# REVIEW

# Optical coherence tomography angiography for assessment of changes of the retina and choroid in different stages of diabetic retinopathy and their relationship with diabetic nephropathy

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## Abstract

Given the prevalence of diabetes worldwide, diabetic retinopathy (DR) has become the most prominent cause of blindness. However, DR can be diagnosed only when it is severe enough to be clinically detectable. Several studies have evaluated the correlation between DR and diabetic nephropathy (DN) by utilizing optical coherence tomography angiography (OCTA). Compared with other diagnostic techniques, such as fluorescein angiography and fundus photography, OCTA has the ability to directly reflect the condition of the retinal and choroidal microcirculation at an early stage. This review focuses on the following aspects: the advantages of OCTA, the pathophysiology of DR, changes in OCTA images in patients with DR, and the relationships between OCTA parameters and renal function. **(Endokrynol Pol 2023; 74 (2): 135–139)**

**Key words:** *optical coherence tomography angiography; diabetic retinopathy; diabetic nephropathy; pathogenesis; correlation*

## Introduction

As the most common cause of blindness, diabetic retinopathy (DR) significantly lowers the quality of life of patients with diabetes. In the past, the limitations of screening techniques impeded early diagnosis of DR. Currently, optical coherence tomography angiography (OCTA) enables us to monitor DR at an early stage. As diabetic microvascular diseases, DR and diabetic nephropathy (DN) probably share similar pathophysiological mechanisms, and the correlation between them has been confirmed by using OCTA [1, 2]. OCTA has its own distinctive advantages, especially in quantitatively evaluating the blood flow condition of the retina and choroid. In this way, OCTA enables us to quantitatively analyse the relationship between DR and DN. Meanwhile, the sensitive areas of OCTA images could be used to detect early signs of DR, which is of great clinical significance. Furthermore, because microcirculation abnormality is one of the pathophysiological mechanisms of DR, we can use OCTA to observe its changes in different DR stages.

## Advantages of OCTA

Compared with fluorescein angiography (FA), the gold standard diagnostic criterion of DR, OCTA has advantages in assessing the condition of retinal microvasculature. As a method that requires venipuncture and dye infusion, FA is invasive and time-consuming. Moreover, FA only provides 2-dimensional images [3, 4]. In addition, the OCTA image of deep capillary plexuses (DCP) is clearer than its FA image. Furthermore, OCTA shows less interobserver variability than FA in measuring the foveal avascular zone (FAZ) [5].

OCTA has several unique advantages in diagnosing DR. It has the ability to detect early signs of microvascular abnormality ahead of microaneurysms (MAs), which include capillary dropout, dilated capillary loops, and tortuous capillary branches [6]. Furthermore, it can detect some MAs that are not captured by FA [7, 8] and identify the location of MAs and the affected capillary plexus [9]. Considering its ability to clearly identify the structural relationship between the proliferative membrane and the posterior hyaloid membrane [10–12], OCTA has

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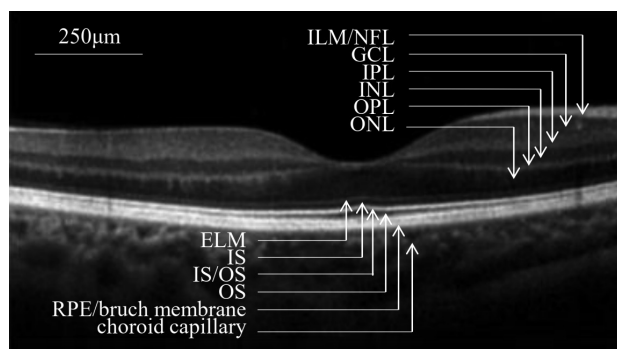
**Figure 1.** *OCT image of the retina and choroid. ILM — internal limiting membranes; NFL — nerve fibre layer; GCL — ganglion cell layer; IPL — inner plexiform layer; INL — inner nuclear layer; OPL — outer plexiform layer; ONL — outer nuclear layer; ELM — external limiting membranes; IS — inner segment; IS/OS — inner segment/outer segment; OS — outer segment; RPE — retinal pigment epithelium*

clear advantages in studying the mechanism of proliferative diabetic retinopathy (PDR).

## Pathophysiology of DR

Neurodegeneration and microvascular abnormality are the main pathophysiological mechanisms of DR. The authors have shown that neurodegeneration precedes microvascular abnormality [13–15]. Although retinal neurodegeneration plays a central role in the progression of DR, subtle microvascular abnormality rather than ganglion cell loss might be associated with early functional changes in patients with non-diabetic retinopathy (NDR) [16, 17]. Furthermore, a sequence of microvascular changes has been discovered in patients with DR: microvascular ischaemia originates from the choroid, then it extends inward to the superficial capillary plexus (SCP) and DCP [18]. Moreover, the disruption of the blood–retinal barrier (BRB), particularly the inner BRB (iBRB), is critical in the pathogenesis of DME [19].

Recently, the American Diabetes Association defined DR as a highly tissue-specific neurovascular complication caused by the impairment of the neurovascular unit (NVU) [20]. The NVU is composed of diverse cell types, including neurons, glia, immune cells, and vascular endothelial cells. The gradual dysfunction of the NVU possibly accelerates the progression of DR [21].

## Changes in OCTA images of DR

### Histological characteristics and OCTA images of normal retina

Histologically, the retina can roughly be divided into 2 parts: the retinal pigment epithelium (RPE)

and the neurosensory retina. The latter is composed of 9 layers: the layer containing photoreceptors, the external limiting membrane (ELM), the outer nuclear layer (ONL), the outer plexiform layer (OPL), the inner nuclear layer (INL), the inner plexiform layer (IPL), the ganglion cell layer (GCL), the nerve fibre layer (NFL), and the internal limiting membrane (ILM). The structure of the retina in OCTA images is similar to its histological structure except the first layer. In OCTA images, the first layer of the retina can be divided into 3 layers: the inner segment (IS), the inner segment/outer segment (IS/OS), and the outer segment (OS).

The macula and optic disc are 2 important parts of the retina. Anatomically, the macula can be divided into 3 parts: the fovea, parafovea, and perifovea. The fovea is the centre of the macula. Additionally, the centre of the fovea is the foveola, which is the thinnest part of the retina and is composed of a layer containing photoreceptors, ELM, and ILM. The parafovea is located outside the macula, and it is the thickest part of the macula, which consists of GCL, INL, and ONL. The perifovea is located outside the parafovea. In OCTA, the fovea is described as a circular area measuring 1 mm in diameter; the parafovea is defined as a middle circle area measuring 3 mm in diameter; and the perifovea is described as an outer circle area measuring 6 mm in diameter. The peripapillary area is defined as a 700-$\mu$m-wide elliptical annulus extending outward from the optic disc borders.

### Histological structure of the retina and choroid

The blood supply of the retina is mainly derived from 2 sources. The retina within the INL is supplied by retinal capillaries. The remaining parts, including the RPE and the layer containing photoreceptors, are supplied by choroidal capillaries. In particular, the blood supply of the FAZ is derived from the choriocapillaris.

The retina contains 2 capillary plexuses: SCP and DCP. The SCP is located in the NFL or GCL, while the DCP is situated in the INL [22]. In OCTA, the SCP is defined as a slab between the ILM and IPL/INL interface, and the DCP is defined as a slab between the IPL/INL interface and the OPL/ONL interface. In addition, between the RPE and choroid is Bruch's membrane, and these 3 membranes form a crucial complex named the RPE–Bruch's membrane–choroid capillary complex.

### Pathological changes in the retina

OCTA has clear advantages in quantitatively evaluating microvascular changes of the retina and choroid. Therefore, we can diagnose DR in advance by detecting abnormalities in OCTA parameters. For example, the enlargement of the FAZ area indicates abnormality

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of the choriocapillaris and the possibility of macular ischaemia, and the decrease of vessel density (VD) indicates ischaemia of the retina and choroid.

The VD of the SCP and DCP, mainly in the parafovea and perifovea, is significantly reduced in patients with NDR [5, 17, 23–26]. Compared with NDR, the VD of the parafovea in the SCP and DCP is significantly reduced in mild NPDR, especially in the temporal and nasal areas. Compared with mild NPDR, the reduction of VD extends to the inferior area in moderate NPDR. Compared with moderate NPDR, the progressive reduction of VD in all areas has been found in severe NPDR. Compared with severe NPDR, the VD in the superior area of SCP is significantly increased in PDR [18]. Unlike the reduced perfusion density (PD) in the DCP, Karst et al. [27] found a temporary increased PD in the SCP in patients without DR.

Parameters related to FAZ are frequently utilized as measures of macular ischaemia [6]. Di et al. [28] identified an enlargement of the FAZ area as an early marker of the retinal microvascular abnormalities in patients with diabetes. Moreover, the FAZ area in the SCP and DCP becomes larger in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). As DR progresses, the enlargement of the FAZ area and the decrease in the VD are severer in the DCP in both types of diabetes [29–31].

The thickness of the retina changes greatly in patients with diabetes. The thickness of the NFL, especially in the nasal and temporal quadrants, is substantially decreased in patients with NDR [13, 17, 23], which is later than the loss of ganglion cells [32, 33]. With the occurrence of diabetic peripheral neuropathy (DPN) [23], the thickness of GCL becomes thinner in patients with diabetes [13]. In patients with NPDR, the thickness of the GCL/IPL is significantly decreased, the INL/OPL thickness is significantly increased [13], and the thicknesses of the ONL/ELM and IS/OS RPE is not changed. In contrast, Scarinci et al. [34] reported that the ONL became thinner.

*Pathological changes in the choroid*
As a complication involving microcirculation abnormalities, DR simultaneously influences the capillaries of the choroid [35]. The choroidal thickness is increased in patients with diabetes [36, 37]. Furthermore, several studies have shown that the subfoveal choroid thickness (SFCT) is increased in diabetes [36, 38, 39], especially in patients with subretinal detachment (SRD)–type DME [37]. In contrast, other studies have shown a significant decrease in the choroidal thickness in patients with diabetes [40]. The VD of the fovea in the choroid capillary plexus (CCP) is significantly decreased in patients with NDR [18]. Furthermore, Kim et al. [37] claimed that

the choroidal thickness is significantly increased with the progression of diabetes from mild/moderate NPDR to PDR and significantly decreased in patients treated with panretinal photocoagulation (PRP).

*Different changes in the retina in T1D and T2D*
Changes in microcirculation abnormalities vary according to the type of diabetes. Compared with patients with T2D, the FAZ area in the DCP is significantly larger in patients with T1D. The VD of the fovea in the SCP is significantly lower in both types of diabetes. The morphological parameters of FAZ, including FAZ irregularity and capillary tortuosity, show significant differences in different types of diabetes [41]. Furthermore, the speed in the enlargement of the FAZ area is fast in the DCP compared with the SCP. The patterns of ischaemic changes differ according to the type of diabetes. In T1D, the decline rate of VD in the DCP is significantly steeper when DR progresses from severe NPDR to PDR, while it is more gradual in patients with T2D. In conclusion, the damage of DCP is severe when DR progresses from severe NPDR to PDR in patients with T1D [29].

## The relationship between the parameters of OCTA and DN

As a common diabetic microangiopathy, DR often coexists with DN. Meanwhile, microalbuminuria is an early marker of endothelial damage; the risk of DR is greatly increased in patients with microalbuminuria [42, 43], which indicates that DR and DN share the same pathophysiological mechanisms. Based on the advantages of OCTA in the assessment of microcirculation, parameters of OCTA can be used as reference indices for the individual risk stratification of DN. Moreover, numerous studies have shown that the onset of DR precedes the onset of DN [44–46]. Similarly, Cankurtaran et al. [47] showed that the alterations in retinal microcirculation are earlier than in microalbuminuria.

Several studies have evaluated the correlation between DR and DN. The VD of the retina is gradually decreased according to the progression of DN [47, 48], and the size of the FAZ area in the SCP and DCP is larger in patients with clinical albuminuria [49]. The level of urinary albumin moderately correlates with the VD of the SCP in patients with diabetes, and eGFR is significantly correlated with the size of retinal nonperfusion (RNP) area in patients with DN [50]. The VD of the retina and choroid is decreased after haemodialysis [51, 52], while there is no significant correlation between the VD of choriocapillaris and choroidal thickness (CT).

Some scholars have also used OCT to measure the thickness of the retina and choroid in patients with

DN. After haemodialysis, the thickness of the retina is decreased, while the SFCT does not change [51]. To date, the effect of haemodialysis on the choroid remains unclear. Ulas et al. [53] showed that haemodialysis could induce the thinning of the choroid, while Jung et al. [54] reported the opposite result.

## Conclusion

In terms of screening for and diagnosing DR, OCTA has incomparable advantages. By utilizing OCTA, we can compare the changes of the retina and choroid between different types of diabetes and quantitatively evaluate the correlation between DN and DR at the microvascular level. Even though the choriocapillaris is the most sensitive area of microcirculation, studies related to choroid changes are scarce. Compared with areas closed to the fovea, the areas outside the parafovea were more sensitive in reflecting capillary perfusion deficits [27], which indicates the advantages of wide-field swept source OCTA (SS-OCTA). Future studies need to focus on these points, so that we can diagnose DR at an early stage.

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