Effects of Tadalafil on Macular Parameters and Choroidal Thickness in Diabetic Patients

Diyabetik Hastalarda Tadalafilin Koroid Kalınlığı ve Makula Parametreleri Üzerine Etkileri

Murat Atabey ÖZER[1], Serkan ÖZEN[1], Nihat POLAT[2], Ercan ÖĞREDEN[3], Erhan DEMİRELLİ[3], Ali BEYTUR[4], Yaşar KÜÇÜKSÜMER[5]

ABSTRACT

Objective: To investigate the effects of tadalafil on macular parameters and choroidal thickness in diabetic patients with erectile dysfunction (ED).

Materials and methods: Total 37 diabetic patients with ED were included in this single-centred, open-label prospective study. The treatment was initiated with 5 mg tadalafil hydrochloride daily for 3 months. Choroidal thickness, central macular thickness (CMT), and total macular volume (TMV) measurements were performed using spectral domain optical coherence tomography (SD-OCT). SD-OCT and visual acuity (VA) measurements were repeated during all visits. Fundus fluorescein angiography (FFA) was also performed at baseline and at the 12th week.

Results: There was a statistically significant increase in the choroidal thickness compared to that at baseline at all visits except at the first visit (mean central foveal choroidal thickness, baseline; 248.7 ± 21.5, 1st day; 247.4 ± 23.2, 4th week; 275.9 ± 21.3, and 12th week; 275.1 ± 24.4, µm, $p < 0.001$). There was no statistically significant change in the mean VA (baseline; 0.21 ± 0.07, 12th week; 0.22 ± 0.06, logMar), mean CMT (baseline; 236.7 ± 32.4, 12th week; 234.8 ± 32.8, µm), mean TMV (baseline; 9.88 ± 1.21, 12th week; 9.83 ± 1.26, mm^3), and FFA compared to the baseline values ($p > 0.05$).

Conclusions: Choroidal thickness safely increases in response to systemic tadalafil administration. The long-term use of systemic tadalafil does not cause any adverse effects on the retina and the macula in diabetic patients with ED.

Keywords: Choroidal thickness; Diabetes Mellitus; Macula; Tadalafil.

ÖZ

Amaç: Erektil disfonksiyonlu(ED) diyabetik hastalarda tadalafilin koroid kalınlığı ve maküla parametreleri üzerine etkilerini araştırmak.

Materyal ve Metod: Bu tek merkezli açık etiketli prospektif çalışmaya ED tanılı diyabetik 37 hasta dahil edildi. Bu hastalara 3 ay boyunca günlük 5 mg Tadalafil hidroklorür başlandı. Koroidal kalınlık, santral makuler kalınlık(SMK) ve total makuler volüm(TMV) spectral optik kohorens tomografi(SD-OKT) kullanılarak değerlendirildi. tüm vizitlerde tekrarlandı. Tüm kontrollerde SD-OKT ve görme keskinliği(GK) ölçümleri tekrarlandı. Ayrıca başlangıçta ve 12. haftada tüm hastalara fundus floresein anjiografi(FFA) uygulandı.

Sonuçlar: İlk visit hariç diğer tüm kontrollerde başlangıca gore koroid kalınlığında istatistiksel olarak anlamlı düzeyde artış olduğu görüldü(ortalama santral foveal koroidal kalınlık, başlangıç; 248.7 ± 21.5, 1. gün; 247.4 ± 23.2, 4. hafta; 275.9 ± 21.3, ve 12. hafta; 275.1 ± 24.4, µm, $p<0.001$). GK (başlangıç; 0.21 ± 0.07, 12. Hafta; 0.22 ± 0.06, logMar), ortalama SMK (başlangıç; 236.7 ± 32.4, 12.hafta; 234.8 ± 32.8, µm), ortalama TMV (başlangıç; 9.88 ± 1.21, 12. hafta; 9.83 ± 1.26, mm^3) ve FFA' da istatistiksel açıdan anlamlı fark tespit edilmedi($p>0.05$).

Tartışma: Uzun süreli, düşük doz sistemik tadalafil kullanımı diyabetik hastalarda güvenli bir şekilde koroid kalınlığını artırmaktadır. Ayrıca retina ve maküla üzerinde yan etkiye sebep olmamaktadır.

Anahtar Kelimeler: Diyabet; Koroid kalınlığı; Maküla; Tadalafil.

1- Yrd. Doç. Dr., Giresun Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Giresun, Türkiye

2- Yrd. Doç. Dr., İnönü Üniversitesi Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Malatya, Türkiye

3- Yrd. Doç. Dr., Giresun Üniversitesi Tıp Fakültesi, Üroloji Anabilim Dalı, Giresun, Türkiye

4- Prof. Dr., İnönü Üniversitesi Tıp Fakültesi, Üroloji Anabilim Dalı, Malatya, Türkiye

5- Prof. Dr., Giresun Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Giresun, Türkiye

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Yazışma Adresi / Correspondence Adress:
Murat Atabey ÖZER
Giresun Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Giresun, Türkiye

Phone: +90 505 601 1944
E-mail: dratabeyozer@yandex.com

INTRODUCTION

Erectile dysfunction (ED) is a common disorder with a prevalence of 50%–70% among 40–70-year old individuals, as reported in various studies. This rate may be higher in populations with disorders involving progressive vascular pathology such as diabetes[1]. ED is currently treated using pharmacologic agents such as the phosphodiesterase type 5 enzyme (PDE-5) inhibitors, sildenafil, tadalafil, and vardenafil in the absence of any contraindication. These agents dilate the smooth muscles of the vessel wall through the nitric oxide pathway, resulting in the vasodilatation necessary for erection[2]. They have been used in various doses and in various ways for patients with ED secondary to diabetes with successful outcomes[3].

Choroidal thickness and perfusion are reportedly lower in patients at various stages of diabetes and diabetic retinopathy (DR) than in the normal population[4-7]. Macular thickness has been shown to decrease significantly with a mild increase in the choroidal thickness in diabetic macular ischemia (DMI) compared to that in other types of diabetic macular oedemas. This is believed to be attributable to the choroidal response secondary to retinal ischemia[8].

PDE-5 inhibitors are observed to increase the choroidal thickness significantly in the normal population[9-11]. The acute effects of PDE-5 inhibitors have been evaluated in the normal population as well as in patient groups with adult macular degeneration (AMD); however, the long-term effects have not been investigated. Dundar et al. found no statistical difference in the ocular hemodynamic parameters after regular sildenafil use for 3 months[12]. Some studies have reported that choroidal perfusion, previously observed to decrease in AMD[13], increases with sildenafil use with potential positive effects on visual acuity and contrast sensitivity; however, this effect has not been investigated further[14].

We aimed to use optical coherence tomography (OCT) to evaluate the effects and adverse effects of the long-term use of low-dose tadalafil on macular and choroidal parameters in diabetic patients who had ED but did not have advanced DR or diabetic maculopathy that required treatment.

METHOD

This study followed the principles of the Declaration of Helsinki. The protocol for the present study was approved by the institutional review board. Written informed consent was obtained from all the study subjects. Total 37 eyes of 37 male patients with diabetes who presented to the urology department of our hospital and were diagnosed with ED secondary to diabetic neuropathy and scheduled for tadalafil treatment were included in this single-centred, open-label prospective study. Only the right eye was included if both the eyes of a patient were suitable for the study. All patients underwent complete ophthalmologic examination, visual acuity measurement, OCT, and fundus fluorescein angiography (FFA).

The patients for whom oral tadalafil administration was initiated were called for follow-up visits after the first use, at the fourth week, and then at the twelfth week. OCT and visual acuity measurements were repeated during these visits. FFA was also performed at the first and last follow-up visit for all patients.

Study inclusion criteria

All patients aged 30–60 years with Type 1 or Type 2 diabetes who were diagnosed with ED at the urology department of our hospital between November 2016 and February 2017 were included in the study.

Study exclusion criteria

Patients with uncontrolled diabetes or an additional systemic disorder who had been previously treated for ED; had undergone intraocular surgery; had DR and/or maculopathy requiring treatment, such as clinically significant macula oedema, cystoid macular oedema, diffuse macular thickening, or neovascularization; or had other ocular disorders such as uveitis or keratitis were excluded from the study.

Treatment protocol

Treatment was started with 5 mg tadalafil hydrochloride (Cialis®, Lilly USA, LLC Indianapolis, USA) for patients who were diagnosed with diabetes and ED and had not been previously treated. The first dose was administered at the urology department under the supervision of a healthcare technician. Thereafter, the patients were prescribed 1 tablet/day for 12 weeks (08:00 p.m.) after the necessary information was provided. The OCT scan and visual acuity measurement were repeated for all patients 1 hour after the first administration and at the fourth and twelfth weeks (09:00 a.m.).

Visual acuity

Best-corrected visual acuity (BCVA) was evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Chart "R"; Precision Vision, La Salle, Illinois, USA). The results were converted using the logMAR (logarithm of the minimal angle of resolution) logarithm before conducting the statistical analyses.

Macular parameters

The same Spectral (OCT) scanner (RS-3000, NIDEK Co. Ltd, Japan) was used for all measurements. The same

physician (MAÖ) performed the screening in all eyes. Mydriatic drops were not used.

Central macular thickness (CMT) was evaluated as the distance between the internal limiting membrane and the Bruch membrane at the central fovea.

The total macular volume (TMV) was calculated as the sum of the volumes at 9 sectors around the fovea measured using a Macular Map analysis, as defined in the ETDRS chart[15].

Choroidal thickness (CT) was measured manually as the perpendicular distance between the hyperreflective outer border of the retinal pigment epithelium layer and the sclera-choroidal interface. This measurement was taken from the following 5 separate points in all patients: the centre of the fovea (CF), temporal 1.5 mm, nasal 1.5 mm (N), superior 1.5 mm (S), and inferior 1.5 mm (I) (Figure-1).

Fundus fluorescein angiography

A Canon CX-1 fundus camera (Canon INC. Tokyo, Japan) was used for all FFA images. The same physician (MAÖ) performed the screening in all eyes.

Statistical analyses

The data were analysed using the Statistical Package for Social Sciences (SPSS) software (version 22.0 for Windows). The results are expressed as mean ± standard deviation (SD) values. The repeated measures analysis of variance (rANOVA) test was used, and P-value < 0.05 or < 0.001 was considered statistically significant.

RESULTS

We had to exclude one of the 37 study subjects owing to worsening of the diabetic condition; another subject was excluded because he refused to continue treatment.

The mean patient age was 48.5 ± 8.7 years, and the mean diabetes duration was 11.6 ± 2.1 years. The patients' baseline clinical characteristics and demographic data are presented in Table-1.

As shown in Table-2, there was no statistically significant change in BCVA from that at baseline (baseline; 0.21 ± 0.07, 12th week; 0.22 ± 0.06, logMar, $p > 0.05$). Further, there was also no statistical difference in the CMT and TMV measurements ($p > 0.05$). The mean CMT values at baseline, 1st day, 4th week, and 12th week were 236.7±32.4, 234.5±30.6, 235.1±35.7, and 234.8±32.8 µm,respectively. The mean TMV values were 9.88±1.21 mm^3 at baseline and 9.83±1.26 mm^3 at the 12th week.

There was a statistically significant increase in the mean CT compared to that at baseline at all the follow-up visits except for that at the 1st day (baseline; 248.7 ± 21.5, 1st day; 247.4 ± 23.2,4th week; 275.9 ± 21.3,and 12th week; 275.1 ± 24.4 µm, for the mean central foveal choroidal thickness, $p < 0.001$) (Table-3).

Moreover, there was no difference in the baseline FFA and that at the 12th week visit.

DISCUSSION

PDE-5 inhibitors are currently the treatment of choice for ED. Their mechanism of action involves the prevention of

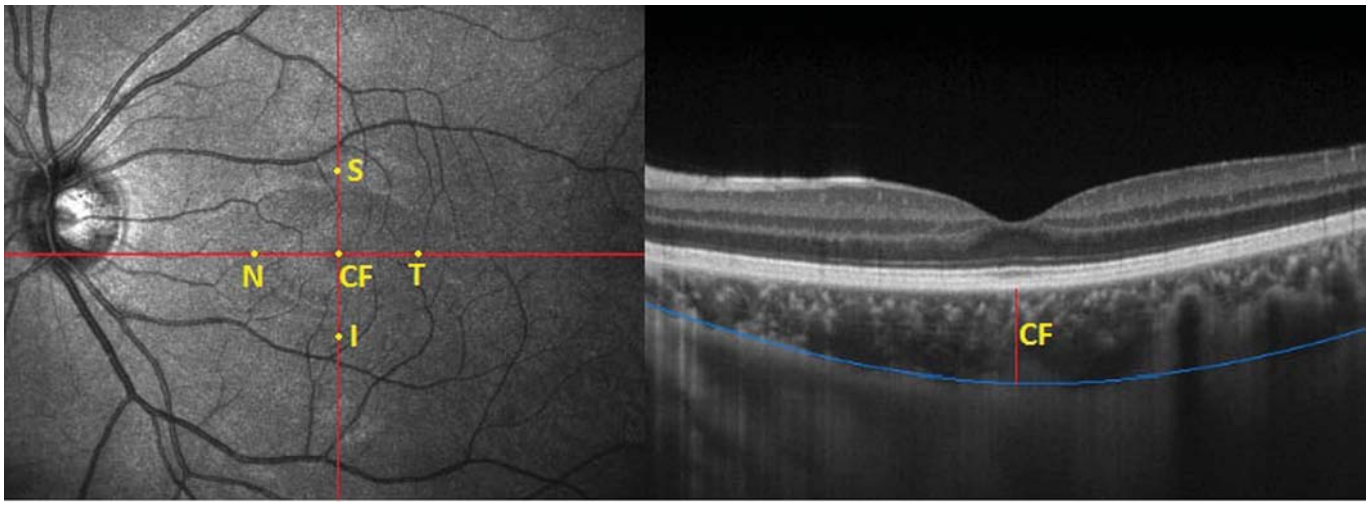

Figure 1. Left: *Scheme showing choroidal thickness measurements at 5 points: central fovea(CF), at 1.5 mm temporal(T), nasal(N), superior(S), and inferior(I) to the central fovea.*

Right: *A horizontal optical cohorens tomography scan in the macula showing choroidal structure. Choroidal thickness is determined as the perpendicular distance between the hyperreflective outer border of the retinal pigment epithelium and the sclero–choroidal interface drawn manually.*

Table 1. *Baseline Characteristics of Participants*	
Age (mean in years)	48.5±8.7
Type of diabetes, (%)	
Type 1	7(20)
Type 2	28(80)
Duration of diabetes (mean in years)	11.6±2.1
HbA1c levels, (%)	
≤6.0	2(6)
>6.0 to 8.0<	18(51)
8.0≤	15(43)
Duration of ED since first diagnosis (mean in years)	1.4±1.1
*Severity of ED, (%)	
Mild (17-21)	1(3)
Mild to moderate(12-16)	2(6)
Moderate(8-11)	20(58)
Severe(5-7)	12(34)
Features of retina, (%)	
Presence of DMP	10(29)
Presence of DMI	5(14)
History of PRP	9(26)
History of Focal/Grid	11(31)

* The International Index of Erectile Function (IIEF-5) Questionnaire. ED:Erectile dysfunction; DMP: Diabetic maculopathy; DMI: Diabetic macular ischemia; PRP: panretinal photocoagulation; Values are given as mean±SD.

cyclic guanosine monophosphate (cGMP) inactivation by transformation to guanosine monophosphate (GMP). cGMP is the intracellular mediator of the nitric oxide (NO) pathway. NO causes relaxation in the smooth muscles, resulting in the vasodilatation required for erection[2].

Table 2. *Changes in visual acuity and macular parameters*			
	VA	CMT	TMV
Baseline	0.75±0.21	236.7±32.4	9.88±1.21
1 st day	0.73±0.23	234.5±30.6	9.81±1.45
4 th week	0.77±0.23	235.1±35.7	9.86±1.28
12 th week	0.76±0.17	234.8±32.8	9.83±1.26
P*	>0.05	>0.05	>0.05

VA: Visual acuity (LogMAR); CMT: Central macular thickness (micrometer); TMV: Total macular volume(cubic millimeter); P*: Baseline vs. the other visits; Values are given as mean±SD.

PDE-5 inhibitors (tadalafil and vardenafil) have rapidly gained popularity as the treatment of choice for ED following the introduction of sildenafil to the market in 1998. Currently, the most commonly used drugs are sildenafil, tadalafil, and vardenafil. Tadalafil differs from the other agents in that it takes longer to reach its maximum concentration (15-120 minutes) and has a longer half-life (17.5 hours)[16]. It has been clinically demonstrated that treatment with 5 mg/day tadalafil in men with ED is well tolerated and effective[17]. In addition, studies suggest that 5 mg/day tadalafil may improve the erectile function in patients with partial response to on-demand PED5I therapy. Moreover, they evaluated the efficacy of daily use of tadalafil in the third month[18].

Considering the above-mentioned reasons and the fact that the only FDA-approved molecule for daily use is tadalafil, we routinely initiate treatment with 5 mg/day tadalafil for patients with ED in our clinic, with follow-up visits scheduled at 3 months.

To our knowledge, this is the only study that has investigated the effect of this treatment on the choroid and retina in diabetic patients. We evaluated the effect of long-term administration of low dose tadalafil on the choroidal and macular parameters in diabetic patients to investigate the

Table 3. *Changes in choroidal thickness, µm*					
	CFCT	TCT	NCT	SCT	ICT
Baseline	248.7±21.5	239.1±18.4	235.3±17.9	237.8±20.1	236.5±17.8
1 st day	247.4±23.2	239.6±23.5	237.7±23.8	239.3±22.5	237.4±22.3
4 th week	275.9±21.3	262.1±20.7	260.8±25.1	264.2±26.8	266.7±21.4
12 th week	275.1±24.4	260.6±22.9	258.4±23.7	261.2±27.2	267.7±20.7
P	P^1>0.05 P^2<0.001	P^1>0.05 P^2<0.001	P^1>0.05 P^2<0.001	P^1>0.05 P^2<0.001	P^1>0.05 P^2<0.001

CFCT: Central foveal choroidal thickness; TCT: Temporal choroidal thickness; NCT: Nazal choroidal thickness; SCT: Superior choroidal thickness; ICT: Inferior choroidal thickness; P^1: Baseline vs. first day; P^2, Baseline vs. the other visits; Values are given as mean±SD; µm: micrometer.

possible effects.

DR is the most common cause of blindness in adults. The main pathologic events in DR are retinal, neural, and vascular changes. The vascular permeability increases in the retinal vessels, and damage to the blood-retina barrier is known as the main cause of retinal ischemia and oedema[19]. Clinical and histopathological findings have demonstrated that the choroidal, and therefore, the retinal blood supply is compromised due to factors such as choriocapillaris obstruction, choroidal aneurysms, and neovascularization. The choroid supplies blood and oxygen to the retina; therefore, choroid hypoperfusion can cause dysfunction in the retina, especially in the outer layers[20,11].

Many studies have reported significantly lower choroidal thickness in diabetic patients than in the normal population[22-24].This partially explains the ischaemia and decreased oxygenation of the retina.

The effects of PDE-5 inhibitors on choroidal thickness and blood flow have previously been evaluated, giving varied results[25]. Dündar et al. studied the effects of sildenafil on ocular dynamics and reported no statistically significant difference in the retrobulbar blood flow levels based on the measurements conducted with colour Doppler imaging during and after 3 months of sildenafil use[26]. Kim et al. investigated choroidal perfusion and thickness following sildenafil use and found a significant increase in both; however, in this study, the measurements were obtained in the second hour after a single dose of drug was administered[9]. We found an increase in the choroidal thickness after the first use that continued for 3 months following long-term, low-dose use in our study.

Many studies have reported the ocular adverse effects of PDE-5 inhibitors. PDE-5 inhibitors have been reported to increase the intraocular pressure[27] and anterior chamber protein levels[28]. Adverse effects such as non-arterial anterior ischemic neuropathy and central serous retinopathy have also been reported[29]. We did not observe any macular or retinal problems related to tadalafil or other factors in our study. No statistically significant change was found in the retinal thickness at the macular region due to increased choroidal thickness or vascular supply.

Some previous studies have reported increased choroidal thickness and perfusion in eyes with AMD and stated that this change may be beneficial for this patient group in the long-term; however, these findings have not been supported by other studies[13,14].

In conclusion, the long-term use of low-dose tadalafil increased choroidal thickness at the submacular area in our diabetic patient group where the choroidal thickness and vascular supply were expected to decrease. Moreover, there were no retinal or macular adverse effects. We believe that low-dose tadalafil may have safely increased the long-term NO secretion in the choroidal vessels, increasing the choroidal thickness and perfusion, and thereby the retinal vascular supply and oxygenation. According to our results, tadalafil can be safely used to treat ED in diabetic patients.

Our study is limited by the fact that we did not include patients with advanced DR. The relatively lower sample size and the fact that ocular perfusion and choroidal blood flow were not evaluated are other limitations. The effects of tadalafil on macular parameters should be verified in prospective, multi-centre studies, especially those including patients diagnosed with severe DR.

Conflict of Interest

The authors declare that there is no conflict of interest.

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