ORIGINAL ARTICLE

# Retinal Nerve Fibre Layer, Macular and Choroidal Thickness in Erectile Dysfunction Patients on Sildenafil

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## ABSTRACT

**Introduction:** Sildenafil citrate is an effective treatment for erectile dysfunction (ED). Despite established safety profile, its long-term ocular implications remain unclear. We evaluate the relationship between the duration of use with retinal nerve fibre layer (RNFL), macular and choroidal thickness. **Materials and methods:** A cross-sectional study was done between July 2020 and June 2021, among 47 ED patients on sildenafil. The subjects fulfilling the inclusion criteria underwent optical coherent tomography (OCT) to evaluate RNFL, macular and choroidal thickness. Linear regression analysis was done to assess the relationship between duration of use with OCT parameters. Other possible associated factors were evaluated. **Results:** Forty-seven patients with the mean age of 54.30±8.41 years old recruited. These patients had not experienced visual disturbance on each sildenafil use. There were significant correlations between diabetes mellitus (DM) (r=0.330, P=0.023), erection hardness score (EHS) (r=-0.469, P=0.001) and total cumulative dose (r=0.806, P=<0.001) with duration of use. Duration of use had significant negative linear relationship with the average RFNL (b = -0.284, P=<0.001), superior RNFL (b = -0.195, P=0.018), and inferior RNFL (b = -0.887, P=<0.001). Multiple linear regression (MLR) reveals average RNFL was also influenced by total cumulative dose (b = -0.003, P = 0.029). No significant relationship observed to the macular thickness. Significant linear relationship observed between duration of use with sub-foveal choroidal thickness (b = 0.640, P<0.001). **Conclusion:** Sildenafil in general does not cause visual symptoms, however subclinical ocular changes; RNFL thinning and choroidal thickening may be influenced by its duration of use. Long term ocular monitoring is recommended.
*Malaysian Journal of Medicine and Health Sciences* (2024) 20(4): 89-96. doi:10.47836/mjmhs20.4.12

**Keywords:** Sildenafil citrate, Erectile dysfunction, Tomography, Optical coherence, Nerve fibers, Retina, Choroid

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## INTRODUCTION

Erectile dysfunction (ED) is an inability to attain and/or maintain penile erection for satisfactory sexual intercourse, resulting from discoordination of biopsychosocial erection process (1). Sildenafil citrate is a potent selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) enzymes, which enhances the nitric oxide (NO)-cGMP pathway. It improves the rate of successful erection and sexual intercourse, by significantly improving penile blood flow by NO-mediated smooth muscle relaxation of the corpora cavernosa and penile arteriolar smooth muscles (2–5).

At the ocular level, sildenafil has a tenfold less potent inhibitory activity than on PDE5 against the cGMP dependent PDE6 enzyme, a unique isoenzyme abundantly located in the retina where the photoreceptor outer segments are in high concentration (6,7). The expected visual symptoms such as blurry vision, transient colour tinge, heightened sensitivity to light as well as transient impairment of colour discrimination were mild and in consistent with the pharmacokinetic profile of sildenafil, as they occurred in relation to peak plasma free concentrations and resolved in time with the drug metabolism and elimination (8-11).

Despite the well-established safety profile, concerning

reports of sildenafil associated serious ocular complications kept emerging, although post-marketing reports and controlled trials couldn't find the causal link of sildenafil to optic nerve, retinal and choroidal injury. Not less than 40 case reports and case series have associated ischemic optic neuropathy with PDE5 inhibitors, while Pomeranz et al found 553 cases of Non-arteritic anterior ischemic optic neuropathy (NAION) reported in the United States Food and Drug Administration (FDA) adverse event reporting system (12). Case of sildenafil related retinal toxicity also has been reported by Yanoga et al. post ingestion of an incorrect dose of liquid sildenafil (13). Additionally, Li et al. reported a case of outer retinal damage in the foveal area, following consumption of 2000 mg sildenafil (14). At least 12 cases of central serous chorioretinopathy (CSCR) were reported associating them to sildenafil use (15). Furthermore, cases of sildenafil-associated serous macular detachment with leakage across the retinal pigment epithelium (RPE) and accumulation of subretinal fluid were also documented in patients using sildenafil for extended duration (16).

These reported ocular insults are believed to result from persistent sildenafil-induced high plasma noradrenaline levels causing focal ischemia (17), transient repetitive increase in intraocular pressure (IOP) leading to mechanical compression of the optic nerve head (ONH) as well as (18), NO induced autoregulation disruption causing limited retinal perfusion (19). All these mentioned are especially worrying, especially considering sildenafil as a form of treatment, not a cure; hence requiring prolonged duration of use (20). This places sildenafil-dependent-gentlemen at risk of getting possible blinding ocular events throughout their duration of use. Although acute dose-related toxicity effects have been established, the implication of long-term regular use of sildenafil and total cumulative sildenafil dose effects to the optic nerve, retina and choroid are still somewhat unclear.

In this study, we explore the relationship between duration of sildenafil use with retinal nerve fibre layer (RNFL) thickness, macular thickness, and choroidal thickness. Additionally, we also evaluate other possible confounders affecting these parameters.

## MATERIALS AND METHODS

This cross-sectional study was approved by the Human Research Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/ 20020121), and conducted in accordance with the tenets of the Declaration of Helsinki.

Recruitment of ED patients on sildenafil were done in the Men's Health Clinic, Hospital Universiti Sains Malaysia (HUSM) between July 2020 and June 2021. The sample size was calculated with OpenEpi, v3.01, referencing Men's Health HUSM Clinic 2019 census and Nicolosi et al (21). A total of 47 patients aged 40 and above, diagnosed with ED by men's health physician with the International Index of Erectile Function questionnaire (IIEF-5) diagnostic tool were recruited. Patients must be on regular sildenafil with the minimum dosage of 50 mg for at least a month before the study. The duration of sildenafil use is quantified in months, by cross referencing follow-up records with patients' self-reporting. Subjects with a pre-existing optic neuropathy, retinopathy, maculopathy, history of trauma or previous ocular surgery, and systemic neurological and demyelinating diseases, as well as those on systemic oculo-toxic drugs such as chloroquine, hydroxychloroquine were excluded. Other exclusion criteria include subjects with impaired media opacity including corneal scar, significant cataract, and vitreous opacity. Patients with poorly controlled diabetes mellitus of HbA1c >8.0% within 3 months, poorly controlled hypertension of more than 140/90 mmHg and uncontrolled hyperlipidemia of LDL > 3.0 mmol/L were also excluded from the study.

Consenting patients underwent visual acuity assessment, IOP, thorough ocular and fundus examinations with slit lamp biomicroscope (Topcon Corp, Japan). Optical Coherence Tomography (OCT) examination was done to measure RNFL, macular and choroidal thickness using Cirrus HD-OCT (Carl Zeiss Meditec Inc, USA) machine. Tests were done by a single well-trained operator, with accepted scan of signal strength of 6/10 and more. Measurement taken on the right eye, which include superior, inferior, nasal, temporal and average RNFL thickness. Retinal thickness values were obtained on all images for foveal subfield and the inner and outer rings of a standard Early Treatment of Diabetic Retinopathy Study (ETDRS) grid. Sub-foveal choroidal thickness was carefully measured manually with OCT setting changed to high definition (HD) 1-line 100x, using the Cirrus linear measurement tool from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera with a forethought that slight positional difference will potentially affect the measurement.

Data analysis was performed using IBM SPSS statistics version 27.0 (IBM Corp, Armonk, NY) with the descriptive analysis done to describe the demographic data and ocular parameters. Duration of sildenafil use in month is decided as the independent variable. Correlation between the clinical profile variables with the duration of use is measured by Pearson's correlation following Cohen strength of association of r value of less than 0.3 as weak, more than 0.5 as strong, and between 0.3 and 0.5 as moderate. Simple linear regression analysis was used to identify the relationship and associations of duration of sildenafil use with the RNFL, macular and choroidal thickness, while other possible factors to affect the OCT parameters were further analysed with multiple linear regression analysis. R-square is analysed to see how well the regression model fits the data set.

The correlation and regression analysis of P<0.05 are considered as statistically significant.

## RESULTS

A total of 47 Malay ED patients on sildenafil were recruited in this study. The mean age was 54.30±8.41 years old (range 41-71). As detailed in Table Ia, majority of the ED patients had an erection hardness score (EHS) of 2 accounting for 44 patients (93.6%), while the remaining had a score of 1. The mean duration of sildenafil use was 14.51±8.90 months with mean cumulative dose of 937.23±607.78 mg. Majority had underlying medical illnesses of which diabetes mellitus (DM) accounts the highest for 68.1% (32 patients). No significant visual disturbance was reported among the patients on every sildenafil intake with the mean Logarithm of the Minimum Angle of Resolution (logMAR) best corrected visual acuity (BCVA) was 0.31±0.25 and the mean IOP of 15.00±3.54 mmHg. The ocular parameters are described in Table Ib.

**Table Ia.: Demographic data and ocular parameters of ED patients on sildenafil (n = 47)**

| Variables | Mean (SD) |
|---|---|
| **Age (years)** | 54.30 (8.41) |
| **Medical illness** | |
| No medical illness | 8 (17.0)* |
| DM | 32 (68.1)* |
| Hypertension | 27 (57.4)* |
| Hyperlipidemia | 30 (63.8)* |
| CKD | 6 (12.8)* |
| **EHS** | |
| 0 – Penis does not enlarge | 0 (0.0)* |
| 1 – Penis is larger but not hard | 3 (6.4)* |
| 2 – Penis is hard but not hard enough for penetration | 44 (93.6)* |
| 3. – Penis is hard enough for penetration but not completely hard | 0 (0.0)* |
| 4. – Penis is completely hard and fully rigid | 0 (0.0)* |
| **Duration of sildenafil use (months)** | 14.51 (8.90) |
| **Total cumulative sildenafil dose (mg)** | 937.23 (607.78) |

*n (%)
DM = Diabetes mellitus, CKD = Chronic kidney disease, EHS = Erection hardness score

**Table Ib. : Ocular parameters of ED patients on sildenafil (n = 47)**

| Variables | Mean (SD) |
|---|---|
| **LogMAR BCVA** | 0.31 (0.25) |
| **IOP** | 15.00 (3.54) |
| **RNFL thickness (µm)** | |
| Average | 92.98 (3.81) |
| Superior | 114.06 (5.03) |
| Inferior | 117.62 (10.91) |
| Nasal | 72.11 (3.88) |
| Temporal | 68.13 (3.59) |

CONTINUE

**Table Ib. : Ocular parameters of ED patients on sildenafil (n = 47) (CONT.)**

| Variables | Mean (SD) |
|---|---|
| **Macular thickness (µm)** | |
| Average | 285.58 (3.09) |
| Central | 248.38 (3.67) |
| Superior outer | 285.62 (6.09) |
| Inferior outer | 271.68 (20.17) |
| Nasal outer | 268.98 (3.08) |
| Temporal outer | 267.53 (11.40) |
| Superior inner | 304.87 (7.16) |
| Inferior inner | 313.19 (3.62) |
| Nasal inner | 304.57 (6.03) |
| Temporal inner | 305.38 (2.98) |
| **Choroidal thickness (µm)** | |
| Sub-fovea | 249.70 (10.64) |

*n (%)
#Range
BCVA = Best corrected visual acuity, IOP = Intraocular pressure, RNFL = Retinal nerve fibre layer

We observe a significant correlation between DM, EHS, and total cumulative sildenafil dose, with the duration of sildenafil use as detailed in Table II. DM noted to have a significant moderate positive correlation with duration of sildenafil use (r = 0.330), while EHS score was found to have a significant moderate negative correlation (r = -0.469). Total cumulative sildenafil dose found to have a strong correlation with duration of use (r = 0.806).

**Table II: Correlation between demographic and clinical profiles with duration of sildenafil use**

| Variables | Pearson's correlation (r) | P-value |
|---|---|---|
| Age | 0.219 | 0.139 |
| DM | 0.330 | **0.023** |
| Hypertension | 0.177 | 0.234 |
| Hyperlipidemia | 0.260 | 0.078 |
| CKD | 0.282 | 0.055 |
| EHS | -0.469 | **0.001** |
| Total cumulative sildenafil dose | 0.806 | **<0.001** |
| IOP | -0.050 | 0.740 |

Significant: P<0.05
DM = Diabetes mellitus, CKD = Chronic kidney disease, EHS = Erection hardness score, IOP = Intraocular pressure

### Relationship between duration of sildenafil use and RNFL thickness

Based of simple linear regression analysis (SLR), we found the duration of sildenafil use to have a significant negative linear relationship with the average RNFL, with the regression coefficient of -0.284. The RNFL quadrants with similar significant findings were superior and inferior quadrants with the regression coefficient of -0.195 and -0.887 respectively as detailed in Table III. The other variables with significant linear relationship with RNFL thickness were total cumulative sildenafil and chronic kidney disease with respective regression coefficient of -0.004 and -3.797.

**Table III: Relationship of duration of sildenafil use (months) with RNFL thickness (µm)**

| Predicted Variables (RNFL thickness) | Crude *b* (95% CI)[a] | t-stat | P-value |
|---|---|---|---|
| Average RNFL | -0.284 (-0.380, -0.188) | -5.939 | **<0.001** |
| Superior RNFL | -0.195 (-0.354, -0.035) | -2.461 | **0.018** |
| Inferior RNFL | -0.887 (-1.141, -0.633) | -7.031 | **<0.001** |
| Nasal RNFL | -0.027 (-0.158, 0.103) | -0.421 | 0.676 |
| Temporal RNFL | -0.026 (-0.147, 0.095) | -0.431 | 0.669 |

[a]Simple linear regression, significant: P<0.05
RNFL = Retinal nerve fibre layer

All significant parameters including parameters with p<0.25 were then included in multiple linear regression (MLR) as detailed in Table IV. Because of its clinical significance, hyperlipidemia and IOP were also included in the analysis. The MLR model revealed duration of sildenafil use and total cumulative sildenafil dose, to have significant linear relationship with RNFL thickness, with the adjusted regression coefficient of -0.157 and -0.003 respectively. Other variables found to have non-significant relationships. These negative regression coefficients signify decreased RNFL thickness with increased duration of sildenafil use and total cumulative dose.

**Table IV: Relationship of other variables with average RNFL thickness**

| Average RNF thickness | Simple Linear Regression | | Multiple Linear Regression | |
|---|---|---|---|---|
| | Crude *b*[a] 95% CI | P-value | Adj. *b*[b] 95% CI | P-value |
| Duration of sildenafil use (months) | -0.284 (-0.380, -0.188) | <0.001 | -0.157 (-0.309,-0.004) | 0.044 |
| Total cumulative sildenafil dose (mg) | -0.004 (-0.006, -0.003) | <0.001 | -0.003 (-0.05, 0.000) | 0.029 |
| Age | -0.118 (-0.249, 0.013) | 0.077 | | |
| DM | -1.720 (-4.092, 0.652) | 0.151 | | |
| Hypertension | -1.778 (-4.004, 0.448) | 0.115 | | |
| Hyperlipidemia | -0.586 (-2.935, 1.762) | 0.618 | | |
| CKD | -3.797 (-6.991, -0.603) | 0.021 | | |
| IOP | 0.042 (-0.281, 0.365) | 0.796 | | |

[a]Crude regression coefficient
[b]Adjusted regression coefficient, $R^2$ = 51%
Assumption for Linear Regression including Linearity and Homoscedasticity were met
Significant: P<0.05
DM = Diabetes mellitus, CKD = Chronic kidney disease, IOP = Intraocular pressure

### Relationship between duration of sildenafil use and macular thickness

As for macular thickness analysis, duration of sildenafil use was found to have no significant linear relationship with macular thickness in our ED patients. Other variables analysed including total cumulative dose, age, DM, hypertension, hyperlipidemia, CKD and IOP also noted to have no statistically significant association with macular thickness.

### Relationship between duration of sildenafil use and choroidal thickness

Regarding sub-foveal choroidal thickness SLR analysis in Table V, duration of sildenafil use was observed to have a significant linear relationship with the sub-foveal choroidal thickness, with the regression coefficient of 0.662. Similar finding was found with the total cumulative sildenafil dose, of which the regression coefficient was noted to be 0.008.

All significant parameters including parameters with p<0.25 were then included in MLR. Because of their clinical significance, age and hyperlipidemia were also included in the analysis. The MLR model revealed the duration of sildenafil use alone to have significant linear relationship with RNFL thickness, with the adjusted regression coefficient of 0.640, while other variables found to have non-significant relationships. Sub-foveal choroidal thickness was observed to increase with the increase of duration of sildenafil use.

**Table V: Relationship of duration of sildenafil use (months) and other variables with sub-foveal choroidal thickness (µm)**

| Sub-foveal Choroidal Thickness | Simple Linear Regression | | Multiple Linear Regression | |
|---|---|---|---|---|
| | Crude *b*[a] 95% CI | P-value | Adj. *b*[b] 95% CI | P-value |
| Duration of sildenafil use (months) | 0.662 (0.363, 0.962) | <0.001 | 0.640 (0.334,0.946) | <0.001 |
| Total cumulative sildenafil dose (mg) | 0.008 (0.004, 0.013) | 0.001 | | |
| Age | 0.152 (-0.226, 0.529) | 0.424 | | |
| DM | 6.067 (-0.480, 12.613) | 0.068 | | |
| Hypertension | 4.289 (-1.987, 10.565) | 0.175 | | |
| Hyperlipidemia | 3.233 (-3.287, 9.754) | 0.323 | | |
| CKD | 7.760 (-1.441, 16.961) | 0.096 | | |
| IOP | 0.132 (-0.772, 1.036) | 0.770 | | |

[a]Crude relation coefficient
[b]Adjusted regression coefficient, $R^2$ = 28.6%
Assumption for Linear Regression including Linearity and Homoscedasticity were met
Significant: P<0.05
DM = Diabetes mellitus, CKD = Chronic kidney disease, IOP = Intraocular pressure

## DISCUSSION

Sildenafil was first approved in 1998 by the FDA for use in men with ED. While the safety profile of sildenafil has been generally established and considered ocular

safe, multiple severe ocular events have been reported associating it to RNFL, macular and choroidal injury. In our study sample, none of the patients reported experiencing visual disturbance upon ingestion of sildenafil and altogether demonstrated relatively good visual acuity.

The demographic profile of our ED patients reveals the mean age of 54.30±8.41 years old (Range 41-71), which is comparable to prevalence age of ED in Malaysia of 58.55±6.88 (22). All the recruited ED patients were Malay males, which can be attributed to Malays making up 94.6% of the Kelantan population (23). A significant majority of them (83%) suffered from one or multiple medical conditions. DM, hypertension, and hyperlipidemia were the most prevalent, accounting for 68.1%, 57.4% and 63.8% respectively. This is in parallel with identified common associations of ED with cardiovascular disease and its risk factors (24).

The majority of the ED patients had an EHS-score of 2 (Penis is hard but not hard enough for penetration), which accounted for 44 patients (93.6%), while the remaining had an EHS-score of 1 (Penis is larger but not hard). The mean duration of sildenafil use was 14.51±8.90 months ranging 2 to 42 months. This supports the notion that ED patients rely on sildenafil for an extended period to achieve satisfactory sexual lifestyle (20). We found a significant correlation between DM and EHS with the duration of sildenafil use. Notably, DM is noted to have a moderate correlation with duration of sildenafil use ($r=0.330$, $P<0.05$). In diabetes, advanced glycation end-products generate oxygen free radicals, inducing oxidative cell damage at the penile cavernosal smooth muscle cells, leading to impaired erection. This explains the need for diabetic patients to use longer duration of sildenafil to attain optimal sexual performance (25).

EHS is a reliable single-item-patient-reported outcome to measure successful erection (26). We found EHS to have a significant negative correlation (-0.469, $P<0.05$) with duration of sildenafil use. A lower EHS score signifies poorer penile hardness which lead unsuccessful penetration. This emphasizes the necessity for an extended duration of sildenafil in these lower EHS scoring patients.

The mean logMAR BCVA was 0.31±0.25 and the mean IOP of 15.00±3.54 mmHg. These findings of good vision; no visual impairments and normal ocular pressure are in correspondence with our exclusion criteria to exclude existing ocular pathology in the study. Although IOP was observed to increase in patients on sildenafil (18), the increase was transient and possibly led undetected among our patients. We also observed the mean OCT parameters to be comparable with normal means in the population, which explains normal visual function among our study population. The mean average RNFL thickness of 92.98±3.81 μm is comparable with normal ethnic Malay mean average RNFL 95.7±9.6 μm (27). Similarly, the mean average macular thickness of 285.58±3.09 μm and mean sub-foveal choroidal thickness of 249.70±10.64 μm are comparable with normal Malaysians values of 277.72±14.74 and 262.30±70.30 respectively (28,29).

In our RNFL analysis, we observed that the thickness of superior, inferior and average RNFL is influenced by the duration of sildenafil use. Although sildenafil is reported to possibly cause post ingestion transient visual disturbances such as transient colour tinge, increased sensitivity to light as well as transient impairment of colour discrimination, these symptoms generally expected to resolve less than 4 hours, consistent with its metabolism and elimination profile (8,11).

However, repeated use of sildenafil could possibly cause RNFL thinning by the postulated NO activation by sildenafil which reduces optic perfusion and disrupt its autoregulation. It also causes disruption of blood ocular barrier as well as limiting retinal perfusion (30). This pathogenesis is also comparable to glaucomatous optic neuropathy of which, NO diffusion into retinal ganglion axons causes peroxynitrate (ONOO-) induced retinal ganglion cells and axon apoptosis (31). This may explain the reduction in superior and inferior RNFL quadrants thickness similar to glaucomatous optic neuropathy picture, as these quadrants are more susceptible to damage due to their thinner supporting connective tissue of RNFL at the lamina cribrosa rendering them more sensitive to glaucomatous effect (32,33). Our findings may corroborate this mechanism, as we observed thinner superior and inferior RNFL with each increasing months of sildenafil use.

The other variables with significant linear relationship with average RNFL thickness were total cumulative sildenafil dose, and chronic kidney disease. Prolonged use and higher total cumulative dose of sildenafil may have caused its accumulation in the RNFL, due to its high affinity towards melanin in the eye (4). This may potentiate RNFL thinning, as observed in a recent animal study which found apoptotic endothelial, pericytic cells and disintegrated myelin sheath of ONH fibres in adult male rats ingested men equivalent dose of sildenafil for eight weeks (34). Moreover, CKD has been linked to retinal neurodegenerations, postulated due to uremic neurotoxicity, as well as associated atherosclerosis which may lead to optic neuropathy (35). The significant linear relationship between these variables and average RNFL thickness provides further insight into the potential mechanisms underlying the observed RNFL thinning in our study population, highlighting the impact of cumulative sildenafil dosage and the presence of chronic kidney disease as contributing factors.

MLR analysis model found both duration of sildenafil and total cumulative dose to be the predictor of RNFL

thinning in our ED patients. This is in parallel with the significant strong positive correlation observed between both variables of which longer duration of use will accumulate higher total cumulative dose ($r=0.806$, $P<0.05$). However, long term dose dependent ocular effect of sildenafil is still somewhat unclear. All other variables and possible confounding factors evaluated in single and multiple linear regression and were found to have no correlation with RNFL thickness. Despite the significant negative association between duration of sildenafil use with RNFL thickness, the thinning observed was still not profound enough to cause thinning lower than the normal range value, nor did it lead to significant visual symptoms.

We did not find a significant linear relationship between the duration of sildenafil use with macular thickness in ED patients. Similarly, other variables including total cumulative dose, age, DM, hypertension, hyperlipidemia and CKD also found to have no association with macular thickness. As the ganglion cell layer accounts for up to 40% of the thickness in the macular area, it is assumed that RNFL thinning may also affect the macula too. However, previous literature by Cunha et al. on traumatic optic neuropathy has shown axonal damage in the macula exhibited smaller and later changes compared to RNFL (36). This may explain our findings, as it is possible that the macula changes may only become apparent when significant RNFL thinning occurs. This is in parallel with Damar et al. findings, of which no effect of macular thickness seen among ED patients using sildenafil 2 to 3 times per month (37).

As discussed prior, the ocular effect of sildenafil may have had similar pattern of glaucomatous optic neuropathy, which could explain the comparable behaviour to the macula and RNFL. Macula is a less sensitive detector to glaucoma than RNFL thickness, as only around 50% or the retinal ganglion cells area sampled in the scanned area compared to RNFL. Macula was found to have threefold lower accuracy than RNFL in evaluating glaucomatous effect on the eye (38). This may elucidate our non-statistically significant findings in the macular thickness analysis. Another attributing factor could be due to sample collection of well-controlled DM and hypertension, of which there might possibly be no significant target organ damage occurring to the eye yet. Given the divergent findings between macular thickness and RNFL parameters in relation to the duration of sildenafil use, further studies are needed to explore the relationship between RNFL and macular thickness in cases of ocular injury or toxicity.

Sub-foveal choroidal analysis with SLR revealed that both the duration of sildenafil use and the total cumulative dose had an influence on choroidal thickness, with the regression coefficient of 0.662 and 0.008 respectively. Both parameters demonstrated a positive correlation, hence may impose similar effects on the choroidal thickness. Multiple studies have found an immediate raise of choroidal perfusion post sildenafil ingestion. Sildenafil's vasodilator effect is believed to cause autonomic-driven vasodilation and congestion through cGMP-mediated smooth muscle relaxation (39). Furthermore, the potent vasodilator properties of sildenafil could lead to idiosyncratic engorgement of the choroidal vasculature(40). This aligns with multiple case reports of sildenafil associated CSCR, where increased choroidal thickness is recognised as one of its risk factors (41).

Upon considering other variables and confounders in MLR, we found that duration of sildenafil alone to have significant relationship with choroidal thickness. However, the R-square value of 0.32 indicates that the MLR model can explain only 32% of the variability observed in choroidal thickness analysis. We believe that our findings may be strongly affected by the diurnal variation of choroidal thickness, which was not considered in the study, as the thickness was found to have approximately 30 to 60 μm of difference between noon and midnight (42). Diurnal variation could potentially be the stronger confounding factor in this case. However, as the OCT measurement time was not fixed due to our clinical settings, the limitation should be acknowledged and be considered in future study design.

## CONCLUSION

While sildenafil in general does not cause severe visual symptoms, our study underscores the importance of monitoring subclinical ocular changes, particularly in relation to the RNFL and choroidal thickness. The RNFL can be influenced negatively by the duration of use and total cumulative dose of sildenafil, while choroidal thickness showed a positive relationship with duration of use. Further prospective studies with larger study sample may provide a good prediction of the sildenafil effect to the eye.

## ACKNOWLEDGEMENT

The authors thank Dr. Anas Rosdi for the assistant with data analysis, as well as Mr. Roslan form men's health clinic in assisting the patients' recruitment.

## REFERENCES

1. NIH Consensus Conference. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA. 1993 Jul 7;270(1):83–90. doi:10.1001/jama.1993.03510010089036
2. Beavo JA. Cyclic nucleotide phosphodiesterases: Functional implications of multiple isoforms. Physiol Rev. 1995;75(4):725–48. doi: 10.1152/physrev.1995.75.4.725
3. Moreland RB, Goldstein I, Traish AM. Sildenafil,

a novel inhibitor of phosphodiesterase type 5 in human corpus cavernosum smooth muscle cells. Life Sci. 1998 Apr 10;62(20):PL 309-18. doi: 10.1016/s0024-3205(98)00158-1.
4. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. J Urol. 1998 Jun;159(6):2164–71. doi: 10.1016/S0022-5347(01)63299-3
5. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral Sildenafil in the Treatment of Erectile Dysfunction. New England Journal of Medicine. 1998 May 14;338(20):1397–404. doi: 10.1056/NEJM199805143382001.
6. Bischoff E. Potency, selectivity, and consequences of nonselectivity of PDE inhibition. Int J Impot Res. 2004;16(SUPPL. 1):0–3. doi: 10.1038/sj.ijir.3901208.
7. Lagnado L. Visual Signals in the Retina: From Photons to Synapses. Exp Physiol. 2000 Jan 1;85(1):1–15. https://doi.org/10.1111/j.1469-445X.2000.01966.x
8. Laties AM, Fraunfelder FT. Ocular safety of Viagra, (sildenafil citrate). Trans Am Ophthalmol Soc. 1999;97:115–8.
9. Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH. Clinical safety of oral sildenafil citrate (VIAGRA®) in the treatment of erectile dysfunction. Int J Impot Res. 1998 Jun;10(2):69–74. doi: 10.1038/sj.ijir.3900354.
10. Laties AM, Zrenner E. Viagra® (sildenafil citrate) and ophthalmology. Prog Retin Eye Res. 2002 Sep;21(5):485–506. doi: 10.1016/s1350-9462(02)00013-7.
11. Milligan PA, Marshall SF, Karlsson MO. A population pharmacokinetic analysis of sildenafil citrate in patients with erectile dysfunction. Br J Clin Pharmacol. 2002 Mar 6;53(1):45S-52S. doi: 10.1046/j.0306-5251.2001.00032.x
12. Pomeranz HD. Erectile Dysfunction Agents and Nonarteritic Anterior Ischemic Optic Neuropathy. Neurol Clin. 2017;35(1):17–27. doi: 10.1016/j.ncl.2016.08.007.
13. Yanoga F, Gentile RC, Chui TYP, Freund KB, Fell M, Dolz-Marco R, et al. Sildenafil Citrate Induced Retinal Toxicity — Electroretinogram, Optical Coherence Tomography, And Adaptive Optics Findings. Retin Cases Brief Rep. 2018;12:S33–40. doi: 10.1097/ICB.0000000000000708.
14. Li Y yun, Yu Y jie, Liu X pu, Liu N pu. Visual impairment with possible macular changes after a high dose of sildenafil in a healthy young woman. Int J Ophthalmol. 2018 Feb 18;340–2. doi: 10.18240/ijo.2018.02.27
15. Arora S, Surakiatchanukul T, Arora T, Cagini C, Lupidi M, Chhablani J. Sildenafil in ophthalmology: An update. Surv Ophthalmol. 2022;67(2):463–87. doi: 10.1016/j.survophthal.2021.06.004
16. Quiram P, Dumars S, Parwar B, Sarraf D. Viagra-associated serous macular detachment. Graefe's Archive for Clinical and Experimental Ophthalmology. 2005 Apr 9;243(4):339–44. DOI:10.1007/s00417-004-1099-0
17. Phillips BG, Kato M, Pesek CA, Winnicki M, Narkiewicz K, Davison D, et al. Sympathetic Activation by Sildenafil. Circulation. 2000 Dec 19;102(25):3068–73. doi: 10.1161/01.cir.102.25.30
18. Gerometta R, Alvarez LJ, Candia OA. Effect of sildenafil citrate on intraocular pressure and blood pressure in human volunteers. Exp Eye Res. 2011 Jul;93(1):103–7. doi: 10.1016/j.exer.2011.05.010
19. Danesh-Meyer H V., Levin LA. Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: Casual or causal association? Vol. 91, British Journal of Ophthalmology. 2007. p. 1551–5. doi: 10.1136/bjo.2007.125880
20. McMurray JG, Feldman RA, Auerbach SM, DeRiesthal H, Wilson N. Long-term safety and effectiveness of sildenafil citrate in men with erectile dysfunction. Ther Clin Risk Manag. 2007;3(6):975–81.
21. Nicolosi A, Glasser DB, Kim SC, Marumo K, Laumann EO, Group GI. Sexual behaviour and dysfunction and help-seeking patterns in adults aged 40–80 years in the urban population of Asian countries. BJU Int. 2005 Mar 1;95(4):609–14. doi: 10.1111/j.1464-410X.2005.05348.x.
22. Khoo EM, Tan HM, Low WY. Erectile dysfunction and comorbidities in aging men: An urban cross-sectional study in Malaysia. Journal of Sexual Medicine. 2008;5(12):2925–34. doi: 10.1111/j.1743-6109.2008.00988.x
23. Dept of Statistics M. Population distribution and basic demographic characteristics 2010, Dept of Statistics, Malaysia. Dept of Statistics, Malaysia. 2011.
24. Eardley I. The incidence, prevalence, and natural history of erectile dysfunction. Sex Med Rev. 2013;1(1):3–16. doi: 10.1002/smrj.2.
25. Thorve VS, Kshirsagar AD, Vyawahare NS, Joshi VS, Ingale KG, Mohite RJ. Diabetes-induced erectile dysfunction: Epidemiology, pathophysiology and management. J Diabetes Complications. 2011;25(2):129–36. doi: 10.1016/j.jdiacomp.2010.03.003.
26. Mulhall JP, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. OUTCOMES ASSESSMENT: Validation of the Erection Hardness Score. J Sex Med. 2007 Nov 1;4(6):1626–34. doi: 10.1111/j.1743-6109.2007.00600.x.
27. Ho H, Tham YC, Chee ML, Shi Y, Tan NYQ, Wong KH, et al. Retinal Nerve Fiber Layer Thickness in a Multiethnic Normal Asian Population: The Singapore Epidemiology of Eye Diseases Study. Ophthalmology. 2019;126(5):702–11. doi: 10.1016/j.ophtha.2018.11.031.

28. Abd Hamid MR, Wan Hitam WH, Abd Halim S. Retinal Nerve Fiber Layer and Macular Thickness in Parkinson's Disease Patients. Cureus. 2021;13(7). doi: 10.7759/cureus.16224
29. Tan CY, Vengadasalam SR, Samsudin A, Khaliddin N. Choroidal thickness in Malaysian eyes with full-thickness macular holes. International Eye Science. 2018;18(3):401–5.DOI:10.3980/j.issn.1672-5123.2018.3.01
30. Kerr NM, Danesh-Meyer H V. Phosphodiesterase inhibitors and the eye. Clin Exp Ophthalmol. 2009 Jul;37(5):514–23. DOI: 10.1111/j.1442-9071.2009.02070.x
31. Mozaffarieh M, Flammer J. Ocular blood flow and glaucomatous optic neuropathy. Ocular Blood Flow and Glaucomatous Optic Neuropathy. 2009. 1–105 p. DOI:10.1007/978-3-540-69443-4
32. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma: II. The site of injury and susceptibility to damage. Archives of ophthalmology. 1981;99(4):635–49. doi: 10.1001/archopht.1981.03930010635009.
33. Jampel HD, Singh K, Lin SC, Chen TC, Francis BA, Hodapp E, et al. Assessment of visual function in glaucoma: A report by the American academy of ophthalmology. Ophthalmology. 2011;118(5):986–1002. doi: 10.1016/j.ophtha.2011.03.019.
34. Eltony SA, Abdelhameed SY. Effect of chronic administration of sildenafil citrate (Viagra) on the histology of the retina and optic nerve of adult male rat. Tissue Cell. 2017;49(2):323–35. doi: 10.1016/j.tice.2017.01.006.
35. Jung S, Bosch A, Ott C, Kannenkeril D, Dienemann T, Harazny JM, et al. Retinal neurodegeneration in patients with end-stage renal disease assessed by spectral-domain optical coherence tomography. Available from: https://doi.org/10.1038/s41598-020-61308-4. doi: 10.1038/s41598-020-61308-4
36. Cunha LP, Costa-Cunha LVF, Malta RFS, Monteiro MLR. Comparison between retinal nerve fiber layer and macular thickness measured with OCT detecting progressive axonal loss following traumatic optic neuropathy. Arq Bras Oftalmol. 2009;72(5):622–5. doi: 10.1590/s0004-27492009000500004.
37. Damar E, Yoklu Y, Tuncel A, Balci M, Simsek S, Atan A. The Impact Of Sildenafil Citrate Therapy On Macular Thickness In Patients With Erectile Dysfunction. Journal of Urology. 2011 Apr;185(4S):34. doi:10.1016/j.juro.2011.02.1836
38. Na JH, Sung KR, Baek S, Sun JH, Lee Y. Macular and retinal nerve fiber layer thickness: Which is more helpful in the diagnosis of glaucoma? Invest Ophthalmol Vis Sci. 2011;52(11):8094–101. doi:https://doi.org/10.1167/iovs.11-7833
39. Vance SK, Imamura Y, Freund KB. The Effects Of Sildenafil Citrate On Choroidal Thickness As Determined By Enhanced Depth Imaging Optical Coherence Tomography. Retina. 2011 Feb;31(2):332–5. DOI: 10.1097/IAE.0b013e3181eef0ae
40. McCulley TJ, Luu JK, Marmor MF, Feuer WJ. Effects of sildenafil citrate (Viagra) on choroidal congestion. Ophthalmologica. 2002;216(6):455–8. DOI: 10.1159/000067549
41. Tsuiki E, Suzuma K, Ueki R, Maekawa Y, Kitaoka T. Enhanced depth imaging optical coherence tomography of the choroid in central retinal vein occlusion. Am J Ophthalmol. 2013;156(3):8–10. doi: 10.1016/j.ajo.2013.04.008.
42. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(1):261–6. doi: 10.1167/iovs.11-8782