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## A comparative Study of Tadalafil versus Tadalafil combined with Alpha Lipoic Acid in the treatment of Erectile Dysfunction in Diabetic Patients

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### ABSTRACT

**Background:** Erectile dysfunction (ED) is a worldwide health issue that has an influence on men's and their spouses' quality of life. The etiology of ED may be organic, psychogenic or mixed. The first line of therapy is oral phosphodiesterase type 5 inhibitors. Tadalafil is one of the PDE5 inhibitors. Diabetes-related erectile dysfunction is a type of endocrinal erectile dysfunction that impacts around 75% of patients with diabetes. Alpha-lipoic acid (ALA) is a powerful antioxidant that can improve diabetes and its problems. It is commonly referred to be a universal antioxidant.

**Aim of the study:** To compare the efficiency of ALA when it combined with tadalafil versus Tadalafil alone in diabetic with ED.

**Patients and Methods:** A total of 40 patients with type 2 diabetes mellitus (DM) and ED participated in the current study. Patients have been recruited from the Dermatology, Venereology, and Andrology Departments of the Faculty of Medicine at Al-Azhar University Hospitals' outpatient clinic from March 2020 to October 2021. A regimen of tadalafil 5mg daily dose for 6 weeks. ALA (Thioctic acid 300mg) daily was added to the previous regimen for additional 6 weeks.

**Results:** The results revealed significant improvement after adding ALA to tadalafil in comparison to the same studied group taking tadalafil only (P-value > 0.05). The evaluation was done utilizing the International Index of Erectile Function (IIEF-5).

**Conclusion:** Treatment of diabetic patients with ED by tadalafil 5mg daily dose is an effective method. Adding ALA to tadalafil adds more significant improvement.

**Keywords:** Erectile dysfunction; diabetes mellitus; Tadalafil; Alpha-Lipoic acid...

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### INTRODUCTION

Erectile dysfunction (ED) is characterized by a persistent failure to achieve or sustain a sexually satisfying erection.<sup>1</sup> It is an age-related disease, with roughly 5% of males between the ages of 20–39 years, 14.8% of males between 40–59 years, and 70% of males aged 70 years and older suffering from it.<sup>2</sup> The etiologies of ED include neurogenic, vasculogenic, endocrine, psychogenic, and drug induced.<sup>3</sup>

Tadalafil is one of Oral phosphodiesterase type 5 inhibitors (PDE5i) (sildenafil, tadalafil, vardenafil and avanafil). The first-line treatment for ED is PDE5i. PDE5i does not cause spontaneous erections; however, erections do occur when combined with sexual arousal (visual, cerebral, or physical). PDE5i is responsible for the hydrolysis of cyclic guanylate monophosphate (cGMP) to 5'GMP, which causes

penile cavernous smooth muscle relaxation and penile erection.<sup>4</sup>

Diabetic erectile dysfunction (DED) is a form of ED that is a subtype of endocrine erectile dysfunction (EED). It's one of the most frequent reasons for dysfunction in diabetics, with a complicated pathophysiology.<sup>5</sup>

DED appears at a young age and is three times more common in diabetic males than in nondiabetic males, affecting about 35–90% of men with diabetes.<sup>6</sup>

ALA is among the most effective biological antioxidants, and because of its water and fat solubility, it is referred to as a "universal antioxidant".<sup>7</sup>

ALA is a significant antioxidant that helps to prevent diabetes and its sequelae. It is commonly referred to as a universal antioxidant as it has the ability to

regenerate additional antioxidants such as vitamin C, vitamin E, coenzyme Q10, and glutathione.<sup>8</sup>

Extensive data shows that ALA may be useful in decreasing glucose levels in diabetes patients by affecting the intracellular redox state, which influences insulin action and insulin resistance.<sup>9</sup>

This work aimed to compare the efficacy of ALA (Thioctic acid 300 mg) daily when it combined with tadalafil 5mg daily versus Tadalafil 5mg daily alone in patients with T2D with erectile dysfunction.

## PATIENTS AND METHODS

From March 2020 to October 2021, this study was conducted on 40 diabetic patients with ED. The patients were detected by history (medical, sexual, International Index of Erectile Function (IIEF-5) Questionnaire, examination (general, genital), intracavernosal injection (ICI), and investigations such as fasting plasma glucose (FBS), HBA1C, total cholesterol, triglycerides, serum prolactin, and serum total testosterone for all patients.

The patients were able to read and give agreements. Patients under 18 years old, on medications that interfere with the drugs in the study and with severe end organ damage, were excluded. Patients have been chosen from the Dermatology, Venereology, and Andrology Department of the Faculty of Medicine Al-Azhar University Hospitals' outpatient clinic.

The studied patient group:

All the studied patients started the therapy with tadalafil 5 mg every day for 6 weeks. ALA (Thioctic acid, 300 mg) was added to the previous regimen for an additional 6 weeks.

The patients were evaluated according to IIEF-5 questionnaire and were obtained before starting treatment and after 6 weeks from adding tadalafil 5 mg daily then 6 weeks after adding ALA (Thioctic acid 300 mg) daily to tadalafil.

An approved was obtained from the Ethical Research Board (ERB) of the Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Before the study proceeding, all patients assigned informed consent after the obvious explanation of the possible adverse events.

## RESULTS

		IIEF		Stat. test	P-value
		Before TTT (N = 40)	After tadalafil (N = 40)		
IIEF	Mean	17.3	19.1	T = 2.8	0.006 S
	±SD	2.5	2.9		

**Table 4:** Comparison of IIEF before treatment and after tadalafil in studied patients. (T: independent sample T test; S: p-value < 0.05 is regarded as significant.).

The current research involved 40 diabetic patients who had ED. The Statistical Program for Social Science (SPSS) version 24 was used to investigate the data. The mean±average deviation (SD) has been employed to express quantitative statistics. Frequencies and percentages have been employed to express qualitative statistics. All patients studied had a mean age of  $47.9 \pm 9.7$  years with minimum age of 28 years and maximum age of 66 years (Table 1 & 2).

The mean duration of ED of all studied patients was  $3.44 \pm 2.6$  years with minimum duration of 0.25 years and maximum duration of 11 years (Table 2).

All patients in the study were evaluated for medical diseases and revealed that 100 % of patients (n=40) had DM, 37.5 % of patients (n=15) had hypertension, 30 % of patients (n=12) had benign prostatic hyperplasia (Table 3).

Studied patients (N = 40)		
Age (years)	Mean ±SD	$47.9 \pm 9.7$
	Min - Max	28 – 66

**Table 1:** Description of age in all studied patients.

Studied patients (N = 40)		
Duration of ED (years)	Mean ±SD	$3.44 \pm 2.6$
	Min - Max	0.25 – 11

**Table 2:** Description of duration in all studied patients.

Studied patients (N = 40)			
Medical diseases	DM	40	100%
	HTN	15	37.5%
	BPH/LUTs	12	30%

**Table 3:** Description of medical diseases in all studied patients.

The current study showed a statistically significant (p-value < 0.05) increased IIEF after tadalafil ( $19.1 \pm 2.9$ ) when compared with IIEF before treatment ( $17.3 \pm 2.5$ ). There was highly statistically significant (p-value < 0.001) increased IIEF after combination ( $20.5 \pm 3.4$ ) when compared with IIEF before treatment ( $17.3 \pm 2.5$ ). There was statistically significant (p-value < 0.05) increased IIEF after combination ( $20.5 \pm 3.4$ ) when compared with IIEF after tadalafil ( $19.1 \pm 2.9$ ) (Table 4).

		IIEF		Stat. test	P-value
		Before TTT (N = 40)	After Comb. (N = 40)		
IIEF	Mean	17.3	20.5	MW = 378.5	< 0.001 HS
	±SD	2.5	3.4		

**Table 5:** Comparison of IIEF before treatment and after Combination in studied patients. This table displays statistically significant (p-value < 0.05) increased IIEF after tadalafil (19.1 ± 2.9) when compared with IIEF before treatment (17.3 ± 2.5). (MW: Mann Whitney U test; HS: p-value < 0.001 is regarded as highly significant).

		IIEF		Stat. test	P-value
		After tadalafil (N = 40)	After Comb. (N = 40)		
IIEF	Mean	19.1	20.5	MW = 585.5	0.038 S
	±SD	2.9	3.4		

**Table 6:** Comparison of IIEF after tadalafil and after Combination in studied patients. This table displays highly statistically significant (p-value < 0.001) increased IIEF after combination (20.5 ± 3.4) when compared with IIEF before treatment (17.3 ± 2.5). This table displays statistically significant (p-value < 0.05) increased IIEF after combination (20.5 ± 3.4) when compared with IIEF after tadalafil (19.1 ± 2.9). (MW: Mann Whitney U test; HS: p-value < 0.05 is regarded as highly significant).

## DISCUSSION

Many studies have demonstrated that diabetic patients can be treated with ED. Erectile dysfunction (ED) is a prevalent problem among diabetic men. It is described as the failure to achieve and/or sustain an erection adequate to allow successful sexual intercourse. It was found that it has a detrimental influence on patients of all ages' quality of life.<sup>10</sup>

Diabetes mellitus is associated with erectile dysfunction (DMED) due to late age, diabetes, high blood pressure, hyperlipidemia, smoking, as well as various diabetic comorbidities. Its etiology remains unknown. However, it is usually associated with the synergistic effects of neurological, vascular, as well as endocrine disorders. DMED is usually thought to be caused by diabetic neuropathy. The etiology of diabetic neuropathy is believed to be affected by oxidative stress, which can have an important role in its development. Much research has shown that patients with diabetes mellitus (DM) have high levels of oxidative stress that cause pathological alterations in cavernous smooth muscles, penile erection-linked neurons, and blood vessels.<sup>5</sup>

A PDE-5 inhibitor is an active and largely nontoxic medication for the therapy of male erectile dysfunction. It is currently used as a first-line therapy for DED.<sup>5</sup>

PDE5i hydrolyzes cyclic guanylate monophosphate (cGMP) particularly to 5'GMP that cause penile cavernous smooth muscle relaxation and penile erection.<sup>4</sup>

Alpha-lipoic acid (ALA) is a potent biological antioxidant that is known as a "universal antioxidant" owing to its solubility in both water and fat. ALA is easily absorbed from the intestines and crosses the blood-brain barrier with ease, leading to optimal bioavailability.<sup>11</sup>

ALA is a powerful antioxidant that helps to prevent diabetes and its consequences. It is commonly referred to as a universal antioxidant because it has the ability to regenerate additional antioxidants such as vitamin C, vitamin E, coenzyme Q10, and glutathione.<sup>8</sup>

Our study shows significant improvement in diabetic patients with ED when using tadalafil 5 mg daily, and this agrees with Statsenko et al. 12, that evaluated the efficiency and safety of tadalafil 5 mg daily low dose versus tadalafil 20 mg on demand alone in erectile dysfunction. They found that both groups' IIEF-EF scores increased, but the daily dose of 5mg of tadalafil showed the best results. These data imply that daily or on-demand dosages of tadalafil are successful therapeutic choice for treatment of ED.

Also, this study shows significant improvement by combination therapy of tadalafil 5mg daily dose and ALA (Thioctic acid 300 mg) daily and this agrees with Nangare et al.13, that evaluated the efficacy of ALA based tadalafil transdermal patch using a self-emulsion drug delivery system (SEDDS) in management of erectile dysfunction. ALA can guard the endothelial cell against oxidative injury in a diabetic patient. This patch enhances the skin absorption and bioavailability of tadalafil and reduces/protect the epithelial cells lined penile vessels from oxidative stress in hyperglycemic condition. ALA improves the cell survival rate of about 1.3-fold. Therefore, it determines that ALA with tadalafil loaded SEDDS is a recent method for management of DMED.

In the current study, the route of administration is orally and the IIEF-EF scores is increased in the group that given ALA (Thioctic acid 300 mg) every day for six weeks in combination with regular daily dose of tadalafil 5mg.

The patients were assessed using the IIEF-EF, and the IIEF-EF score in the combination group was significantly greater than in the tadalafil only group.

The diabetic patients with ED were registered and randomly assigned to either treatment for a 12-week course, 6 weeks tadalafil only and another 6 weeks mixture of tadalafil besides ALA. Patients are assessed according to IIEF-5 score and showed that there is significant difference among both sets as analysis showed a statistically highly important improvement in the severe ED in the combination group compared with group of the monotherapy. So, the mixture of tadalafil and ALA may be an important direction for treating diabetic patients with ED.

### CONCLUSION

Management of diabetic patients with ED by tadalafil 5mg daily dose is an effective method. Adding ALA to tadalafil adds more significant improvement. The combination of tadalafil and ALA could represent a treatment option for diabetic patients with ED.

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