

Quantifying peripapillary vessel density and retinal nerve fibre layer in type 1 diabetic children without clinically detectable retinopathy using OCTA

Ling Chen, Yun Feng, Sha–Sha Zhang, Yan–Fang Liu, Ping Lin

Xi'an Children's Hospital Affiliated to Xi'an Jiaotong University, Xi'an 710002, Shaanxi Province, China

Correspondence to: Yan-Fang Liu and Ping Lin. Xi'an Children's Hospital Affiliated to Xi'an Jiaotong University, Xi'an 710002, Shaanxi Province, China. duckling911@163.com; 2837090220@qq.com

Received: 2023-03-02 Accepted: 2023-12-12

Abstract

• **AIM:** To quantify changes in radial peripapillary capillary vessel density (ppVD) and the peripapillary retinal nerve fiber layer (pRNFL) in children with type 1 diabetes without clinical diabetic retinopathy by optical coherence tomography angiography (OCTA), providing a basis for early retinopathy in children with type 1 diabetes.

• **METHODS:** This was a retrospective study. A total of 30 patients (3–14y) with type 1 diabetes without clinical diabetic retinopathy (NDR group) were included. A total of 30 age-matched healthy subjects were included as the normal control group (CON group). The HbA1c level in the last 3mo was measured once in the NDR group. The pRNFL thickness and ppVD were automatically measured, and the mean pRNFL and ppVD were calculated in the nasal, inferior, temporal, and superior quadrants. The changes in ppVD and pRNFL in the two groups were analyzed.

• **RESULTS:** Compared with CON group, the nasal and superior ppVDs decreased in the NDR group (all $P < 0.01$). The thickness of the nasal pRNFL decreased significantly ($P < 0.01$), while the inferior, temporal and superior pRNFLs slightly decreased but not significant in the NDR group (all $P > 0.05$). Person and Spearman correlation analysis of ppVD and pRNFL thickness in each quadrant of the NDR group showed a positive correlation between nasal and superior (all $P < 0.01$), while inferior and temporal had no significant correlation (all $P > 0.05$). There was no significant correlation between the HbA1c level and ppVD and pRNFL in any quadrant (all $P > 0.05$). There was no significant correlation between the course of diabetes mellitus and ppVD and pRNFL in any quadrant (all $P > 0.05$).

• **CONCLUSION:** ppVD and pRNFL decrease in eyes of children with type 1 diabetes before clinically detectable retinopathy and OCTA is helpful for early monitoring.

• **KEYWORDS:** diabetic retinopathy; children; peripapillary vessel density; peripapillary retinal nerve fiber layer; optical coherence tomography angiography

DOI:10.18240/ijo.2024.02.08

Citation: Chen L, Feng Y, Zhang SS, Liu YF, Lin P. Quantifying peripapillary vessel density and retinal nerve fibre layer in type 1 diabetic children without clinically detectable retinopathy using OCTA. *Int J Ophthalmol* 2024;17(2):278-281

INTRODUCTION

In recent years, the incidence of type 1 diabetes (T1DM) has been increasing^[1-2]. T1DM progresses rapidly, and its complications appear early, which results in a heavy burden to the family and society^[3]. T1DM is an autoimmune disorder that leads to multiorgan microvascular impairment. The prevalence of diabetic retinopathy (DR) development for patients with a diabetes duration $< 5y$ is 17%, reaching 98% for patients with systemic disease for 15y or more^[4-5]. DR and diabetic optic neuropathy (DON) are typical DM eye complications. There are many studies on DR, but DON is rarely reported in children. Since DON may cause visual impairment and even optic nerve atrophy, early detection and reasonable intervention can protect the visual function of children to the greatest possible extent. In recent years, the development of optical coherence tomography (OCT) technology has brought about major changes in the field of ophthalmology; due to the optimization of this technology, OCT angiography (OCTA) can enable direct observation of retinal blood vessels in the fundus without invasiveness. A noninvasive imaging technique that can perform retinal and optic disk blood flow imaging in real time and quickly. OCTA can clearly display the retinal microvascular structure without a contrast agent and can quantitatively analyse blood flow density with good reproducibility and consistency^[6]. Studies have shown that OCTA can quantify the changes in macular

blood flow in DR patients, providing an effective means for early monitoring of diabetes progression, and a number of studies have found that OCTA can detect a decrease in retinal blood flow density before DR is clinically visible in DM patients^[7-9]. However, OCTA has not been used to study the changes in paraoptic blood flow density in early T1DM. In this study, OCT and OCTA were used to measure the blood flow density of the peripapillary capillary vessel density (ppVD) and the peripapillary retinal nerve fibre layer (pRNFL) in a group of T1DM patients without clinically visible DR, and their changes were observed and analysed.

SUBJECTS AND METHODS

Ethical Approval This study conformed to the principles of the Declaration of Helsinki and was reviewed and approved by the Hospital Ethics Committee (No.20230089). The informed consent was obtained from subjects' guardians.

Patients Children with nonclinically visible DR who attended Xi'an Children's Hospital from January 2022 to December 2022 were enrolled. The inclusion criteria were as follows: 1) met the diagnostic criteria for T1DM^[10]; 2) met the criteria for non-diabetic retinopathy (NDR); 3) age 3 to 14y. A total of 30 healthy physical subjects, aged 3 to 14y, were selected as the control group (CON).

Methods This was a retrospective study. Thirty eyes of NDR were included. The eyes underwent examinations for visual acuity and intraocular pressure, slit lamp microscopy, fundus colour photography, and OCTA examination.

Two consecutive OCTA images were obtained using the Canon HD-OCT 100 along with software (version) provided with the device by a single skilled examiner. All subjects underwent OCTA examination with a 6 mm× 6 mm field of view of 5 visual fixations (1 central fixation and 4 peripheral fixations) to compose a OCTA image^[11].

The centre of the optic disc of the inspected eye was defined as a ring area with a central width of 2 mm (inner and outer ring diameters of 2 and 4 mm, respectively). pRNFL thickness and radial peripapillary capillary (RPC) vessel density (ppVD) were automatically measured. The pRNFL and ppVD parameter values were calculated in the nasal (N), inferior (I), temporal (T), and superior (S) quadrants (Figure 1). Fundus colour photography and OCTA examination were performed by the same skilled technician. Two experienced physicians of fundus disease were assigned to review the graphs independently for diagnosis and classification, and patients were excluded if a diagnosis consensus could not be reached. The values of each group were collected and analysed statistically.

Statistical Analysis SPSS 22.0 software was used for statistical analysis and processing. The measurement data were normally distributed, as determined by the Shapiro-Wilk test, and are expressed as the mean±standard deviation (SD).

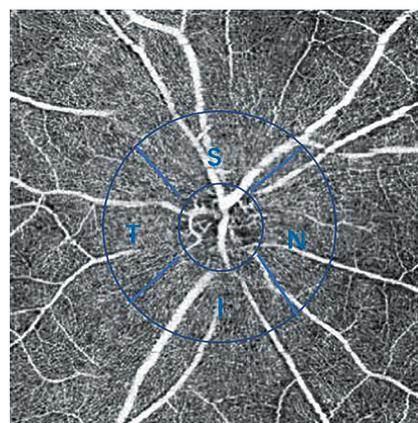


Figure 1 Four quadrants beside the optic disc N: Nasal, I: Inferior; T: Temporal; S: Superior.

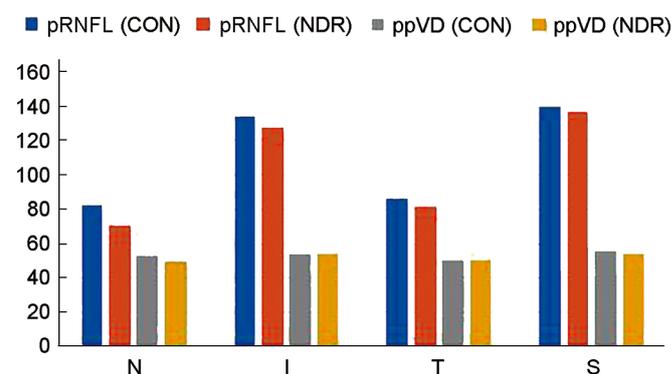


Figure 2 Distribution of ppVD and pRNFL in each quadrant of CON group and NDR group N: Nasal, I: Inferior; T: Temporal; S: Superior; ppVD: Peripapillary capillary vessel density; pRNFL: Peripapillary retina nerve fibre layer; CON: Control group; NDR: Non-diabetic retinopathy group.

The nonnormal distribution parameter is expressed as median (quartile range). The ppVD and pRNFL parameters of the two groups were compared with independent sample *t* tests. Pearson and Spearman correlations were used to analyse the correlation between ppVD and pRNFL, between HbA1c and ppVD and pRNFL, and between diabetes course and ppVD and pRNFL in each quadrant of the NDR group. $P < 0.05$ was statistically significant.

RESULTS

In the NDR group, there were 30 patients with 30 eyes, with an average age of 8.78 ± 2.18 y and an average disease duration of 3.00 ± 1.42 y. During the same period, 30 healthy physical patients with 30 eyes were selected, aged 8.35 ± 1.91 y. There was no significant difference in age between the two groups ($t=1.004, P=0.320$).

ppVD and pRNFL in the NDR group and the CON group were highest in the S quadrant and lowest in the N quadrant (Figure 2). This is consistent with Giacinto Triolo's opinion that RPCs are mainly located in the subtemporal and peritemporal papillae and are not very prominent in the subnasal and supranasal sectors^[12].

Table 1 Comparison of ppVD in each quadrant adjacent to the optic disc of the two groups

	mean±SD or median (quartile range), %		
ppVD	CON (n=30)	NDR (n=30)	P
N	53.26±2.44	49.70±2.72	0.000
I	54.14±1.83	53.81±1.56	0.456
T	50.63±1.83	50.22±3.50	0.573
S	55.80 (54.30–56.30)	53.75 (51.85–55.73)	0.009

ppVD: Peripapillary capillary vessel density; CON: Control group; NDR: Non-diabetic retinopathy group; N: Nasal; I: Inferior; T: Temporal; S: Superior.

Table 2 Comparison of pRNFL thickness in each quadrant of the eye in the two groups

	mean±SD or median (quartile range), μm		
pRNFL	CON (n=30)	NDR (n=30)	P
N	83.00 (63.00–93.00)	70.50 (63.25–76.25)	0.000
I	134.33±13.81	127.90±13.06	0.069
T	86.00 (75.75–92.00)	82.00 (75.00–93.00)	0.953
S	139.87±16.86	137.07±12.35	0.466

pRNFL: Peripapillary retina nerve fibre layer; CON: Control group; NDR: Non-diabetic retinopathy group; N: Nasal; I: Inferior; T: Temporal; S: Superior.

Compared with the normal control group, the nasal and superior ppVDs were reduced in the NDR group. The inferior and temporal ppVDs were reduced in the NDR group, but the difference was not statistically significant (Table 1). The thickness of the nasal pRNFL decreased in the NDR group. The thickness of the inferior, temporal and superior pRNFLs decreased in the NDR group, but the difference was not statistically significant (Table 2).

Pearson and Spearman correlation analysis of ppVD and pRNFL thickness in each quadrant of the NDR group showed a positive correlation between the N and S quadrants ($r=0.341$, $P=0.008$; $r=0.407$, $P=0.001$), while the I and T quadrants had no significant correlation ($r=-0.008$, $P=0.923$; $r=-0.107$, $P=0.414$). There was no significant correlation between HbA1C and ppVD and pRNFL in any quadrant ($r=-0.154$, $P=0.417$; $r=0.171$, $P=0.365$; $r=-0.117$, $P=0.538$; $r=0.045$, $P=0.813$; $r=0.154$, $P=0.416$; $r=-0.120$, $P=0.526$; $r=0.033$, $P=0.864$; $r=-0.214$, $P=0.256$). There was no significant correlation between the course of DM and ppVD and pRNFL in any quadrant ($r=0.320$, $P=0.367$; $r=-0.080$, $P=0.826$; $r=-0.424$, $P=0.222$; $r=-0.384$, $P=0.274$; $r=0.221$, $P=0.539$; $r=0.156$, $P=0.667$; $r=0.187$, $P=0.604$; $r=-0.117$, $P=0.747$).

DISCUSSION

T1DM diabetes is prone to retinopathy, especially early and severe complications. The clinical examination of diabetes is mainly performed through ocular fluorescein angiography (FFA) and indole cyan green angiography (ICGA), but because of its invasive operation and poor reproducibility, the procedure is rejected by the majority of children. In recent years, the

development of OCT technology has brought about major changes in the field of ophthalmology, and with the optimization of the technology, OCTA enables direct observation of retinal blood vessels in the fundus without invasiveness. FFA can only provide flat images, while OCTA's high resolution of the retina can observe the deep and superficial capillary network of the retina^[13]. A noninvasive imaging technique that can perform retinal and optic disk blood flow imaging in real time and quickly. OCTA can clearly display the retinal microvascular structure without a contrast agent and can quantitatively analyse blood flow density with good reproducibility and consistency^[6]. In addition to hyperglycaemia, hypoperfusion of the peripheral vessels of the optic nerve and a decrease in the supply of neurotrophic factors caused by ischaemia and hypoxia may be one of the main reasons for the occurrence and development of DR. At the same time, retinal ganglion cells, as part of the optic nerve axon, have high glucose in patients with ischaemia and hypoxia, so a large number of toxins and reactive oxygen radicals are produced, which may lead to apoptosis of retinal ganglion cells. The thickness of the RNFL depends on the number of ganglion axons and ganglion cells, and the thickness decreases when its ganglion axons and ganglion cells are damaged.

RPCs are vascular network located at the top layer of the RNFL around the optic disc, and the capillaries are relatively long and straight, parallel to the retinal ganglion cell axons, and are the most important nutrient supply for RNFL^[14-15]. Studies of OCTA applied to RPC and RNFL in normal human eyes have shown that RPCs are proportionally present in the superficial retina around the optic disc^[16]. There is already substantial evidence that neurovascular damage occurs in diabetic patients prior to clinically visible fundus damage^[17]. As an important blood supply source for the RNFL, RPCs are closely related to the structure and function of nerve fibres. Histological studies have shown that they originate in arterioles deep in the retina around the optic disc, with less anastomosis and consistent with the movement of nerve fibres^[18].

In the current study, we found that retinal vascular and nerve damage has begun in the absence of clinically visible retinopathy. The ppVDs in the N and S quadrants of the NDR group were lower than those in the CON group, and the differences were statistically significant, which was consistent with the studies by Zeng *et al*^[17] and Vujosevic *et al*^[19]. The cause may be hypoperfusion of the perivascular vessels of the optic nerve due to hyperglycaemia and a decrease in the supply of neurotrophic factors due to ischaemia and hypoxia^[20]. This study also validates the idea that RPCs are reduced on the nasal side of the papilla^[12]. The nasal pRNFL thickness was lower in the NDR group than in the CON group, and pRNFL thinning was positively correlated with a decrease in ppVD, which was

consistent with the results of Vujosevic *et al*^[19].

In this study ppVD and pRNFL in the I, T, and S quadrants of the NDR group decreased compared with the normal control group, although the difference was not statistically significant, we found that there was a positive correlation between the decrease in ppVD in the NDR group and the decrease of pRNFL in the N and S quadrants. We speculate that the decline in ppVD can occur before the pRNFL thins. We should focus on the changes in ppVD in clinical practice to provide a theoretical basis for the early detection and treatment of DR. In addition, we found in the study that the HbA1c level and disease course of NDR patients were not significantly correlated with ppVD and pRNFL in any quadrant, which was inconsistent with previous literature reports^[21], and it may be related to the short course of disease (<5y) in the included children, which is also a deficiency of this study. The sample size of this study is small, and prospective large samples are needed to verify the results of this study.

In summary, retinal microvascular changes can occur in children with early T1DM, and clinical attention should be given to the corresponding changes in ppVD to facilitate the early detection of clinically significant pRNFL thinning and provide ideas and references for vascular damage repair and neuroprotective treatment in the field of DR.

ACKNOWLEDGEMENTS

Foundations: Supported by Xi'an Municipal Health Commission Scientific Research Project (No.2023yb22); Hospital Level Project of Xi'an Children's Hospital (No.2021H12; No.2022F08).

Conflicts of Interest: Chen L, None; Feng Y, None; Zhang SS, None; Liu YF, None; Lin P, None.

REFERENCES

- 1 Lu X, Zhao C. Exercise and type 1 diabetes. *Adv Exp Med Biol* 2020;1228:107-121.
- 2 Pang HP, Luo SM, Xiao Y, Xia Y, Li X, Huang G, Xie ZG, Zhou ZG. Emerging roles of exosomes in T1DM. *Front Immunol* 2020; 11:593348.
- 3 Besser R, Ng SM, Robertson E. Screening children for type 1 diabetes. *BMJ* 2021;75:937.
- 4 Klein R. The Wisconsin epidemiologic study of diabetic retinopathy. *Arch Ophthalmol* 1984;102(4):520.
- 5 Barrett EJ, Liu ZQ, Khamaisi M, *et al*. Diabetic microvascular disease: an endocrine society scientific statement. *J Clin Endocrinol Metab* 2017;102(12):4343-4410.
- 6 Lee MW, Kim KM, Lim HB, Jo YJ, Kim JY. Repeatability of vessel density measurements using optical coherence tomography angiography in retinal diseases. *Br J Ophthalmol* 2019;103(5):704-710.
- 7 Sun ZH, Yang DW, Tang ZQ, Ng DS, Cheung CY. Optical coherence tomography angiography in diabetic retinopathy: an updated review. *Eye (Lond)* 2021;35(1):149-161.
- 8 Parravano M, Ziccardi L, Borrelli E, *et al*. Outer retina dysfunction and choriocapillaris impairment in type 1 diabetes. *Sci Rep* 2021; 11:15183.
- 9 Cao D, Yang DW, Huang ZN, Zeng YK, Wang J, Hu YY, Zhang L. Optical coherence tomography angiography discerns preclinical diabetic retinopathy in eyes of patients with type 2 diabetes without clinical diabetic retinopathy. *Acta Diabetol* 2018;55(5):469-477.
- 10 Ziegler R, Neu A. Diabetes in childhood and adolescence. *Dtsch Arztebl Int* 2018;115(9):146-156.
- 11 Hashmi S, Lopez J, Chiu B, Sarrafpour S, Gupta A, Young J. Fractal dimension analysis of OCTA images of diabetic retinopathy using circular mass-radius method. *Ophthalmic Surg Lasers Imaging Retina* 2021;52(3):116-122.
- 12 Triolo G, Rabiolo A, Shemonski ND, *et al*. Optical coherence tomography angiography macular and peripapillary vessel perfusion density in healthy subjects, glaucoma suspects, and glaucoma patients. *Invest Ophthalmol Vis Sci* 2017;58(13):5713-5722.
- 13 Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol* 2015;133(1):45.
- 14 Scoles D, Gray DC, Hunter JJ, *et al*. In-vivo imaging of retinal nerve fiber layer vasculature: imaging histology comparison. *BMC Ophthalmol* 2009;9:9.
- 15 Mansoori T, Sivaswamy J, Gamalapati JS, Balakrishna N. Topography and correlation of radial peripapillary capillary density network with retinal nerve fibre layer thickness. *Int Ophthalmol* 2018;38(3): 967-974.
- 16 Mase T, Ishibazawa A, Nagaoka T, Yokota H, Yoshida A. Radial peripapillary capillary network visualized using wide-field montage optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016;57(9):OCT504-OCT510.
- 17 Zeng YK, Cao D, Yu HH, *et al*. Early retinal neurovascular impairment in patients with diabetes without clinically detectable retinopathy. *Br J Ophthalmol* 2019;103(12):1747-1752.
- 18 Campbell JP, Zhang M, Hwang TS, Bailey ST, Wilson DJ, Jia Y, Huang D. Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. *Sci Rep* 2017;7:42201.
- 19 Vujosevic S, Muraca A, Gatti V, Masoero L, Brambilla M, Cannillo B, Villani E, Nucci P, De Cillà S. Peripapillary microvascular and neural changes in diabetes mellitus: an OCT-angiography study. *Invest Ophthalmol Vis Sci* 2018;59(12):5074.
- 20 Wang XN, Cai X, Li SW, Li TT, Long D, Wu Q. Wide-field swept-source OCTA in the assessment of retinal microvasculature in early-stage diabetic retinopathy. *BMC Ophthalmol* 2022;22(1):1-11.
- 21 Lee SR, Liu T, Zhou JD, Zhang QP, Wong WT, Tse G. Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. *Acta Diabetol* 2021;58(2):171-180.