# Structural network topology correlates to cognitive impairment and iPTH level in End-stage renal disease patients with peritoneal dialysis

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# Abstract

Objective: The burden of cognitive impairment in patients with end-stage renal disease (ESRD) undergoing peritoneal dialysis has received more attention lately. It is associated with hospitalization, mortality and poorer quality of life. We aimed to assess the topological alterations of the brain white matter structural network in ESRD and the correlation between network metrics with Montreal Cognitive Assessment scores and clinical data. Methods: The study included 25 ESRD patients with secondary hyperparathyroidism (SHPT group), 25 patients without SHPT (Non-SHPT group) and 25 healthy controls (HC group) of comparable age and sex. Montreal Cognitive Assessment was used to assess the cognitive function. The WM structural network was constructed by DTI technique, and then we used graph theoretical approaches to detect changes in the global and regional properties of the WM networks in these participants through deterministic tractography method. Results: ESRD patients showed cognitive impairment compared to HC, and the SHPT patients had lower cognitive scores than the Non-SHPT patients. The global topological organization and local efficiency of the WM network was significantly disrupted in the SHPT but not in the Non-SHPT patients compared with the HC group. Moreover, lower regional efficiency was found in the ESRD patients, mainly distributed in the frontal and parietal cortices. In addition, an association was found between iPTH, shortest path length and cognitive impairment, and the iPTH level was negatively correlated with small-worldness by two indexes, the normalized clustering coefficient and the normalized shortest path length. Conclusion: The present study indicated that the brain structural connectome in ESRD patients with high iPTH levels was disrupted in association with cognitive impairment and it is a potential connectome-based biomarker for early detection.


# Background

The chronic hyperglycemia of diabetes mellitus (DM) can cause microvascular abnormalities[1] and complications of eyes[2]. It affects the retinal circulation and the choroidal vasculature. Diabetic retinopathy (DR) is one of the most severe complications of DM which can cause permanent visual impairment and affect the quality of life[3,4]. DR is gradually occurring with the development of DM. But due to the limitations of clinical diagnostic techniques, the pathological changes of DR have already occurred and has a certain effect on the patient's vision when diagnosed. It is essential to improve the early diagnosis rate of DR.

The capillary closure resulting in non-perfusion of retinal capillaries is the most important pathologies in DR[5]. Hidayat et al.[6] reported the choroidal abnormal performance included capillary drop-out, luminal narrowing of capillaries and choroidal neovascularization. Choroidal thickness (CT) is a parameter to evaluate abnormalities in choroidal vasculature. There is increasing interest in development of quantitative methods to assess choroidal structural characteristics and their associations with ocular diseases. Advancement in technology has provided further insight into both qualitative and quantitative measurements of choroidal vasculature and other volumetric data in choroidal pathology. Many recent studies focus on using CT as an indicator of retinal and choroidal blood flow[7,8,9,10]. But various variables

can affect CT and retinal vessels. So, there is a need to explore more robust and stable marker for the assessment of retinal and choroidal vascular structural characteristics.

After the image segmentation technique proposed by Sonoda et al.[11,12], Agrawal et al.[13] proposed a new parameter-choroidal vascularity index (CVI) to assess vascular structure through enhanced depth imaging optic coherence tomography (EDI-OCT) images. After binarization of the OCT images, the total choroidal area (TCA), the stromal area (SA) as well as vascular luminal areas (LA) are identified and measured. With growing evidence, CVI is emerging as a potentially more robust marker and a complimentary tool for choroidal vascularity in various ocular diseases. CVI can indirectly measure choroidal vascularity quantitatively, overcoming the limitation of using CT alone[14]. In the study of Kim[14], they assessed choroidal changes in diabetic patients by measuring CVI and CT in conjunction with DR stage. But they did not assessed the other indicators, such as TCA, SA and LA. In this study, we aimed to determine the difference in the choroidal vasculature in patients with DM, NPDR, PDR and in healthy controls by measuring choroidal vascular density parameters.

## Methods

# Study Population

This was observational cross-sectional study. 104 eyes were included in this study. Eyes were divided into 4 groups: Healthy controls (n = 38), DM with no DR eyes (n = 22), NPDR eyes (n = 24), PDR eyes (n = 20). The last 3 groups were also called the DM groups (n = 66). The severity of the diabetic eye disease was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS). The study was conducted with the approval from the Ethics Committee of Beijing Chaoyang Hospital, the Third Clinical Medical College of Capital Medical University. All procedures performed in studies involving human participants were in accordance with the 2013 Helsinki declaration. Written informed consent was obtained from the subjects after explanation about any potential risks involved with the study.

The inclusion criteria were (1) spherical equivalent refractive error <6.00 diopter or axial length no more than 26 mm; (2) obscuration of choroidal images by existence of significant media opacity or thick subfoveal hemorrhage; (3) bilateral pathological myopia; (4) previous vitrectomy, intraocular surgery (including cataract surgery) in the study eye within 2 years. Eyes with NPDR/PDR were grouped under study groups and normal eyes were used as comparison group.

# Clinical Examination

All patients underwent standardized measurement of best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp biomicroscopy, dilated fundal examination, fluorescence angiography (FA) with a confocal scanning laser system (HRA Spectralis; Heidelberg Engineering, Germany), and the EDI-OCT

scan was performed using the Heidelberg Spectralis (Version 5.3.2.0; Heidelberg Engineering, Heidelberg, Germany). Snellen visual acuities were converted to logMAR equivalent for statistical analysis.

# Measurement of CT

EDI-OCT scans of the macula were performed for all eyes using spectral-domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany). The choroidal and RNFL thicknesses were measured using the in-built callipers tool at three points (subfoveal, 0.5 mm temporal and nasal to the fovea) (Figure 1).

# Image Binarization and Choroidal Vascular Density Parameters Calculation

One central scan passing through the fovea was selected for binarization using the protocol described by Sonoda et al[11]. Raster scans through the fovea in B-scan OCT were binarized using the Niblack autolocal threshold tool. The image binarization was done using public domain software, Image J. Binarization of the subfoveal choroidal area in the OCT image was done by a modified Niblack method. (Figure 2). After binarization of the OCT images, the total choroidal area (TCA), the stromal area (SA) as well as vascular luminal areas (LA) are identified and measured. The TCA was calculated by multiplying the standard width of 1500 um (750 um on nasal and temporal side of the fovea) by the subfoveal choroidal thickness. The ratio of the luminal to choroidal area was calculated as the ratio of LA over the TCA.

# Statistical analysis

The Kolmogorov–Smirnov test was used to identify the normality of distribution. Descriptive statistics were calculated as the mean and standard deviation for normally distributed variables and median, first quartile, and third quartile for nonnormally distributed variables. The categorical data were analyzed using the Fisher's exact test. The Independent t-test, one-way analysis of variance (ANOVA) test for normal distributions and Kruskal-Wallis tests for nonnormal distributions were used to compare other parameters between groups. The Tamhane's T2 test was performed to adjust for multiple comparisons between groups within each analysis.

All reported P values were two sided. P <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software version 21 (SPSS, Inc., IL, USA).

# Results

## Demographic and clinical characteristics

The demographic, ocular, and systemic characteristics of the subjects are shown in Table 1. The study population consisted of 38 healthy controls (mean age, 63.42 ± 7.24 years; male/female, 21/17), 22 DM with no DR patients (mean age, 61.77 ± 7.63 years; male/female, 12/10), 24 patients with NPDR (mean age, 61.83 ± 8.62 years; male/female, 12/12), and 20 patients with PDR (mean age, 63.55 ± 6.39 years; male/female, 9/11), respectively.

Compared with both DM with no DR and NPDR patients, PDR patients had significantly lower mean self-reported history of diabetes and HbA1c ($P < 0.001$, $P = 0.002$; respectively), and they had also lower BCVA compared with the no DR and NPDR patients ($P < 0.001$). There were no statistically significant differences between mean BMI, fasting blood glucose, systolic BP, diastolic BP, IOP and axial length among groups. (Table 1)

62 patients received insulin treatment (19 in DM with no DR eyes, 23 in NPDR eyes and 20 in PDR eyes) in all 66 DM patients. 42 DM patients received fundus laser photocoagulation treatment (19 DM with no DR eyes, 23 NPDR eyes and 20 PDR eyes). (Table 1)

## OCT parameters between healthy controls and diabetes group

The DM group included the DM with no DR patients, the NPDR patients and the PDR patients (n = 66). EDI-OCT scans of 38 healthy controls and 66 eyes of patients with DM were analyzed.

Independent t-test showed that the ratios of the luminal to choroidal area were significantly different between the two groups ($P < 0.001$). But there were no statistically significant differences in RNFL, retinal thickness and SCT measurements between the two groups ($P = 0.407$, $P = 0.654$ and $P = 0.849$; respectively).(Table 2)(Fig 3)

## Choroidal parameters between DM groups

Age-adjusted 1-way ANOVAs showed that the vessel density values were significantly different among the three groups ($P < 0.001$ for both SCT, TCA and SA). The SCT values were significantly lower in DM with no DR eyes (194.18 ± 5.68 um), followed by NPDR eyes (217.29 ± 14.07 um) and the PDR eyes (229.25 ± 13.89um); all three pairwise comparisons were statistically significant (Tukey-Kramer HSD, $P < 0.05$ for all comparisons). For TCA and SA, the pairwise comparisons showed that DM with no DR eyes (0.81 ± 0.06 mm2; 0.28 ± 0.03 mm2) were significantly lower compared with both NPDR eyes and PDR eyes (0.86 ± 0.09 mm2; 0.31 ± 0.05 mm2) and healthy eyes (0.90 ± 0.08 mm2; 0.34 ± 0.03 mm2) (Tukey-Kramer HSD, $P < 0.001$ for both). (Table 3) (Fig 4)

The ratio of the luminal to choroidal area in the three groups were 65.30 ± 2.75, 63.35 ± 5.21 and 61.48 ± 4.35, respectively. Relative to the eyes of DM with no DR, the ratio of the luminal to choroidal area in eyes of NPDR and PDR patients were significant lower($P = 0.019$), all three pairwise comparisons were

statistically significant (Tukey-Kramer HSD, P < 0.05 for all comparisons). However, there was no significant difference in LA among the three groups (P = 0.507).

# Discussion

The microvascular complication-diabetic retinopathy (DR) is one of the most frequent complications of DM and affects the patient's visual quality[15,16,17]. Since DR is one of the leading causes of blindness, the prevention and early detection of DR is key issue. With the development of EDI-OCT, researchers were able to accurately assess in vivo choroidal structure in a non-invasive way[18]. Since the choroid is responsible for supplying blood to the outer retinal layer, choroidal structure changes in DR patients might play an important role in the development of DR[19]. The relation between DM and SCT had been examined by some researchers in the recent years[20,21,22]. But different studies showed contradictory results. Querques et al.[8]showed patients with DM had significantly thinner choroids compared with normal controls. On the contrary, Kim et al.[21] showed that the healthy eyes had thinner choroids when compared to DM patients. Vujosevic et al. found no difference CT values between DM and normal controls[23]. In our study, we found that SCT was not significant different in 66 patients with DM as compared to controls (213.21 ± 19.02um vs. 212.63 ± 11.99, p=0.849). But when we divided these DM patients into 3 groups (DM with no DR group, NPDR groupand the PDR group), SCT were significantly lower in DM with no DR eyes compared with NPDR and PDR eyes. We suspected that SCT was reduced in the early stage of DM, and increased with progressive severity of DM. These findings carefully suggest that changes in choroidal vasculature could be the primary event in diabetes even where there is no DR.

We can know from the above studies that the effect of DM on the choroid thickness changes remains unclear. There may be several reasons for this. First, the CT measurement process is different in these studies; second, the duration of DM can potentially affect the choroidal thickness; third, numerous physiologic variables can affect CT. All these reasons may lead to possible discrepancies in the results in different studies. Based on these factors, CT may not be a robust tool to evaluate the DR progression because there are many physiological factors such as diurnal variation, refractive error and age that affect it.

As the choroid is composed of blood vessels, connective tissue and extracellular fluid, measuring CT does not reflect which structure change within the choroid change. It is very meaningful to find a better indicator to quantify the changes of choroid structure. Several studies have been made to unfold the change of the typical angio-architecture of choroid in normal and diseased choroid[24,25,26,27]. Branchini et al.[28] first described the concept of analyzing choroidal vasculature in their study, they used customized software to calculate the ratio of light pixels to dark pixels in choroid. Sonoda et al.[11] used an image binarization tool to post-processing the OCT image and calculate the vascular value. Agrawal et al.[29] have demonstrated relatively stable CVI to evaluate the choroid structure change, and because it is ratio defined as the proportion of LA to TCA, which is less affected by physiological factors.

Recently, there are more and more studies on the microscopic structure changes of diabetic retinopathy, and some researchers have focused on the relationship between CVI and choroidal microstructure changes in DR patients. Agrawal et al.[13] also observed an increase in TCA in eyes of patients with DR. They hypothesized that as there is narrowing of capillaries in the choroid of the eyes of patients with DM and the proportion of vasculature-CVI would be decreased in patients with DM. Tan et al.[30] evaluated CVI in DM patients compared to controls and found that CVI was reduced (65.10 ± 0.20 versus 67.20 ± 0.16, P < 0.001), but they did not analyze CVI according to DR stage. In the study of Kim[14], they assessed choroidal changes in diabetic patients by measuring CVI and CT in conjunction with DR stage. These findings carefully suggest that changes in choroidal vasculature could be the primary event in diabetes even where there is no DR. CVI has been widely used in other ocular diseases in the recent years. Koh et al.[31] found CVI was lower in age-related macular degeneration (AMD) eyes as compared to normal controls, suggested that possible reduction in choroidal vascularity in eyes with AMD.

We used the ratio of the luminal to choroidal area to describe the change of choroid structure in different stage of DR, which has the same meaning of CVI. In the study of Kim[14], they assessed choroidal changes in diabetic patients by measuring choroidal vascularity index (CVI) and choroidal thickness (CT) and found that the PDR eyes exhibited a significantly lower CVI value than the healthy control, no DR, and NPDR eyes; the CVI in DM eyes was significantly lower than those of healthy controls even without DR. So they came to the conclusion that changes in choroidal vasculature could be the primary event in diabetes eyes even with no DR. Our research is different from their study, we compared LA, TCA and the ratio of the luminal to choroidal area in this study. We showed significantly smaller ratio of the luminal to choroidal area and bigger SA in patients with DM, compared to normal controls, regardless of the presence of DR. In this study, we also observed the choroidal structure indicators with different stages of DR, SA and TCA were significantly lower in DM with no DR eyes, followed by NPDR eyes and the PDR eyes (P <0.001). The ratio of the luminal to choroidal area were decreased in eyes of DM with no DR patients, NPDR and PDR patients (65.30 ± 2.75, 63.35 ± 5.21 and 61.48 ± 4.35, P=0.019). But LA were not change with the progression of DR. This may because the thickening of the choroid in the different stages of DR is stromal thickening, not vascular change. Animal model showed that choroidal blood flow deficit can be an early pathologic change in DR[32]. Similar to animal research, with the progression of DR, the diameter of choroidal vessels may reduce due to vascular constriction secondary to choroidal hypoxia, and changes of choroidal blood flow may occur before retinopathy manifestation[33,34]. Choroidal blood flow deficit can be an early pathologic change in DR, as shown in an animal model. These findings carefully suggest that changes in choroidal vasculature could be the primary event in diabetes even where there is no DR.

The current research investigated the choroidal thickness and choroidal vascularity index (CVI) and their correlation with severity of diabetic retinopathy (DR) in diabetes mellitus (DM) patients. Our study selected new parameters that represent the microstructure of the fundus and found choroidal thickness and the ratio of the luminal to choroidal area significantly increased with severity of DR eyes compared with DM eyes and normal. However, our research also has some limitations. The sample size of this

study was relatively small, which may have limited the statistical strength of the analysis and reduced our ability to perform correlational analyses for DM and the fundus microstructure. Future studies should be performed with larger cohorts and longer follow-up periods to determine the fundus microstructure changes in patients with different degrees of DR. The other limitation was that our image processing technology clearly displays and quantifies vascular tissue in the choroidal cross section, but it can only reflect the choroidal vasculature change in a certain part, not a wide range of fundus choroidal change. Therefore, future research can analyze choroidal vascular density in a wide range of fundus with OCTA simultaneously. did not show clearly the structural of choroidal vessels, there were measurement errors in choroidal vascular density. Later studies require OCT-A devices with better choroidal imaging quality to analyze choroidal vascular changes.

# Conclusions

In conclusion, choroidal thickness and ratio of the luminal to choroidal area significantly increased with severity of DR eyes compared with DM eyes and normal. Choroidal blood flow deficit can be an early pathologic change in DR. The ratio of the luminal to choroidal area may predict DR development or recurrence before they are otherwise evident clinically. Ischemic changes in choroidal vasculature is the primary event in diabetes, even when DR is absent.

# List Of Abbreviations

BCVA: Best-corrected visual acuity

BMI: Body mass index

DM: Diabetes mellitus

DR: Diabetic retinopathy

EDI-OCT: Enhanced depth imaging optic coherence tomography

FA: Fluorescence angiography

IOP: Intraocular pressure

LA: Luminal areas

RNFL: Retinal nerve fiber layer

SA: Stromal area

SCT: Subfoveal choroidal thickness

TCA: Total choroidal area

## Declarations

# Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the local ethics committee of Beijing Chaoyang Hospital and with the 2013 Helsinki declaration. Written informed consent was obtained from each patient before the study.

# Consent to publish

Not applicable.

# Availability of data and materials

A supplemental material which included the primary data has been uploaded accordingly (see Additional file 1 and 2).

# Competing interests

The authors declare that they have no competing interests.

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# Authors' Contributions

Involved in the design of the study (HW, YT); conduct of the study (HW, YT); collection, management, analysis of the data (HW); preparation of the manuscript (HW); and critical revision of the manuscript (HW, YT). All authors read and approved the final manuscript.

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## References

1. for the ADVANCE Collaborative group, Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia. 2014;57:2465–74.

2. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2009;32 Suppl 1:S62–7.

3. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. Diabetic retinopathy. Diabetes Care. 2003;26 Suppl 1:S99–102.

4. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet Lond Engl. 2010;376:124–36.

5. Kohner EM, Porta M. Vascular abnormalities in diabetes and their treatment. Trans Ophthalmol Soc U K. 1980;100:440–4.

6. Hidayat AA, Fine BS. Diabetic choroidopathy. Light and electron microscopic observations of seven cases. Ophthalmology. 1985;92:512–22.

7. Esmaeelpour M, Povazay B, Hermann B, Hofer B, Kajic V, Kapoor K, et al. Three-dimensional 1060-nm OCT: choroidal thickness maps in normal subjects and improved posterior segment visualization in cataract patients. Invest Ophthalmol Vis Sci. 2010;51:5260–6.

8. Querques G, Lattanzio R, Querques L, Del Turco C, Forte R, Pierro L, et al. Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci. 2012;53:6017–24.

9. Rasheed MA, Goud A, Mohamed A, Vupparaboina KK, Chhablani J. Change in choroidal vascularity in acute central serous chorioretinopathy. Indian J Ophthalmol. 2018;66:530–4.

10. Xu J, Xu L, Du KF, Shao L, Chen CX, Zhou JQ, et al. Subfoveal choroidal thickness in diabetes and diabetic retinopathy. Ophthalmology. 2013;120:2023–8.

11. Sonoda S, Sakamoto T, Yamashita T, Shirasawa M, Uchino E, Terasaki H, et al. Choroidal structure in normal eyes and after photodynamic therapy determined by binarization of optical coherence tomographic images. Invest Ophthalmol Vis Sci. 2014;55:3893–9.

12. Sonoda S, Sakamoto T, Yamashita T, Uchino E, Kawano H, Yoshihara N, et al. Luminal and stromal areas of choroid determined by binarization method of optical coherence tomographic images. Am J Ophthalmol. 2015;159:1123–31.e1.

13. Agrawal R, Gupta P, Tan K-A, Cheung CMG, Wong T-Y, Cheng C-Y. Choroidal vascularity index as a measure of vascular status of the choroid: Measurements in healthy eyes from a population-based study. Sci Rep. 2016;6. doi:10.1038/srep21090.

14. Kim M, Ha MJ, Choi SY, Park Y-H. Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. Sci Rep. 2018;8. doi:10.1038/s41598-017-18511-7.

15. Jee D, Lee WK, Kang S. Prevalence and risk factors for diabetic retinopathy: the Korea National Health and Nutrition Examination Survey 2008-2011. Invest Ophthalmol Vis Sci. 2013;54:6827–33.

16. Kempen JH, O'Colmain BJ, Leske MC, Haffner SM, Klein R, Moss SE, et al. The prevalence of diabetic retinopathy among adults in the United States. Arch Ophthalmol Chic Ill 1960. 2004;122:552–63.

17. Wong TY, Klein R, Islam FMA, Cotch MF, Folsom AR, Klein BEK, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. Am J Ophthalmol. 2006;141:446–55.

18. Spaide RF, Koizumi H, Pozzoni MC, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol. 2008;146:496–500.

19. Shen Z-J, Yang X-F, Xu J, She C-Y, Wei W-W, Zhu W-L, et al. Association of choroidal thickness with early stages of diabetic retinopathy in type 2 diabetes. Int J Ophthalmol. 2017;10:613–8.

20. Farias LB, Lavinsky D, Schneider WM, Guimarães L, Lavinsky J, Canani LH. Choroidal thickness in patients with diabetes and microalbuminuria. Ophthalmology. 2014;121:2071–3.

21. Kim JT, Lee DH, Joe SG, Kim J-G, Yoon YH. Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. Invest Ophthalmol Vis Sci. 2013;54:3378–84.

22. Lee HK, Lim JW, Shin MC. Comparison of Choroidal Thickness in Patients with Diabetes by Spectral-domain Optical Coherence Tomography. Korean J Ophthalmol KJO. 2013;27:433–9.

23. Vujosevic S, Martini F, Cavarzeran F, Pilotto E, Midena E. Macular and peripapillary choroidal thickness in diabetic patients. Retina Phila Pa. 2012;32:1781–90.

24. Gallagher MJ, Yilmaz T, Cervantes-Castañeda RA, Foster CS. The characteristic features of optical coherence tomography in posterior uveitis. Br J Ophthalmol. 2007;91:1680–5.

25. Keane PA, Allie M, Turner SJ, Southworth HS, Sadda SR, Murray PI, et al. Characterization of birdshot chorioretinopathy using extramacular enhanced depth optical coherence tomography. JAMA Ophthalmol. 2013;131:341–50.

26. Flower RW, Lim JI. An ICG angiogram-based clinical method for characterizing the choroidal circulation used to assess the hemorrheologic effects of pentoxifylline. J Fr Ophtalmol. 2000;23:756–62.

27. Hunter RS, Skondra D, Papaliodis G, Sobrin L. Role of OCT in the diagnosis and management of macular edema from uveitis. Semin Ophthalmol. 2012;27:236–41.

28. Branchini LA, Adhi M, Regatieri CV, Nandakumar N, Liu JJ, Laver N, et al. Analysis of choroidal morphologic features and vasculature in healthy eyes using spectral-domain optical coherence tomography. Ophthalmology. 2013;120:1901–8.

29. Agrawal R, Salman M, Tan K-A, Karampelas M, Sim DA, Keane PA, et al. Choroidal Vascularity Index (CVI) - A Novel Optical Coherence Tomography Parameter for Monitoring Patients with Panuveitis? PLOS ONE. 2016;11:e0146344.

30. Tan K-A, Laude A, Yip V, Loo E, Wong EP, Agrawal R. Choroidal vascularity index - a novel optical coherence tomography parameter for disease monitoring in diabetes mellitus? Acta Ophthalmol (Copenh). 2016;94:e612–6.

31. Koh LHL, Agrawal R, Khandelwal N, Sai Charan L, Chhablani J. Choroidal vascular changes in age-related macular degeneration. Acta Ophthalmol (Copenh). 2017. doi:10.1111/aos.13399.

32. Muir ER, Rentería RC, Duong TQ. Reduced ocular blood flow as an early indicator of diabetic retinopathy in a mouse model of diabetes. Invest Ophthalmol Vis Sci. 2012;53:6488–94.

33. Lutty GA, Cao J, McLeod DS. Relationship of polymorphonuclear leukocytes to capillary dropout in the human diabetic choroid. Am J Pathol. 1997;151:707–14.

34. Nagaoka T, Kitaya N, Sugawara R, Yokota H, Mori F, Hikichi T, et al. Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. Br J Ophthalmol. 2004;88:1060–3.

# Tables

**Table 1. Epidemiologic Characteristics and Ophthalmologic Clinical Presentation of Patients**

| | Control | DM with no DR | NPDR | PDR | P value |
|---|---|---|---|---|---|
| Number of eyes (n) | 38 | 22 | 24 | 20 | |
| Age (year) | 63.42 ± 7.24 | 61.77 ± 7.63 | 61.83 ± 8.62 | 63.55 ± 6.39 | P=0.739* |
| Gender (male/female) | 21/17 | 12/10 | 12/12 | 9/11 | P=0.457# |
| Years with diabetes (year) | - | 5.23 ± 1.31 | 9.85 ± 2.32 | 11.68 ± 2.63 | P<0.001* |
| BMI (kg/m2) | 24.38 ± 2.53 | 26.06 ± 2.53 | 24.64 ± 3.94 | 23.77 ± 3.22 | P=0.090* |
| HbA1c (%) | - | 7.54 ± 0.76 | 7.96 ± 0.84 | 8.51 ± 0.96 | P=0.002* |
| Fasting blood glucose (mmol/L) | - | 7.37 ± 0.73 | 7.53 ± 0.91 | 7.85 ± 1.01 | P=0.218* |
| Systolic BP (mmHg) | 124.76 ± 3.78 | 122.36 ± 5.49 | 123.54 ± 4.36 | 124.75 ± 4.96 | P=0.202* |
| Diastolic BP (mmHg) | 80.16 ± 5.81 | 79.64 ± 5.21 | 78.96 ± 5.38 | 79.55 ± 4.83 | P=0.865* |
| Diabetic nephropathy (n) | 0 | 0 | 3 | 5 | - |
| IOP (mmHg) | 15.12 ± 1.48 | 15.14 ± 2.71 | 15.05 ± 3.23 | 13.95 ± 4.02 | P=0.434* |
| Axial length (mm) | 24.10 ± 0.64 | 23.86 ± 0.67 | 24.27 ± 0.55 | 24.01 ± 0.59 | P=0.149* |
| Treatment with insulin (n) | 0 | 19 | 23 | 20 | - |
| Treatment with laser photocoagulation (n) | 0 | 0 | 22 | 20 | - |

BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; IOP, intraocular pressure.

*: Statistical significance tested by ANOVA for normal distributions and Kruskal–Wallis tests for nonnormal distributions; all comparisons were corrected with the post hoc test.

#: p values were calculated using the Fisher's exact test of Chi-Square test.

**Table 2. OCT parameters between healthy controls and diabetes group**

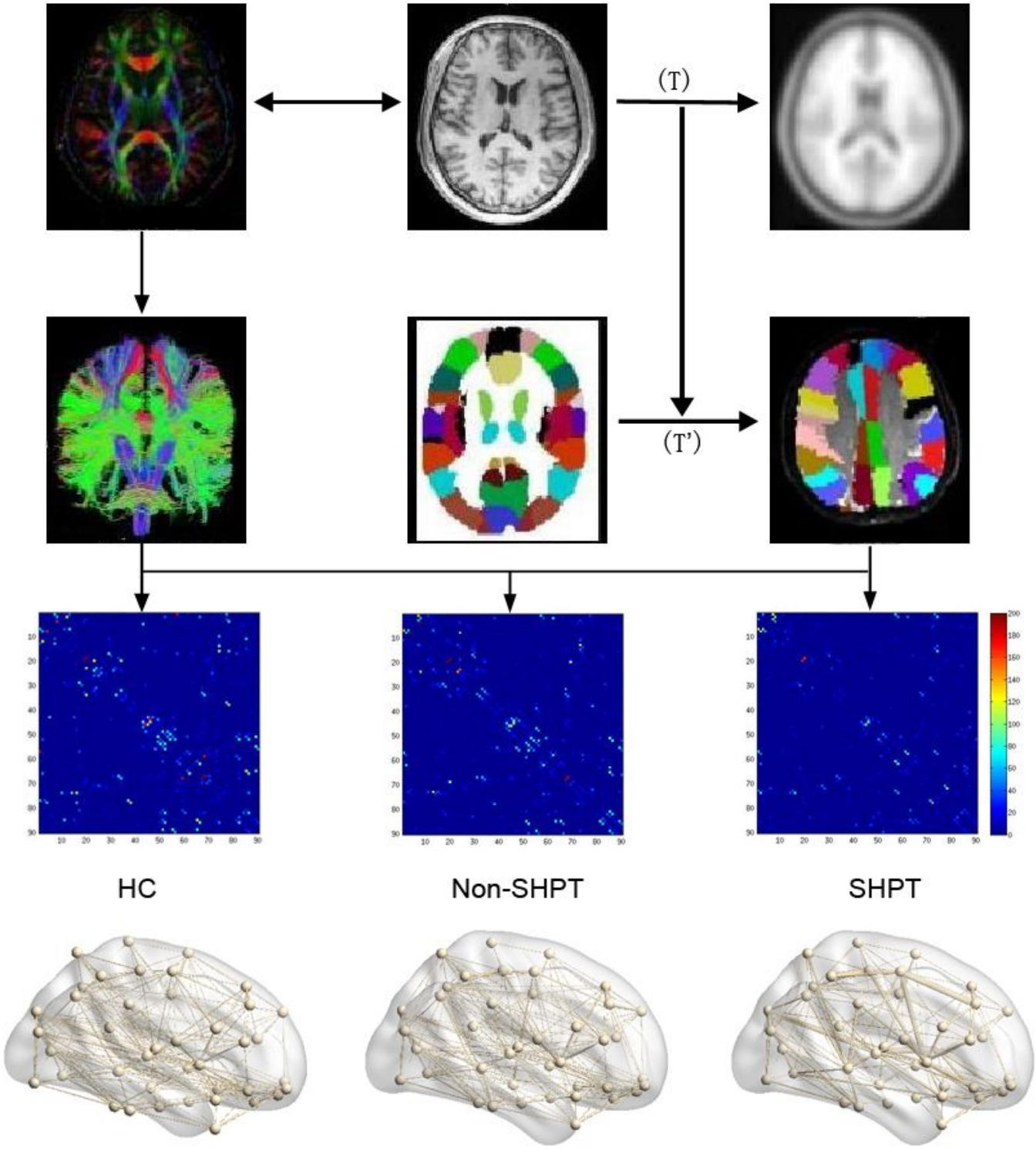
| | Control | DM | P value |
|---|---|---|---|
| Number of eyes (n) | 38 | 66 | |
| RNFL (um) | 11 (10,12.25) | 11 (10,13) | P=0.407# |
| Retinal thickness (um) | 240.58 ± 20.64 | 238.85 ± 15.33 | P=0.654* |
| CT (um) | | | |
| Subfoveal | 212.63 ± 11.99 | 213.21 ± 19.02 | P=0.849* |
| Nasal | 233.03 ± 16.69 | 234.05 ± 19.57 | P=0.788* |
| Temporal | 216.95 ± 19.32 | 219.71 ± 20.61 | P=0.502* |
| Total choroidal area (TCA) in mm2 | 0.81 ± 0.14 | 0.85 ± 0.08 | P=0.086* |
| Luminal area (LA) in mm2 | 0.54 ± 0.09 | 0.54 ± 0.07 | P=0.825* |
| Stromal area (SA) in mm2 | 0.26 ± 0.07 | 0.31 ± 0.04 | P<0.001* |
| Ratio of the luminal to choroidal area (%) | 67.53 ± 6.20 | 63.43 ± 4.47 | P<0.001* |

CT, choroidal thickness ; TCA, total choroidal area; LA, luminal area; SA, stromal area; CVI, choroidal vascularity index.

*: p values were calculated using the Independent t-test.

#: p values were calculated using the Mann-Whitney U test.

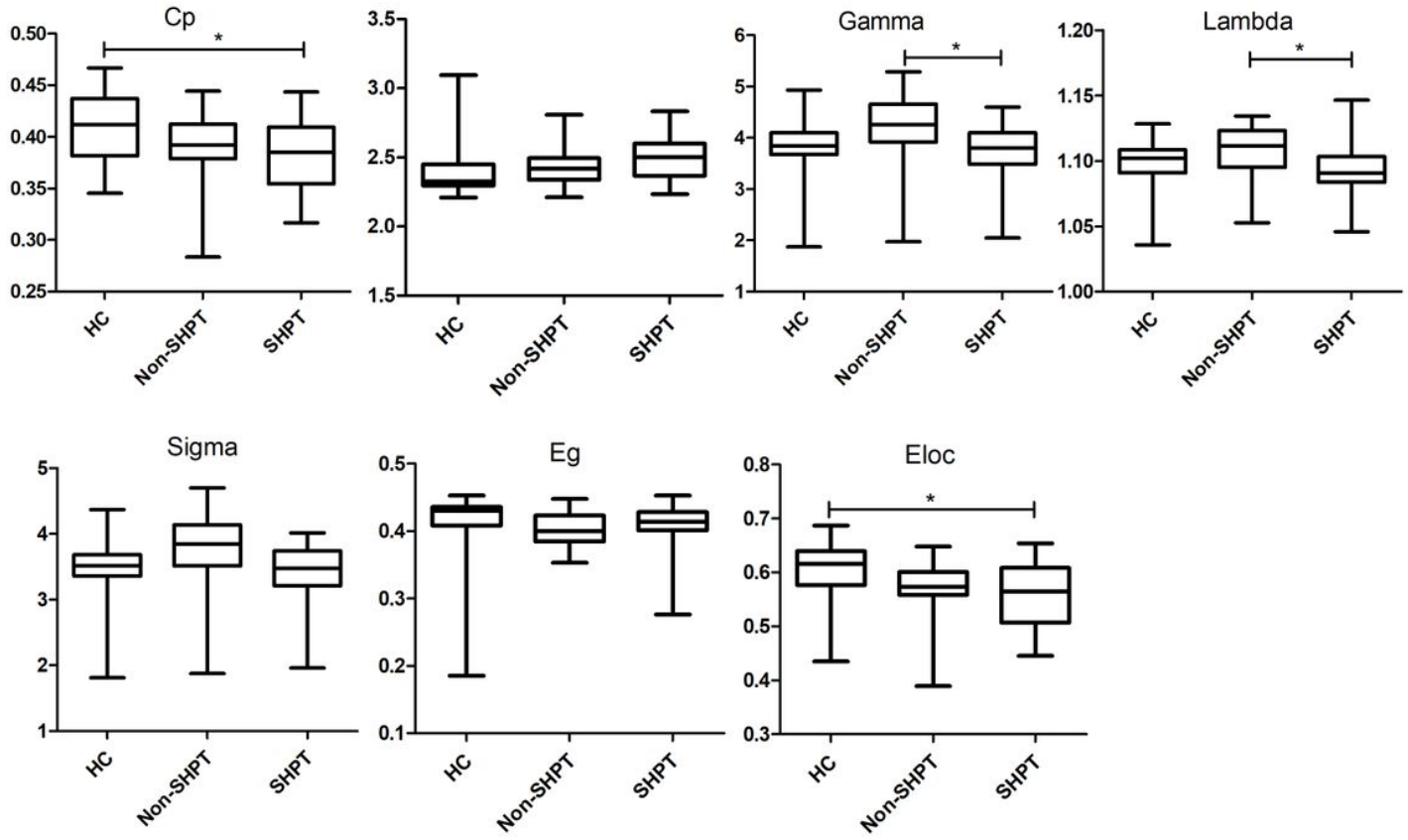
# Figures




## Figure 1

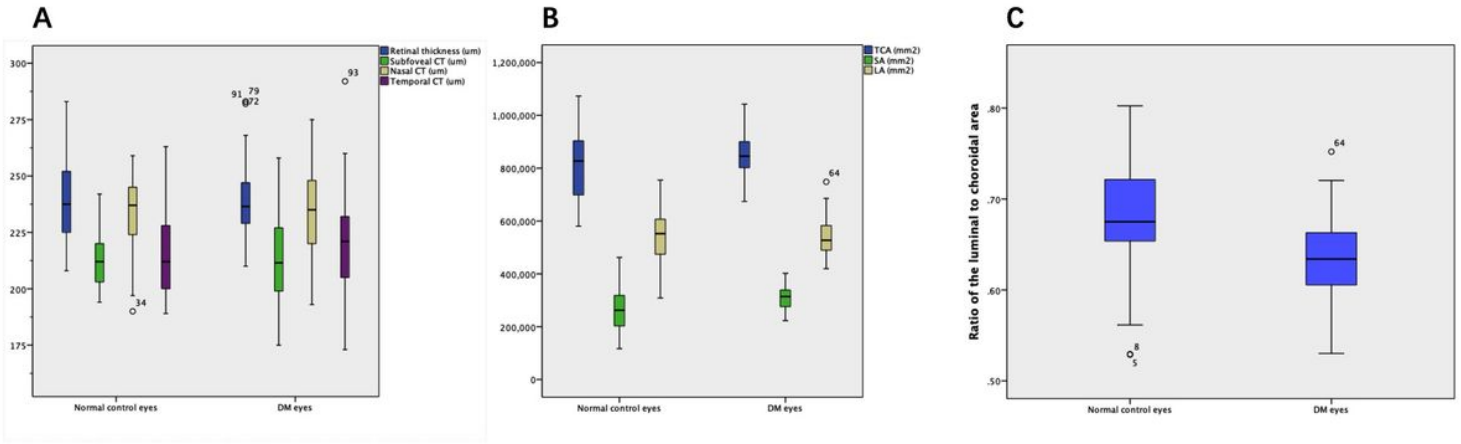
Flowchart for the construction of WM structural network by DTI. 1) The rigid coregisteration from T1-weighted image to the DTI native space. 2) The nonlinear registration from the resultant T1 image to the ICBM152 T1 template in the MNI space resulting a transformation matrix (T). 3) The application of the inverse transformation (T') to the AAL template in the MNI space, resulting in the subject-specific AAL mask in the DTI native space. 4) The whole brain WM fibers were reconstructed by DTI deterministic

tractography method. 5) The fiber number (FN) weighted networks of each subject were created by computing FN that connected each pair of brain regions. The matrices and 3D representations (lateral view) of the mean WM structural network of each group are shown in the bottom panel. The nodes and edges were mapped onto the cortical surfaces by BrainNet viewer software. HC, healthy controls, Non-SHPT, end-stage renal disease (ESRD) without secondary hyperparathyroidism (SHPT) patients, SHPT, ESRD with SHPT patients.



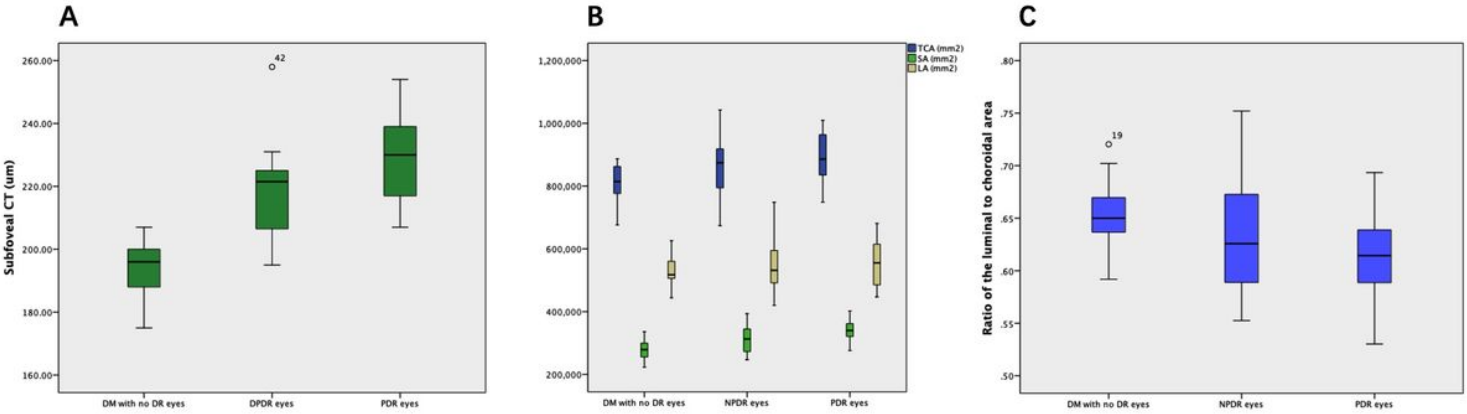

## Figure 2

Boxplot shows the difference in global topological measures among the three group (medical, 50th percentile values, minimum and maximum). Significant differences were observed in Cp, Lp and Eloc between HC and SHPT group. Significant group effects were found in σ by two indexes (γ and λ) between Non-SHPT and SHPT group. *P<0.05.



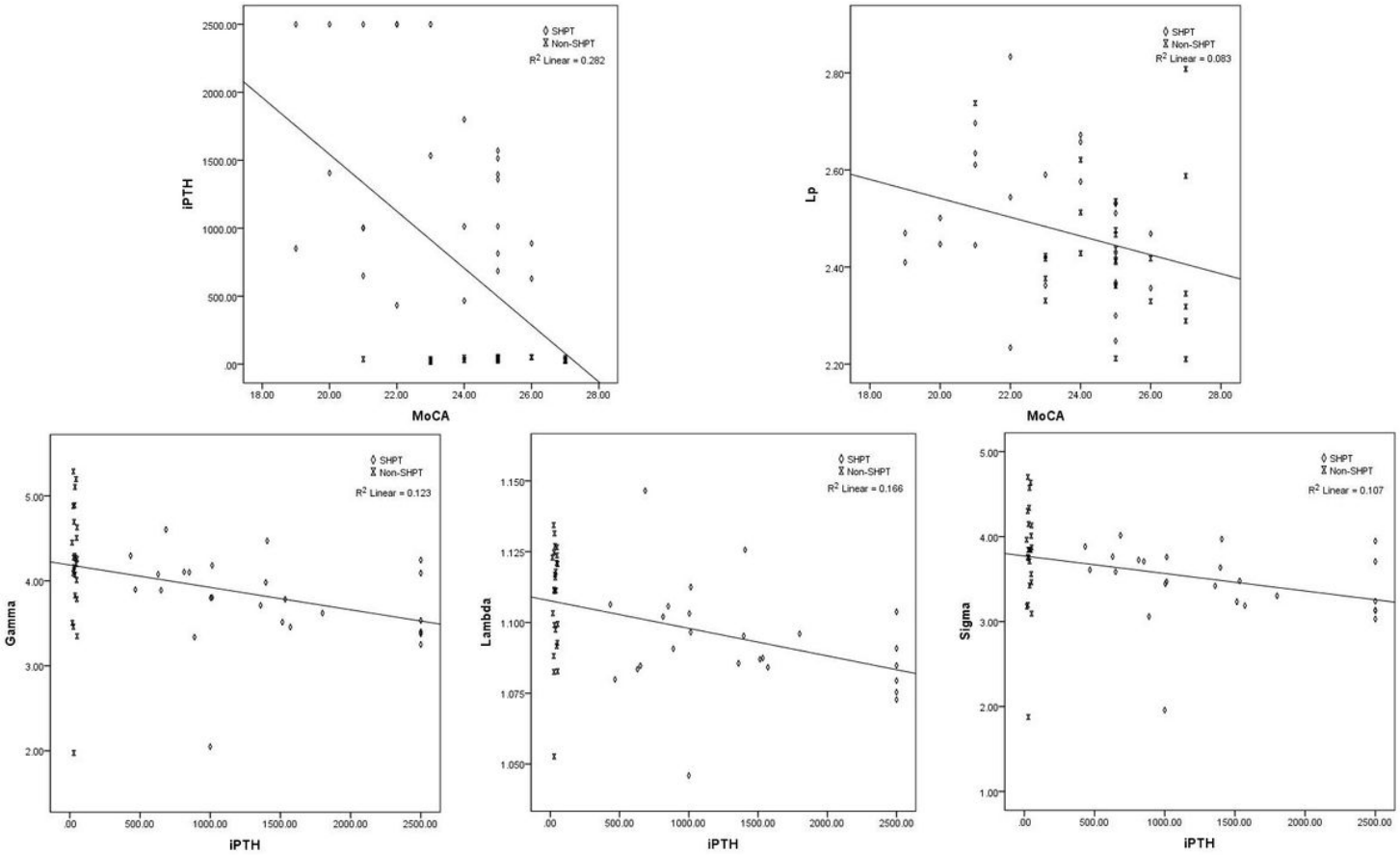

## Figure 3

OCT parameters between healthy controls and diabetes group. (A) Retinal thickness and SCT measurements between the two groups; (B) The total choroidal area (TCA), the stromal area (SA) as well as vascular luminal areas (LA) between the two groups; (C) The ratio of the luminal to choroidal area between the two groups.




## Figure 4

OCT parameters in DM with no DR eyes, NPDR eyes and PDR eyes. (A) Subfoveal CT between the three groups; (B) The total choroidal area (TCA), the stromal area (SA) as well as vascular luminal areas (LA) between the three groups; (C) The ratio of the luminal to choroidal area between the three groups.




## Figure 5

Scatterplots of correlation between network metrics and global cognition scores and clinical data.