive to sildenafil alone. Int J Impot Res;18:400–404.

**22. Porst H, Giuliano F, Glina S, Ralph D, Casabé, Elion-Mboussa, Shen, W and Whitaker JS (2006).** Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. European urology;50(2):351-9.

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

**Table 1: Demographics and laboratory characteristics of ED patients and controls**

| Parameter | | Control (n = 30) | Patient (n = 30) | P-value* |
|---|---|---|---|---|
| Age/years | • Mean SD | 48.33 ± 10.2 | 53.17 ± 7.8 | = 0.053 |
| | • Median (IQR) | 48 (17) | 52.5 (11) | |
| Testosterone level | • Mean SD | 5.87 ± 0.2 | 4.67 ± 0.4 | < 0.001 |
| | • Median (IQR) | 5.5 (0.7) | 4.7 (2.7) | |

**Table 2: Effect of treatment on totoal testosterone level**

| **Parameter (n=30)** | **Pre-treatment** | **Post-treatmen** | **P-value*** |
|---|---|---|---|
| • **Testosterone level** | 4.67 ± 0.4 | 8.31 ± 1.0 | **= 0.002** |

**Table 3: Effect of treatment on degree of erection.**

| **Parameter (n=30)** | **Pre-treatment** | **Post-treatment** | **P-value*** |
|---|---|---|---|
| **Erection** | | | |
| • **E1** | **3 (10%)** | **0 (0%)** | |
| • **E2** | **13 (43.3%)** | **1(3.3%)** | |
| • **E3** | **11 (36.7%)** | **8 (26.7%)** | **< 0.001** |
| • **E4** | **3 (10%)** | **20 (66.7%)** | |
| • **E5** | **0 (0%)** | **1 (3.3%)** | |

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

**Table 4: Effect of treatment on IIEF-5.**

| Parameter (n=30) | Pre-treatment | Post-treatmen | P-value* |
|---|---|---|---|
| **IIEF-5** | 12.67 ± 4.2 | 20.53 ± 2.2 | **< 0.001** |
| **ED categories** | | | |
| • **Normal** | 0 (0%) | 13 (43.3%) | |
| • **Mild** | 8 (26.7%) | 14 (46.7%) | |
| • **Mild/Moderate** | 7 (23.3%) | 1 (3.3%) | **< 0.001** |
| • **Moderate** | 8 (26.7%) | 2 (6.7%) | |
| • **Severe** | 7 (23.3%) | 0 (0%) | |

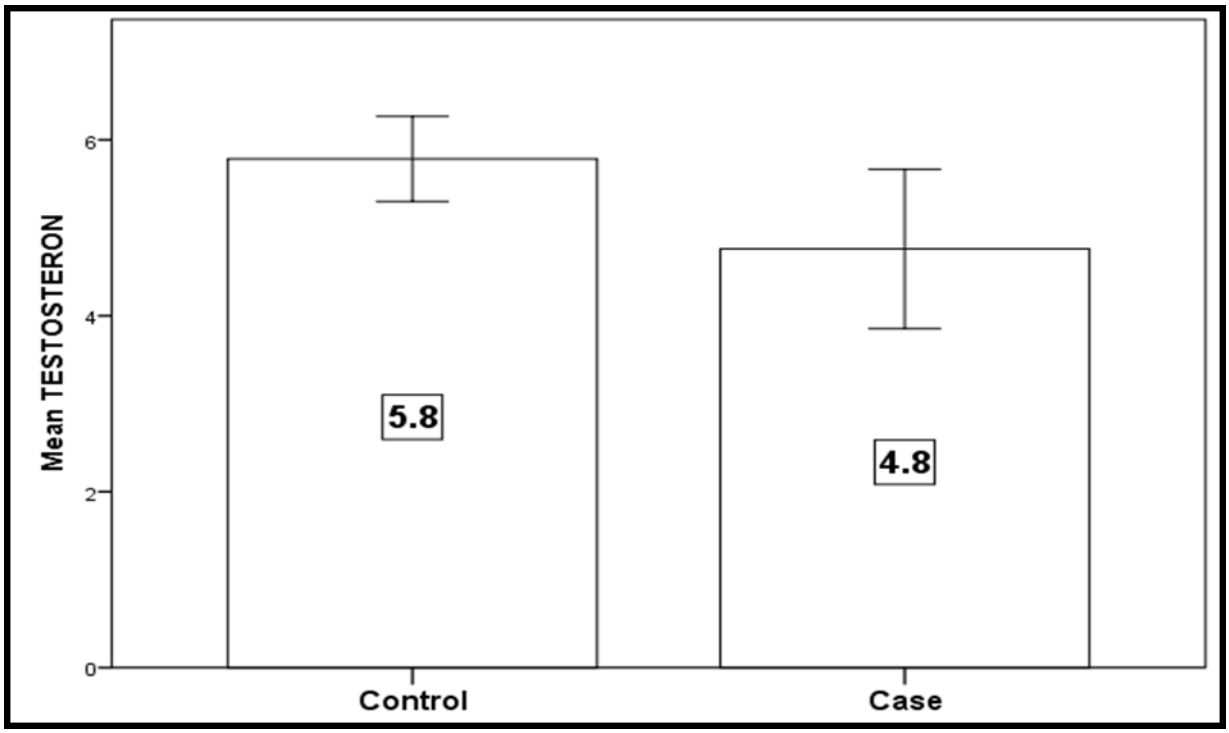


**Fig. 1: Mean testosterone level in patients vs. controls.**

Submission date: (17/3/2023) - acceptance date: (5/4/2023)

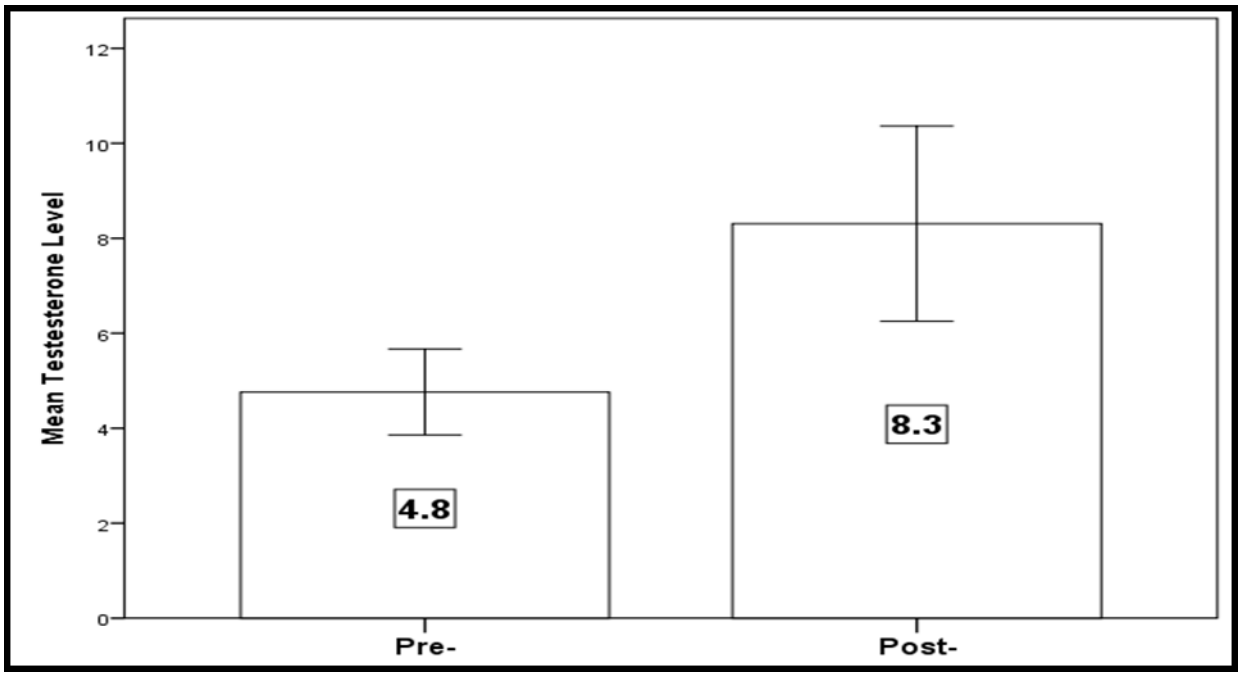


**Fig 2: Effect of treatment on the level of testosterone among patients**

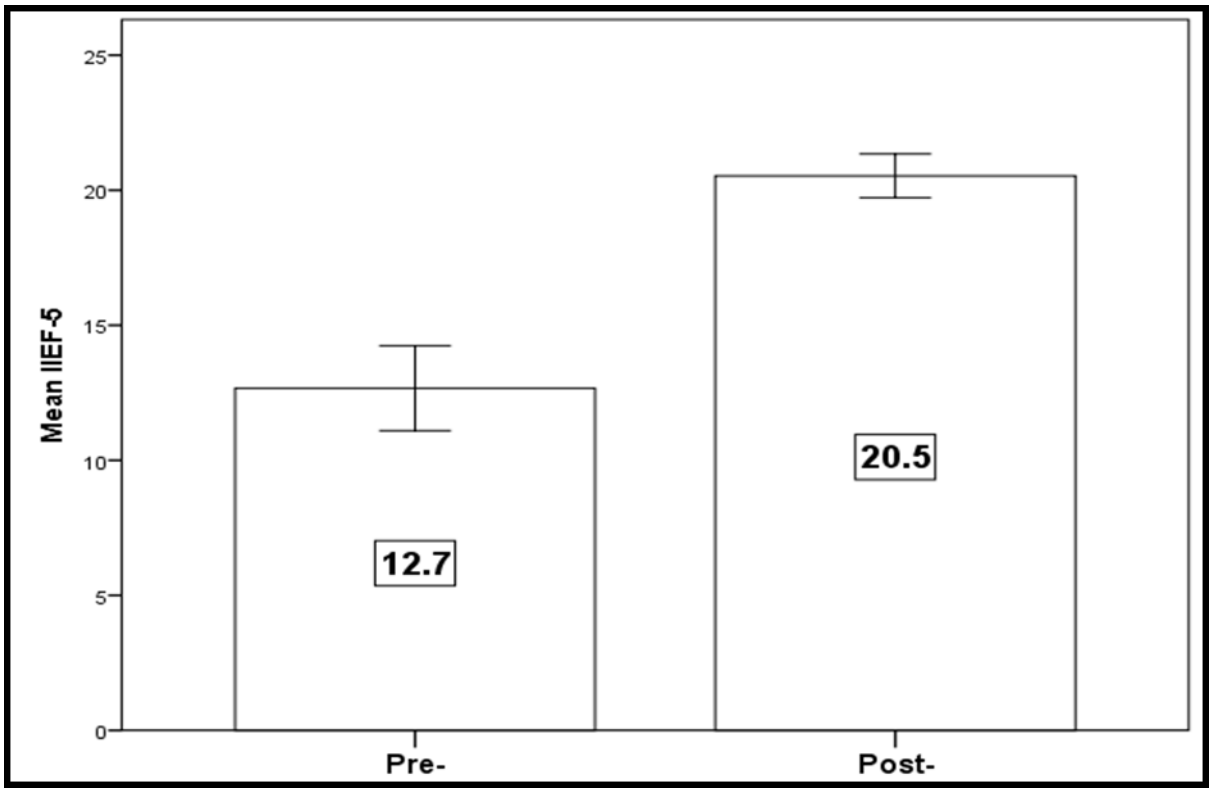


**Fig. 3: Effect of treatment on the IIEF-5 score among patients.**

Submission date: (17/3/2023) - acceptance date: (5/4/2023)