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The Outcome of Daily Low Dose of Tadalafil in Diabetic Men with Erectile Dysfunction

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ABSTRACT

Background: Men with diabetes mellitus frequently experience erectile dysfunction (ED).
Objective: The purpose of this study is to determine whether or not 5 mg of tadalafil daily is effective in treating erectile dysfunction in men who are diabetic.
Patients and methods: In this trial, 50 diabetic males with ED were given 5 mg of tadalafil once daily for 12 weeks. Using the International Index of Erectile Function (IIEF) and penis-specific Color Duplex Doppler Ultrasonography, researchers evaluated tadalafil's effects on erection quality and duration.
Results: Age of 45 was the median, and the average body mass index was 30.3 kg/m², 54 % of them were smokers. We found statistical significant (p-value < 0.001) increased 12 weeks IIEF score (median = 18.5, IQR = 13 – 22) when compared baseline IIEF score (median = 12.4, IQR = 10 – 17). Our results showed statistical significant (p-value < 0.001) increased 12 weeks PSV (median = 36, IQR = 35 – 37) when compared with baseline PSV (median = 33, IQR = 30 – 35). Using multivariate logistic regression analysis, we demonstrated that smoking, BMI, dyslipidemia and bad glycemic control were predictive factors for ED severity.
Conclusion: Taking 5 milligrams of tadalafil once a day may help diabetic men's erectile dysfunction.
Keywords: Treatment outcome, Tadalafil, Erectile dysfunction.

INTRODUCTION

The International Consultation on Sexual Medicine defines erectile dysfunction as the chronic and recurrent inability to get or keep an erection of adequate stiffness and duration to engage in acceptable sexual intercourse. Although ED is quite common, nothing was known about it until the 1970s. The etiology of ED and our understanding of penile physiology have both come a long way since then, thanks to advancements in molecular biology techniques [(1)].

The physiological reaction in the penile vasculature is triggered by a complex interplay of psychological, neurological, and vascular pathways. In men, nitric oxide is secreted by the penile cavernosal tissue in response to parasympathetic transmission from the pudendal and pelvic splanchnic nerve plexuses (NO). Cavernosal smooth muscle is relaxed by nitric oxide via a reduction in intracellular calcium that is mediated by cyclic guanosine monophosphate [(2)]. When the cavernosal sinusoids are filled, the veins in the penis are compressed against the tunica albuginea, preventing blood from leaving the penis and allowing the erection to last. Phosphodiesterase type 5 inhibits the short-lived rise in cyclic guanosine monophosphate [(3)].

Erectile dysfunction affects between 35% and 75% of guys with diabetes. Erectile dysfunction is far more common in men with diabetes than in men without the disease. Sexual dysfunction is thought to be exacerbated by diabetes-related microvascular and macrovascular problems due to hyperglycemia. The decrease in blood flow to the penis is caused by atherosclerosis in the arterial vessels, which is in turn caused by macrovascular complications and endothelial dysfunction characterised by decreased nitric oxide (NO). Reflexogenic erection centre dysfunctions due to microvascular problems causing ischemia in autonomic and peripheral neurons [(4)].

Anti-phosphodiesterase 5 (PDE5) inhibitors have dominated the treatment of erectile dysfunction (ED) in recent years: like vardenafil hydrochloride, tadalafil, as well as sildenafil citrate (sildenafil). The PDE5 inhibitor tadalafil has a significantly longer mean elimination half-life of 17.5 hours compared to the about 4-5 hours required by sildenafil and vardenafil. These effective and well tolerated oral medicines are given on demand, just before desired sexual activity [(5)]. But the effectiveness is diminished in diabetic men with ED, perhaps because of underlying endothelial dysfunction and reduced endothelium-derived factors in penile arteries. This may help explain why men with diabetes have a harder time treating their ED [(6)].

The study's objective was to assess the efficacy of a daily low dose of tadalafil in treating erectile dysfunction in men with diabetes.

PATIENTS AND METHODS

Fifty individuals who had been diagnosed with ED for at least 3 months were included in this prospective case series study.
Setting: Outpatient Clinic of Urology Department, Qena University Hospital.

Inclusion criteria: A history of erectile dysfunction (ED) lasting at least three months in a heterosexual relationship with the same partner, age 18 or older, and type II diabetes.

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Exclusion criteria: Irregular sexual life, history of cardiovascular diseases (e.g., unstable angina, when PDE5 inhibitors are contraindicated), history of radical prostatectomy with subsequent failure to achieve erections, and penile implants or deformities.
All patients were given low daily dose (5 mg) of tadalafil for 12 weeks.

Ethical considerations:

Each patient who took part in this study signed a written consent form. Ethics review and approval for this study were granted by the Qena Faculty of Medicine at South Valley University. The study was performed in accordance with the ethical standards as laid down in the 1964 (Declaration of Helsinki) and its later amendments.

These procedures were performed on every patient:
I. Medical History and Physical Examination:

1- Patients' whole medical histories are taken into account before treatment is administered. This included their smoking habits, any urological or genital symptoms they might be experiencing, as well as their onset, progression, and length.
2- Full clinical examination included assessment of general condition with stress on genital examination. The subjects' anthropometric data were collected. Body mass index (BMI) was established through dividing weight (kg) by square (in meters) of height.

II. Laboratory Investigations: - Blood samples were collected from patients and submitted to the following:

1. Complete blood picture (CBC): platelet count, white blood cells (WBCs), red blood cells (RBCs), hemoglobin concentration (Hb %).
2. Fasting blood glucose level.
3. Lipid profile, which included: High density lipoprotein, low density lipoprotein, very low density lipoprotein, triglycerides and total cholesterol.
4. Hormonal profile, which included: total testosterone, estradiol (E2), prolactin. follicular stimulating hormone (FSH), as well as luteinising hormone (LH).

III. Measuring Outcome:

Assessment of tadalafil's effect on erections was carried out using the International Index of Erectile Function (IIEF) and penile Color Duplex Doppler Ultrasonography (CDDU) by injection of (Alprostadil; as vasoactive dose) intracorporeal. In this study, patients took the IIEF upon presentation and then every four weeks for three months. Subjects' erectile function (EF) IIEF scores were analyzed here. Improvement in erectile function was represented by an increase in the EF score. The total number of points earned from each question was added up to determine the domain score. The severity of ED was measured by looking at the following indicators in the EF domain: No ED: ≥ 26, Mild ED: 17–25, Moderate: ED 11–16, and Severe ED: 1–10.

All patients had a Color Duplex Doppler Ultrasound of the penis (CDDU) performed at presentation and again three months later after receiving an intracorporeal injection of a vasoactive drug (Alprostadil): including peak systolic velocity (PSV), end diastolic volume (EDV) and Resistive Indices (RI): If the PSV above 35 cm/sec during the examination were considered normal for arteriogenic function for the PSV, arterial insufficiency was determined based on an assessment PSV of less than 25 cm/sec, PSVs between 25 and 35 cm/s indicate a diagnosis of arterial insufficiency related to arterial wall stiffness. Asymmetric reading greater than 10 cm /sec means a unilateral arterial insufficiency. End diastolic volume should be less than 5 cm/sec during the examination after finishing the exam, if the EDV value was still greater than 5 cm/s, as a result, venous insufficiency was identified as the diagnosis. The peripheral resistance to blood flow is expressed by the Resistive Indices (RI), which are calculated as follows: RI = (PSV − EDV) / PSV. Penile vascular health has been linked to a RI above 0.9, while a RI below 0.75 is indicative of veno-occlusive dysfunction (venous leak).

Statistical analysis

The analysis was conducted in SPSS 26.0, the statistical package for the social sciences. Quantitative data were provided as median, interquartile range, mean and standard deviation (SD). Qualitative data were presented as frequency and percentage. Area under the curve, the greater the area, the more accurate is the curve. Total area is 1.0, the yellow line is the reference line, it divides the area into 2 halves. 95% CI (Confidence interval) of AUC =It is an interval at which the investigator is 95% confident that the true AUC lies. It was considered statistically significant if the probability level was less than 0.05.

RESULTS

Median age was 45 years with mean BMI of 30.3 **kg/m², 54 % of them were smokers.** Our results showed statistical significant increased 12 weeks PSV when compared with baseline PSV. We found statistical significant increased 12 weeks IIEF score when compared baseline IIEF score (Tables 1, 2, 3).

Table (1): demographic and laboratory data

		Studied patients (N = 50)	
Age (years)	**Median**	45	
	IQR	41 – 53	
Body mass index (BMI) (kg/m²)	**Mean±SD**	30.3±4	
Smoking	**No**	27	54%
	Smoker	23	46%
Fasting Blood Sugar (FBS) (mg/dl)	**Mean±SD**	156±35.2	
HbA1C (%)	**Mean±SD**	7.8±1.3	
Cholesterol (mg/dl)	**Mean±SD**	174±26.8	
Triglyceride (mg/dl)	**Mean±SD**	131±28.5	
High-density lipoprotein (HDL) (mg/dl)	**Mean±SD**	45±9.6	
Low-density lipoprotein (LDL) (mg/dl)	**Mean±SD**	69±12.5	

Table (2): comparisons of IIEF score (baseline and at 12 weeks) in studied patients

		IIEF score		P-value
		Baseline	**At 12 weeks**	
All patients (N = 50)	**Mean±SD**	12.5±2.8	18.5±4.3	**< 0.001 HS**

Table (3): Comparisons of PSV, EDV, and RI between baseline and 12 weeks in studied patients

		Baseline	At 12 week	P – Value
PSV	**Median**	33	36	**< 0.001 HS**
	IQR	30 – 35	35 – 37	
EDV	**Median**	4	4	1.0 NS
	IQR	3 – 4	3 – 4	
RI	**≥ 0.9**	42 **(84%)**	42 (84%)	**1.0 NS**
	≤ 0.75	8 **(16%)**	8 (16%)	

Using multivariate logistic regression analysis, we demonstrated that the following factors were predictive for ED severity: Smoking, BMI, FBS, HbA1C, cholesterol, TG and LDL (Table 4).

Table (4): Multivariate logistic regression analysis for factors predictive of ED severity

	B	SE	p-value	Odds	95% CI	
Age	0.011	0.023	0.647	1.01	0.96	1.05
Smoking	**1.01**	**0.44**	**0.023**	**2.76**	**1.14**	**6.66**
Body mass index (kg/m²)	**0.12**	**0.05**	**0.013**	**1.13**	**1.02**	**1.25**
Fasting Blood Sugar (mg/dl)	**0.029**	**0.008**	**< 0.001**	**1.02**	**1.01**	**1.04**
HbA1C (%)	**0.57**	**0.16**	**< 0.001**	**1.76**	**1.28**	**2.43**
Cholesterol (mg/dl)	**0.023**	**0.007**	**0.001**	**1.02**	**1.01**	**1.03**
Triglyceride (mg/dl)	**0.011**	**0.004**	**0.006**	**1.01**	**1.0**	**1.01**
High-density lipoprotein (mg/dl)	0.033	0.002	0.142	1.03	0.98	1.07
Low-density lipoprotein (mg/dl)	**0.037**	**0.009**	**< 0.001**	**1.03**	**1.01**	**1.05**

B: Regression coefficient, SE: Standard error, CI: Confidence interval.

DISCUSSION

The results of current study showed significant increased IIEF score after 12 weeks when compared with baseline IIEF score.

In agreement with the present study, **McMahon** [(1)] tested 112 males experiencing ED due to diverse factors. For 12 weeks, these males took a little amount of tadalafil once daily. After 4 weeks of daily dosage medication, the mean IIEF-EF domain score significantly increased from 10.3 at baseline to 23.1. The trial included 101 men. After the daily dose phase, the mean IIEF-EF domain score increased significantly compared to the pre-dose and post-dose periods. Researchers found that tadalafil improved all measures of efficacy when administered regularly.

Rajfer *et al.* [(7)] conducted a 24-week, multicenter research comparing 2.5 and 5 milligrammes of tadalafil to a placebo in men with erectile dysfunction. Of the 287 guys who started the protocol, 238 finished it (83 percent). For example, the mean IIEF-EF domain score improved by 6.1 and 7.0 points in the tadalafil 2.5 and 5 mg arms, respectively, demonstrating that tadalafil was more effective than placebo across all primary effectiveness end objectives relative to a rise of 1.2 points in the placebo group. Intercourse satisfaction, sexual confidence, and general sexual life satisfaction were all significantly affected by tadalafil use, as measured by the international erectile functioning questionnaire (IIEF).

Hatzichristou *et al.* [(8)] studied the effects of tadalafil (2.5 and 5 mg daily) versus placebo in treating erectile dysfunction (ED) in males with diabetes at 23 different clinics over the course of 24 weeks. Of the 298 participants, 254 males finished the protocol (85 percent completion). In both doses, tadalafil was shown to be considerably more effective than placebo; more precisely, tadalafil 2.5 mg and 5 mg groups saw larger increases in IIEF-EF domain scores (4.8 and 4.5 points, respectively) than placebo (1.3 points). The average percentage of people who answered "yes" to sexual encounter profile (SEP2) after receiving either 2.5 mg, 5 mg, or a placebo varied from 20% to 29%. On average, the proportion of patients who responded favourably to SEP3 fell by 26% in the 2.5 mg group, 25% in the 5 mg group, and 8% in the placebo group. Satisfaction with sexual relationships, sexual confidence, and overall sexual life satisfaction were all significantly affected by tadalafil.

Out of a total of 234 patients, 208 (88.9 percent) completed the 1-year open-label extension and 139 (58.4 percent) completed the 2-year open-label extension in a randomised controlled trial with open enrollment. The average IIEF-EF domain increased from 13.7 at study onset to 24.1 at the end of the first extension year, and from 14.0 at study onset to 24.8 at the end of the second extension year. The researchers concluded that tadalafil 5 mg, given once daily, was well tolerated and effective in studies of males with ED, and so represented a feasible alternative to the current on-demand dose of tadalafil [(9)].

Patients who met the inclusion and exclusion criteria of a recent randomised, double-blind, placebo-controlled pilot trial were randomly assigned in a ratio of 2:1 to receive either tadalafil 5 mg or placebo once daily. A total of 68 participants participated in the research; 45 received tadalafil and 23 received a placebo. At 6 months, the tadalafil group had significantly higher improvement in International Index of Erectile Function-5 scores compared to the placebo group (P = 0.003). Researchers found that patients with type 2 diabetes and erectile dysfunction benefited from once-daily dosing of low-dose tadalafil [(10)].

The results of current study showed that increased BMI, dyslipidemia and poor glycemic control were associated with erectile dysfunction.

In accordance with our results, **Anwar *et al.*** [(11)] patients with severe ED were shown to have inferior glycemic control, lipid profiles, body mass index, age of onset, and duration of untreated diabetes compared to patients without ED. The danger of severe ED in DM patients is raised by both poor glycemic management and old age.

Saltzman *et al.* [(12)] argued that individuals who are resistant to ED medication may see improvements in their condition after correcting dyslipidemia and that this improvement could be noticeable within three months.

Azad *et al.* [(13)] included 813 adult males with type II diabetes mellitus (T2DM) who were consecutively enrolled. The modified International Index of Erectile Function was used to evaluate sexual performance. Multivariate logistic regression was used to examine, after controlling for other factors, whether ED is associated with dyslipidemia. An extremely high percentage of T2DM patients (72.7%) developed ED, with over half of those experiencing moderate-to-severe ED**.** T2DM patients with ED were 2.3 times more likely to have dyslipidemia than T2DM individuals without ED. Abnormal high density lipoprotein levels increased the risk around threefold, whereas abnormal low-density lipoprotein raised it by two and a half times as much. In T2DM patients, dyslipidemia was linked to an increased risk of ED.

In accordance with our results, **Molina-Vega *et al.*** [(14)] examined at 254 overweight males for a study. High levels of good cholesterol (HDL) were linked to a lower risk of ED, while both obesity and advanced age increased the likelihood of exhibiting ED.

Khatib *et al.* [(15)], studied sixty-two percent of Jordanian males with DM had ED, and 30.3% of those

men had severe ED, according to a study that looked at the frequency, severity, and correlates of ED among this population. Patients under the age of 40 had a frequency of 26.5% (13 of 49), whereas patients beyond the age of 70 had a prevalence of 91.5% (87 of 96). Independent risk factors for ED included poor glycemic control.

CONCLUSION

Tadalafil 5 mg once daily may help improve erectile function in men with diabetes. A higher prevalence of erectile dysfunction was linked to higher body mass index, dyslipidemia, and inadequate glycemic management.

The limitation of our study are small sample size and short period of follow up.

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