

## Choroidal Thickness Values Following the Consumption of Sildenafil and Tadalafil: Comparison of the OCT Records

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### Abstract

**Objective:** The aim of this study is to demonstrate the anatomic and physiologic changes in the choroid following systemic sildenafil and tadalafil.

**Methods:** This cross-sectional randomized study enlisted 20 young and healthy men, who were randomly and equally classified in two groups; group A received 50 mg of Sildenafil, whereas group B received 10 mg of Tadalafil. All participants underwent a measurement of choroidal thickness, based on enhanced depth imaging optical coherence tomography (EDI-OCT). The measurement was repeated two hours after the consumption of each PDE-5 inhibitor.

**Results:** The mean age of participants was  $34.2 \pm 3.0$  and  $34.6 \pm 3.2$  years in group A and B, respectively. The mean values of choroidal thickness (CT) in Group A at baseline were  $306.6 \pm 11.1 \mu\text{m}$ ,  $229.9 \pm 12.7 \mu\text{m}$  and  $311.3 \pm 21.8 \mu\text{m}$  in temporal, nasal and inferior quadrants, respectively. The mean increase in choroidal thickness in Group A two hours after receiving sildenafil was  $29.9 \mu\text{m}$ ,  $23.8 \mu\text{m}$  and  $34.2 \mu\text{m}$  in temporal (CI [-35.18,-24.62],  $p < 0.001$ ), nasal (CI [-27.20,-20.40],  $p < 0.001$ ) and inferior ( $p = 0.005$ ) quadrants, respectively. On the other hand, the mean values of choroidal thickness in Group B at baseline were  $307.2 \pm 10.6 \mu\text{m}$ ,  $227.4 \pm 8.9 \mu\text{m}$  and  $315.8 \pm 9.1 \mu\text{m}$  in temporal, nasal and inferior quadrants, respectively. Significant raise was also noted in Group B two hours after tadalafil intake in temporal ( $13.2 \mu\text{m}$ , CI [-17.77,-8.63],  $p < 0.001$ ), nasal ( $12.7 \mu\text{m}$ , CI [-14.75,-10.65],  $p < 0.001$ ) and inferior ( $15.6 \mu\text{m}$ , CI [-17.36,-13.84],  $p < 0.001$ ) quadrants, respectively. The increment in choroidal thickness observed after the intake of PDE-5 inhibitors was greater in group A and this difference exhibited statistical significance (independent samples t-test, CT temporal:  $t(18) = 5.338$ ,  $p < 0.001$ , 95%CI [9.95, 22.85], Levene's test:  $p = 0.791$ , CT nasal:  $t(18) = 6.332$ ,  $p < 0.001$ , 95%CI [7.48, 14.92], Levene's test:  $p = 0.088$ , Mann-Whitney test, CT inferior:  $p < 0.001$ ).

**Conclusion:** Both sildenafil and tadalafil resulted in the increment of choroidal thickness, but tadalafil caused a lower increase. This alteration could secondary affect retinal function or be a useful adjunct whenever increase choroidal blood flow is demanded.

**Keywords:** Choroidal thickness; Enhanced depth imaging optical coherence tomography; Erectile dysfunction; Pathophysiology; Phosphodiesterase type 5 inhibitors; Sildenafil; Tadalafil

### Introduction

Erectile dysfunction, which is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance, is estimated to affect up to 30 million men in the United States, ranging from 39% around 40 years to 67% among men 70 years old [1,2]. The first line treatment of erectile dysfunction mainly concerns phosphodiesterase type 5 (PDE5) inhibitors, which include Sildenafil citrate (Viagra; Pfizer, Inc, New York, NY), longer active Tadalafil (Cialis; Lilly ICOS LLC, Indianapolis, Ind), Vardenafil hydrochloride (Levitra; Bayer AG, Leverkusen, Germany, and GlaxoSmithKline, Uxbridge, England), and Avanafil (Stendra; Vivus, Mountain View, CA). Mammalian 3',5'-cyclic nucleotide phosphodiesterases (PDEs), which are classified into 11 families (PDE1-11), are responsible for the degradation of cyclic nucleotides. The latter regulate the contraction and relaxation of vascular smooth

muscle [3]. PDE5, which is a cytosolic enzyme, is expressed in smooth and cardiac muscle, platelets, and retina along with PDE2, PDE6 and PDE9 isoforms. PDE2, PDE5 and PDE9 activate the retinal pigment epithelium (RPE) pump, via cGMP (cyclic guanosine monophosphate). On the other hand, PDE6 modifies the visual signal transduction, inducing the reduction of cGMP levels in photoreceptors, the closure of sodium channels in the outer segment cell membrane (of photoreceptors) and the membrane hyperpolarization [3-6].

Sildenafil is a very potent inhibitor of PDE-5 and of PDE-6 (10-fold less potent than on PDE5), resulting in the elimination of cGMP in cavernosal smooth-muscle cells, in smooth muscle relaxation and penile erection. Its maximal levels are achieved within 0.5-2 hours after oral ingestion and its mean terminal half-life is 3-5 hours [2,7-9]. The most common adverse effects of sildenafil are strongly associated with the suspension of PDE5 (headache, nasal congestion, flushing, and dyspepsia), of PDE6 (visual disturbances) and of PDE3 (hypotensive effect) isoforms [2,6]. The maximum concentrations of tadalafil are observed between 30min and 6 hours and it has a longer half-life of

17.5 hours, compared to sildenafil. Tadalafil is 700-fold and 9000-fold more potent for PDE5 than PDE6 and rest PDE, respectively, justifying the eliminated visual disturbances. However, it exhibits hypotensive action [7].

PDE inhibitors used in erectile dysfunction have been implicated in ocular side effects, including changes in color vision and light perception, blurred vision (central haze, transitory lower vision), transient alterations in electroretinogram (ERG), conjunctival hyperemia, ocular pain and photophobia [6]. Idiosyncratic dilation of retinal and choroidal vessels and accumulation of subretinal fluid appear to be responsible for idiopathic serous macular detachment (SMD), observed due to sildenafil citrate use [10]. Moreover, tadalafil administration has been also associated with the development of thickened and markedly hyper-reflective areas in the photoreceptors' internal-outer segment (IS-OS) interface, being accompanied with a serous retinal detachment-like appearance [11]. Both sildenafil and tadalafil have been related to central serous chorioretinopathy (CSC), which recedes after the discontinuation of the medication [12,13].

The aim of the present study was to demonstrate anatomic and physiologic changes in the human choroid following systemic sildenafil and tadalafil, using enhanced depth imaging (EDI) optical coherence tomography (OCT). This the first time in literature that the impact of tadalafil on chorioretinal vascular permeability and choroidal thickness is investigated.

## Methods

### Study design and patients

Twenty young and healthy men participated in this cross-sectional randomized study, which was conducted at the 1st University Eye Clinic of the General Hospital of Athens G. Gennimatas. All participants underwent an OCT measurement of choroidal thickness, which was repeated two hours after the consumption of a PDE-5 inhibitor. The participants were randomly classified in two groups; group A included ten individuals who received 50 mg of Sildenafil citrate (Viagra; Pfizer, Inc, New York, NY) and group B included ten individuals who received 10mg of Tadalafil (Cialis; Lily ICOS LLC, Indianapolis, Ind). The doses were adjusted to the recommended ones, which are 50 mg (maximum 100 mg) for sildenafil and 10mg (maximum 20 mg) for tadalafil [6,7]. We decided to administer the most commonly prescribed medications for erectile dysfunction in the dosage that they are usually received by the patients. Subjects were instructed to refrain from eating for at least four hours prior to the study.

The exclusion criteria were a history of any ocular or systemic disease such as retinal, choroidal or cardiovascular pathology and refractive errors >-5D. The study was performed in accordance to the tenets of the Declaration of Helsinki and the protocol used was approved by the ethics committee of the University Hospital. Written informed consent was obtained from all participants.

### OCT measurements

Choroidal thickness records were based on Heidelberg Spectralis (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). This device combines a spectral domain OCT and a confocal scanning laser ophthalmoscope in a single instrument. The acquisition rate of the Spectralis OCT is 40,000 A-scans per second. Its optical depth resolution is 7  $\mu$ m, the digital depth resolution amounts

to 3.5  $\mu$ m, while its transverse and axial resolutions are 20  $\mu$ m and 5  $\mu$ m, respectively. The subjects were not repositioned nor the instrument realigned during the whole scanning procedure, in order to keep the measurement conditions as constant as possible. Before examination, the pupils were dilated with drops containing 0.5% tropicamide and 2.5% phenylephrine.

The images of the choroid were acquired based on the enhanced depth imaging (EDI) OCT method, as already described by Margolis and Spaide [14]. The instrument was placed close enough to the eye to obtain inverted images, which were averaged using the automatic averaging and eye tracking features. Seven sections, each comprised of the 100 averaged scans, were obtained in a 5  $\times$  30 degree rectangle encompassing the macula and optic nerve, and the horizontal section going directly through the center of the fovea was selected. Choroidal thickness (CT) was determined as the distance from the outer surface of the hyper-reflective line, referred to as the RPE layer, to the hyper-reflective line of the inner sclera border. The choroidal thickness in areas of temporal, nasal and inferior quadrants was recorded. The resolution of the CT image is impaired in highly myopic elongated eyes and poorly fixating patients. All CT measurements were performed by the same well-trained and experienced operator at baseline and two hours after the consumption of sildenafil citrate or tadalafil.

### Statistical analysis

The statistical program IBM SPSS Statistics 22.0 was used for the data analysis. Descriptive analysis was carried out for age and choroidal thickness values; the latter were charted in box plots. Non-parametric analysis Kolmogorov-Smirnov was used to check the normal distribution of the variables. The paired two-tailed t-test was utilized to calculate the differences in means of choroidal thickness between baseline values and those after the consumption of the PDE-5 inhibitor within each group. If the data failed the normality test, the non-parametric Wilcoxon matched-pairs signed-rank test was used. Independent samples t-test and Mann-Whitney test were applied to identify the possible differences in means of choroidal thickness between two groups (Mann-Whitney test was used when there was no indication of normal distribution either after Kolmogorov-Smirnov analysis or after Levene's test for equality of variances). A p value less than 0.05 was considered to indicate statistical significance.

## Results

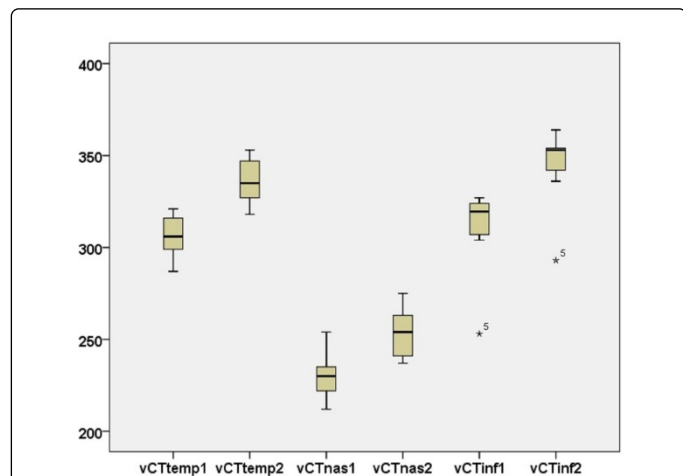
### Demographics

Twenty young and healthy individuals were recruited in this study. The mean age of participants was 34.2  $\pm$  3.0 and 34.6  $\pm$  3.2 years in group A and B, respectively. The distribution of age was normal among participants, according to Kolmogorov-Smirnov test. There were no differences in distribution of age between the groups (independent samples t-test:  $t(18)=-0.291$ ,  $p=0.774$ , Levene's test:  $p=1.000$ ).

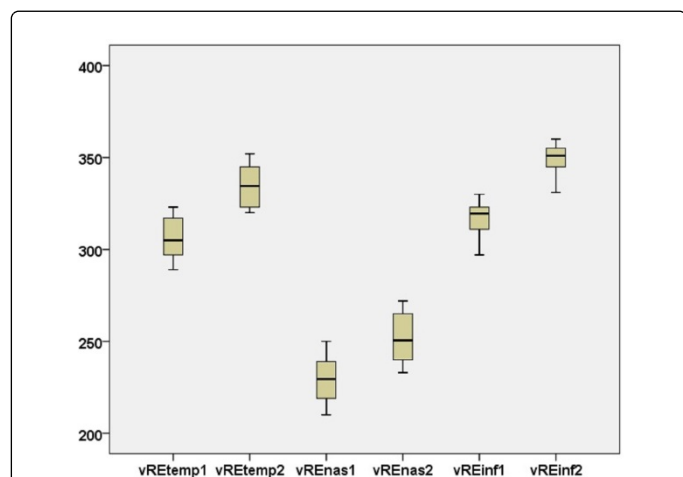
### The impact of PDE-5 inhibitor intake on choroidal thickness of the participants

The mean choroidal thickness (CT) in Group A at baseline was 306.6  $\pm$  11.1  $\mu$ m, 229.9  $\pm$  12.7  $\mu$ m and 311.3  $\pm$  21.8  $\mu$ m in temporal, nasal and inferior quadrants, respectively (Figure 1). The correspondent values for the same group after receiving 50 mg of sildenafil citrate were 336.5  $\pm$  12.4  $\mu$ m, 253.7  $\pm$  13.2  $\mu$ m and 345.5  $\pm$  20  $\mu$ m in temporal, nasal and inferior quadrants, respectively (Figure 1).

The mean values of choroidal thickness, as recorded in all three quadrants for each eye separately in group A before and after the consumption of sildenafil citrate are presented in Table 1 and Figures 2 and 3. The mean choroidal thickness in Group A was significantly increased in each quadrant after the intake of sildenafil (Table 2). Assessing each eye separately, significant raises in choroidal thickness were also noted in all areas (Table 3).



**Figure 1:** Distribution of mean choroidal thickness (CT) in three quadrants before and after the consumption of sildenafil citrate in group A.



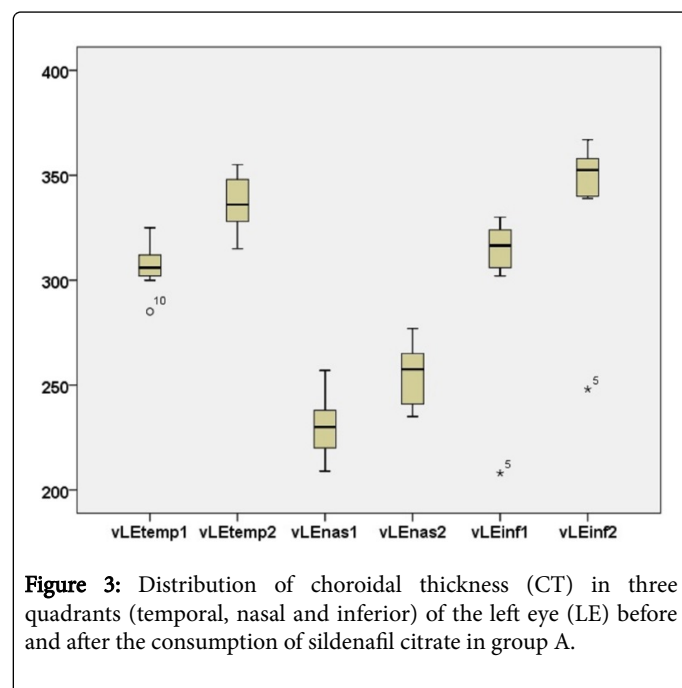
**Figure 2:** Distribution of choroidal thickness (CT) in three quadrants (temporal, nasal and inferior) of the right eye (RE) before and after the consumption of sildenafil citrate in group A.

CT (µm)	Mean	SD
vRE temp1	306	12.5
vRE temp2	335.2	12.4
vRE nas1	229.2	12.9
vRE nas2	252.5	13.6
vRE inf1	316	10.8

vRE inf2	349.1	9.2
vLE temp1	306.7	10.8
vLE temp2	336.9	12.9
vLE nas1	229.9	13.3
vLE nas2	254.4	13.5
vLE inf1	306	35.6
vLE inf2	341.3	34.1

vREtemp1: CT of right eye in temporal area at baseline; vREtemp2: CT of right eye in temporal area after sildenafil intake; vREnas1: CT of right eye in nasal area at baseline; vREnas2: CT of right eye in nasal area after sildenafil intake; vREinf1: CT of right eye in inferior area at baseline; vREinf2: CT of right eye in inferior area after sildenafil intake; vLEtemp1: CT of left eye in temporal area at baseline; vLEtemp2: CT of left eye in temporal area after sildenafil intake; vLEnas1: CT of left eye in nasal area at baseline; vLEnas2: CT of left eye in nasal area after sildenafil intake; vLEinf1: CT of left eye in inferior area at baseline; vLEinf2: CT of left eye in inferior area after sildenafil intake

**Table 1:** Choroidal thickness (CT) in all quadrants of the right (RE) and left (LE) eye, separately, in group A, before and after the consumption of sildenafil citrate.



**Figure 3:** Distribution of choroidal thickness (CT) in three quadrants (temporal, nasal and inferior) of the left eye (LE) before and after the consumption of sildenafil citrate in group A.

The mean choroidal thickness in Group B at baseline was  $307.2 \pm 10.6 \mu\text{m}$ ,  $227.4 \pm 8.9 \mu\text{m}$  and  $315.8 \pm 9.1 \mu\text{m}$  in temporal, nasal and inferior quadrants, respectively (Figure 4). The correspondent values were  $320.4 \pm 6.4 \mu\text{m}$ ,  $240.1 \pm 9.4 \mu\text{m}$  and  $331.4 \pm 9.4 \mu\text{m}$  in temporal, nasal and inferior quadrants, respectively, after receiving 10 mg of tadalafil (Figure 4). The mean values of choroidal thickness for each eye separately in group B, before and after the consumption of tadalafil, are presented in Table 4 and Figures 5 and 6. The mean choroidal thickness in Group B was significantly increased in each quadrant after the intake of tadalafil (Table 2). Assessing each eye separately, significant raises in choroidal thickness were also noted in all areas (Table 3).

		Tests	95% CI	Difference in mean
CT temporal (µm)	group A	paired 2-tailed t-test: t(9)= -12.8, p<0.001	-35.18,-24.62	-29.9
	group B	paired 2-tailed t-test: t(9)= -6.5, p< 0.001	-17.77,-8.63	-13.2
CT nasal (µm)	group A	paired 2-tailed t-test: t(9)= -15.8, p< 0.001	-27.20,-20.40	-23.8
	group B	paired 2-tailed t-test: t(9)= -14.0, p< 0.001	-14.75,-10.65	-12.7
CT inferior (µm)	group A	Wilcoxon matched-pairs signed-rank test, p=0.005	-	-34.2
	group B	paired 2-tailed t-test: t(9)= -20.1, p< 0.001	-17.36,-13.84	-15.6

**Table 2:** Assessing the significance of increase in choroidal thickness (CT) in three quadrants, which is noted after each PDE-5 inhibitor intake within each group. (CI= confidence interval).

		Tests	95% CI	Difference in mean
RE temporal	group A	paired 2-tailed t-test: t(9)= -14.8, p< 0.001	-33.65, -24.75	-29.2
	group B	paired 2-tailed t-test: t(9)= -8.4, p< 0.001	-19.05,-10.95	-15
RE nasal	group A	paired 2-tailed t-test: t(9)= -17.2, p< 0.001	-26.37,20.23	-23.3
	group B	paired 2-tailed t-test: t(9)= -11.8, p< 0.001	-12.16,-8.24	-10.2
RE inferior	group A	paired 2-tailed t-test: t(9)= -24.8, p< 0.001	-36.12,30.08	-33.1
	group B	paired 2-tailed t-test: t(9)= -12.1, p< 0.001	-18.75,-12.85	-15.8
LE temporal	group A	paired 2-tailed t-test: t(9)= -9.3, p< 0.001	-37.58,-22.82	-30.2
	group B	paired 2-tailed t-test: t(9)= -11.4, p< 0.001	-14.39,-9.62	-12
LE nasal	group A	paired 2-tailed t-test: t(9)= -14.0, p< 0.001	-28.45,-20.55	-24.5
	group B	paired 2-tailed t-test: t(9)= -9.3, p< 0.001	-19.04,-11.56	-15.3
LE inferior	group A	Wilcoxon matched-pairs signed-rank test, p=0.005	-	-35.3
	group B	paired 2-tailed t-test: t(9)= -11.7, p< 0.001	-17.77,-12.03	-14.9

CI: Confidence Interval; RE: Right Eye, LE: Left Eye

**Table 3:** The significance of increase in choroidal thickness (CT), which follows the PDE-5 inhibitor administration, for each eye separately, between the two groups. (CI= confidence interval).

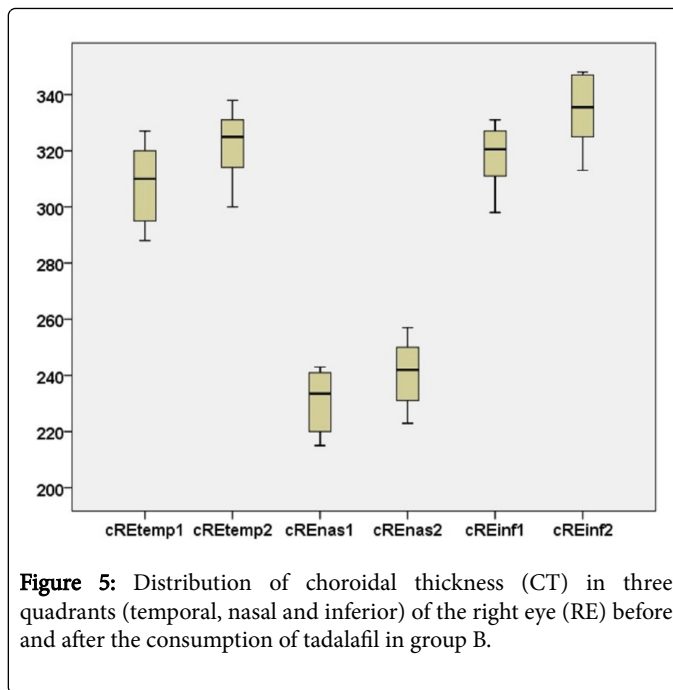
	Mean	SD
cR Etemp1	307.8	14
cR Etemp2	322.8	11.8
cR Enas1	231.1	10.6
cR Enas2	241.3	11.2
cR Einf1	317.6	11.6
cR Einf2	333.4	13.5
cL Etemp1	306	8.2
cL Etemp2	318	7.9
cL Enas1	223.1	8.7
cL Enas2	238.4	10

cL Einf1	313.9	8.8
cL Einf2	328.8	8.2
cREtemp1= CT of right eye in temporal area at baseline, cREtemp2= CT of right eye in temporal area after tadalafil intake, cREnas1= CT of right eye in nasal area at baseline, cREnas2= CT of right eye in nasal area after tadalafil intake, cREinf1= CT of right eye in inferior area at baseline, cREinf2= CT of right eye in inferior area after tadalafil intake, cLEtemp1= CT of left eye in temporal area at baseline, cLEtemp2= CT of left eye in temporal area after tadalafil intake, cLEnas1= CT of left eye in nasal area at baseline, cLEnas2= CT of left eye in nasal area after tadalafil intake, cLEinf1= CT of left eye in inferior area at baseline, cLEinf2= CT of left eye in inferior area after tadalafil intake		

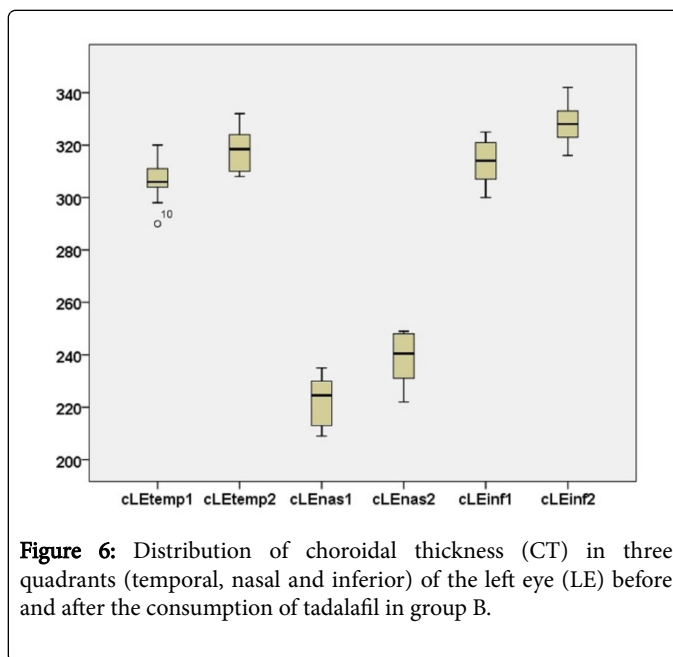
**Table 4:** Choroidal thickness (CT) in all quadrants of the right (RE) and left (LE) eye, separately, in group B, before and after the consumption of tadalafil.

### Comparison of sildenafil and tadalafil effects on participants

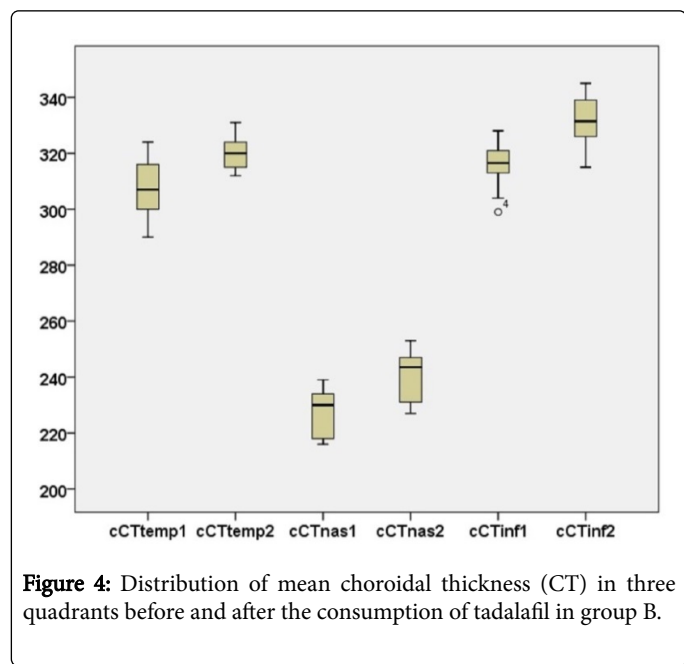
Assessing the mean choroidal thickness (CT) of the participants at baseline, no statistical significant differences were observed between the two groups (independent samples t-test, CT temporal:  $t(18)=-0.124$ ,  $p=0.903$ , Levene's test:  $p=0.935$ , CT nasal:  $t(18)=0.511$ ,  $p=0.616$ , Levene's test:  $p=0.473$ , Mann-Whitney test, CT inferior:  $p=0.912$ ). Similarly, the mean choroidal thickness of each eye separately appeared no statistical significant differences between the two groups at baseline (Table 5). On the other hand, the mean choroidal thickness after the consumption of sildenafil or tadalafil was statistically different between the two groups (Mann-Whitney test, CT temporal:  $p=0.005$ , independent samples t-test, CT nasal:  $t(18)=2.647$ ,  $p=0.016$ , Levene's test:  $p=0.321$ , CT inferior:  $t(18)=2.018$ ,  $p=0.059$ , Levene's test:  $p=0.232$ ). Statistically significant differences were also noted in the mean choroidal thickness of some quadrants for each eye separately, after the administration of the drugs (Table 5). The increase in choroidal thickness observed after the intake of PDE-5 inhibitors was greater in group A and this difference exhibited statistical significance (independent samples t-test, CT temporal:  $t(18)=5.338$ ,  $p<0.001$ , Levene's test:  $p=0.791$ , CT nasal:  $t(18)=6.332$ ,  $p<0.001$ , Levene's test:  $p=0.088$ , Mann-Whitney test, CT inferior:  $p<0.001$ ).



**Figure 5:** Distribution of choroidal thickness (CT) in three quadrants (temporal, nasal and inferior) of the right eye (RE) before and after the consumption of tadalafil in group B.



**Figure 6:** Distribution of choroidal thickness (CT) in three quadrants (temporal, nasal and inferior) of the left eye (LE) before and after the consumption of tadalafil in group B.



**Figure 4:** Distribution of mean choroidal thickness (CT) in three quadrants before and after the consumption of tadalafil in group B.

	t-test			Levene's Test
	t (18)	p	95% CI	p
REtemp1	-0.304	0.765	-14.25, 10.65	0.603
REtemp2	2.296	0.034	-1.05, 23.75	0.676
REnas1	-0.359	0.724	-13.01, 9.21	0.808
REnas2	2.005	0.06	-0.54, 22.94	0.559
REinf1	-0.32	0.753	-12.12, 8.92	0.707



REinf2	3.036	0.007	4.83, 26.57	0.113
LEtemp1	0.164	0.872	-8.29, 9.70	0.563
LEnas1	1.352	0.193	-3.77, 17.37	0.414
LEnas2	3.008	0.008	4.82, 27.18	0.212
LEinf2	1.126	0.275	-10.82, 35.82	0.141

REtemp1= CT of right eye in temporal area at baseline, REtemp2= CT of right eye in temporal area after the drug intake, RENas1= CT of right eye in nasal area at baseline, RENas2= CT of right eye in nasal area after the drug intake, REinf1= CT of right eye in inferior area at baseline, REinf2= CT of right eye in inferior area after the drug intake, LEtemp1= CT of left eye in temporal area at baseline, LEtemp2= CT of left eye in temporal area after the drug intake, LEnas1= CT of left eye in nasal area at baseline, LEnas2= CT of left eye in nasal area after the drug intake, LEinf1= CT of left eye in inferior area at baseline, LEinf2= CT of left eye in inferior area after the drug intake

**Table 5:** Independent Samples Test for the mean choroidal thickness of each eye separately at baseline and after the consumption of sildenafil or tadalafil between the two groups. (CI= confidence interval).

## Discussion

In this study, we noted a significance raise in choroidal thickness in twenty young and healthy individuals, who received 50mg of sildenafil citrate (temporal: from  $306.6 \pm 11.1 \mu\text{m}$  to  $336.5 \pm 12.4 \mu\text{m}$ , nasal: from  $229.9 \pm 12.7 \mu\text{m}$  to  $253.7 \pm 13.2 \mu\text{m}$  and inferior: from  $311.3 \pm 21.8 \mu\text{m}$  to  $345.5 \pm 20 \mu\text{m}$ ) or 10 mg of tadalafil (temporal: from  $307.2 \pm 10.6 \mu\text{m}$  to  $320.4 \pm 6.4 \mu\text{m}$ , nasal: from  $227.4 \pm 8.9 \mu\text{m}$  to  $240.1 \pm 9.4 \mu\text{m}$ , inferior: from  $315.8 \pm 9.1 \mu\text{m}$  to  $331.4 \pm 9.4 \mu\text{m}$ ). This increment was observed in mean choroidal thickness both of each participant and of each eye separately. Moreover, we highlighted that although there were no statistically significant differences in participants' means of choroidal thickness at baseline, the increase of the latter was greater in the group of sildenafil (increase in group A: temporal=9.8%, nasal=10.4%, inferior: 11.0%, increase in group B: temporal=4.3%, nasal=5.6%, inferior: 4.9%).

Similarly, Kim et al. noted raised choroidal perfusion and thickness in seven healthy male subjects two hours after ingesting 50mg of sildenafil. Specifically, the average choroidal thickness for all eyes augmented by 11.6% to  $334 \mu\text{m}$  temporal to the fovea, 9.3% to  $254 \mu\text{m}$  nasal to the fovea, and 10.7% to  $337 \mu\text{m}$  underneath the fovea. Furthermore, the average choroidal thickness in right eyes raised by 11.7% to  $325 \mu\text{m}$  temporal to the fovea, 7.5% to  $243 \mu\text{m}$  nasal to the fovea and 11.2% to  $327 \mu\text{m}$  underneath the fovea, whereas in left eyes it was increased by 11.5% to  $343 \mu\text{m}$  temporal to the fovea, 11.0% to  $265 \mu\text{m}$  nasal to the fovea and 10.2% to  $348 \mu\text{m}$  underneath the fovea [15]. Moreover, Vance et al. measured the choroidal thickness, based on EDI-OCT, in 8 healthy subjects (4 men and 4 women) 1 and 3 hours after the ingestion of 100 mg of sildenafil citrate and they identified its elevation [16].

Kurtulan et al. noted that although sildenafil increases systolic and diastolic systemic arterial blood pressures, it had no effect on central retinal artery circulation, even in subjects with ocular side-effects [17]. The ocular symptoms caused by sildenafil were associated with the alterations in choroidal perfusion and the inhibition of PDE6 [17]. The latter inhibition seemed to be dose- and time-dependent [18]. On the other hand, Quiram et al. attributed the SMD following the receipt of sildenafil to idiosyncratic dilation of retinal and choroidal vessels, leakage across the RPE and accumulation of subretinal fluid [10]. Features such as painful red eye, subretinal and intratumoral hemorrhages, and intratumoral vascular congestion, detected in a patient with a malignant melanoma of the ciliary body and choroid,

after receiving a single tadalafil tablet indicated the vasodilator effect of the latter on the eye [19]. Moreover, tadalafil has been implicated in the development of concurrent central retinal artery occlusion (CRAO) in patients with additional risk factors, such as sickle cell disease [20]. In our study, choroidal thickness after tadalafil intake was measured for the first time in literature. Indeed, we found that tadalafil caused a lower increase of choroidal thickness in all quadrants compared to sildenafil.

Yuan et al. observed that sildenafil activated the synthase of nitric oxide (NO), via extracellular signal-regulated kinase (ERK) signaling, resulting in NO production and guanylyl cyclase activation [21]. The following accumulation of cGMP within vascular smooth muscles elicited the opening of the selective adenosine triphosphate (ATP)-sensitive potassium (KATP) channels in some types of vasculatures [21]. This cascade was implicated in the inhibition of transmembrane influx of calcium through voltage-gated calcium channels due to membrane hyperpolarization, leading to vasorelaxation [21]. Moreover, they highlighted that the clinical doses of sildenafil did not cause potent vasodilation in retinal arterioles, but sildenafil seemed to have a significant impact on retinal perfusion [21]. They observed that 10 ng/mL of sildenafil were the threshold concentration for the dilation of retinal arterioles, whereas, even in the highest concentration (1  $\mu\text{g}/\text{mL}$ ), the elicited dilation reached the 30% of the maximum [21].

Furthermore, sildenafil has been associated with alterations in retinal function. Luu et al. recorded depressed but normal full-field and multifocal cone ERGs in macula and periphery after the administration of 200 mg sildenafil [22]. Prolonged implicit times of rod (maximum response a-wave) and cone (oscillatory potentials, cone response b-wave, 30 Hz-flicker and 3.3 Hz-flicker a-wave and b-wave) ERG responses in subjects receiving a single 100 mg dose of sildenafil were also recorded by Jäggle et al. [23]. Similarly, two more studies supported a higher rod sensitivity (decrease in K) and response to light stimuli, as recorded by ERG 1 and 2 hours after ingesting 50 and 100 mg of oral sildenafil, respectively [24,25]. The anatomical and functional effects of sildenafil seem to be attributed to its high affinity with melanin [12]. The prolonged accumulation of sildenafil in the retina and the potent inhibition of PDE-6, compared to tadalafil, are possible related to the greater augmentation of choroidal thickness induced by the former. Besides, as it has already stated before, the fact that tadalafil is 700-fold more potent for PDE5 than PDE6 eliminates its visual adverse effects.

In summary, we concluded that both sildenafil and tadalafil raised choroidal thickness two hours after their consumption by healthy individuals. Moreover, the former induced greater increment in choroidal thickness, maybe due to its higher affinity with PDE5 compared to PDE6. This the first study in literature which compares both drugs in healthy individuals. This the first time in literature that the effect of tadalafil on chorioretinal vascular permeability and choroidal thickness is investigated. Physicians who prescribe these medications should have in mind these alterations, which could secondary affect retinal function and explain previously reported clinical symptoms and pathologies, including idiopathic serous macular detachment and central serous chorioretinopathy. Both drugs may also be a potential useful adjunct to the treatment of ocular diseases that would benefit from increased choroidal blood flow.

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