Optical Coherence Tomography Angiography in Early Detection of Microvascular Changes in Type I Diabetic Children: A Systematic Review and Meta-Analysis

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Abstract

Background: Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide, especially in the pediatric population. Accurate investigative tools are essential for the early diagnosis and monitoring of the disease.

Aim of Study: To conduct a systematic review and a meta-analysis to detect the early retinal microvascular changes in diabetic eyes with no clinical signs of diabetic retinopathy (DR) on routine fundus examination using optical coherence tomography angiography (OCTA) in pediatrics.

Patients and Methods: From a total of 217 screened citations, seven studies met our inclusion criteria with a total of 708 cases and 1228 eyes. The main outcomes were foveal avascular zone (FAZ) area and perimeter, Acircularity index, non-flow area (mm$^2$), SCP and Foveal density (%) along with superficial (SCP) and deep capillary plexus (DCP).

Data Extraction: If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and defined assessment measures.

Results: Our results suggested several potential biomarkers that could detect early DR in diabetic patients particularly in FAZ perimeter (MD =0.10, 95%CI=[0.03, 0.17], $I^2=31\%$, $p$-value=0.23) and Foveal density (%) (MD=-1.48, 95%CI=[-2.27, -0.70], $I^2=15\%$, value=0.28). Additionally, we pooled data regarding vessels densities and found that a trend towarded a lower SCP vessel densities in the whole retina and Parafoveal area (MD=-0.96, 95%CI=[-1.38, -0.55], $I^2=32\%$, value=0.23 and MDs=-0.87, 95%CI=[-1.20, -0.53], $I^2=0\%$, value=0.82, respectively) and lower DCP vessel densities in Parafoveal area (MD=-1.02, 95%CI=[-1.35, -0.70], $I^2=8\%$, value=0.35).

Conclusion: OCTA enables quantitative evaluation of the microvasculature of diabetic eyes. It has demonstrated the ability to detect early changes in FAZ perimeter and SCP and DCP in the eyes without clinical evidence of DR. It has also been shown to detect progressive changes in the FAZ diameter, and vascular perfusion density, with worsening severity of disease. Additional studies with larger sample size are needed to validate our findings.

Key Words: Diabetes mellitus – Diabetic retinopathy – Optical coherence tomography angiography.

Introduction

DIABETES mellitus (DM) is the third most common chronic disease in children. Although pediatric populations appear to be at minimal risk for Diabetic Retinopathy (DR), some adolescents develop clinically significant macular edema or even proliferative retinopathy [1].

Diabetic retinopathy (DR) is one of the serious complications of diabetes mellitus (DM), and it is a major cause of sight-loss worldwide [2].

Pubertal status and the prepubertal duration of diabetes influence the risk of developing DR, as children under the age of 10 years have minimal risk, and no cases of proliferative DR in the first decade of life were noted [3].

Therefore, early detection of DR through screening programs is crucial for preserving vision in patients with diabetes [4].

The American Diabetes Association recommends annual screening for retinopathy 5 years after the onset of diabetes. Screening is generally not recommended before the onset of puberty. These recommendations are for adults with type 1 diabetes. They also recommend an earlier referral of 3 to 5 years after diagnosis if the patient is 9 years of age [5].

Currently, there is a growing body of scientific evidence indicating that specific neural and vascular
retinal modifications can be present even before the onset of clinically visible signs of DR [6].

Microvasculopathy in the retina has been classically regarded as the pivotal initiating step [7]. The loss of pericytes has been considered as the initially detectable histologic evidence in the retina of DM subjects [8]. However, in the past few years, emerging evidence has suggested that neurodegeneration may occur before microvascular changes in preclinical DR [9].

The potential relationship between neurodegeneration and microvascular impairment has been frequently discussed.

A real-time cross-sectional imaging machine, optical coherence tomography angiography (OCTA), has been widely applied in retinopathy diagnoses. Compared to traditional diagnostic techniques, such as fluorescein fundus angiography (FFA), OCTA is less invasive, more convenient and safer because intravenous injection of dyes is not needed in the examination [10].

Subclinical and early microvascular changes detected on OCT-A mainly consist of remodeling and enlargement of the foveal avascular zone (FAZ), capillary nonperfusion, and reduced vascular density, and recently, also venous beading and increased vascular tortuosity were found to be more frequent in the macular region of patients with DM but with no DR versus healthy controls [6].

OCTA seems to be a promising tool for screening the macular area and follow-up in DR subjects. It is able to detect motion contrast produced by moving blood cells in retinal vessels. Recent advances in the projection artefact removal allowed to not only accurately defining the superficial plexus but also the deep retinal vascular layers [10].

Aim of the work:

The aim of the study was to conduct a systematic review and a meta-analysis to detect the early retinal microvascular changes in the eyes of type I diabetic children with no clinical signs of diabetic retinopathy (DR) on routine fundus examination using optical coherence tomography angiography (OCTA).

Material and Methods

This systematic review was prepared with a careful following of the Cochrane Handbook for Systematic Reviews of Interventions. We also adhered to The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines during the design of our study.

Eligibility criteria:

Inclusion criteria:

The included studies met the following inclusion criteria: Population: Diabetic children with type 1 diabetes aged up to 18 years with no clinical signs of diabetic retinopathy. Intervention: OCTA in diabetic patients. Comparator: OCTA in healthy controls. Outcome parameters: Detecting the early microvascular change in the retina of diabetic children using OCTA. Study design: Clinical trials whether randomized or nonrandomized prospective and retrospective comparative cohort studies, and case-control studies.

Exclusion criteria:

Exclusion of animal studies, reviews, book chapters, thesis, editorial letters and papers with overlapped dataset. There were no restrictions on language, race, sex, year of publication.

Outcome measures:

Our primary outcomes included foveal avascular zone (FAZ) assessment and vessel densities and blood flow parameters across the retina.

Search Methods for identifying studies:

A literature search was conducted on studies published between 2010 to 2020 using PubMed, Scopus, Webof Science, and Cochrane Library databases. We performed a search for all published articles that evaluated the role of Optical Coherence Tomography Angiography (OCTA) in early detection of microvascular changes in pediatric diabetics' patients with no clinical signs of diabetic retinopathy (DR).

The search included article title, abstract, keywords using the following keywords:

"OCTA", "optical coherence tomography angiography", "OCT angiography" "diabetes", "diabetes mellitus", "diabetic", "retinopathy", "Diabetic maculopathy", "children".

“OR” and “AND” operators were used during Literature search as following: (OCTA OR "optical coherence tomography angiography" OR "OCT angiography") AND (diabetes OR "diabetes mellitus" OR diabetic OR retinopathy OR "Diabetic maculopathy") AND children.

The "related articles" function was used to expand the search from each relevant study iden-
identified. Bibliographies of retrieved papers were further screened for any additional eligible studies. We searched for articles that were included in previous related systematic reviews. The identified citations were retrieved using Endnote X8 software package (Thompson Reuter, USA).

Eligibility screening was conducted in a two step-wise manner (title/abstract screening and full-text screening). Each step was done by two reviewers independently according to the predetermined criteria. The duplicated articles were removed primarily using Endnote X8 program (Thompson Reuter, USA) and manually using titles and abstracts screening.

**Data extraction:**

Data were extracted by two independent authors and revised by another two independent authors. The characteristics of each study were extracted as following: Study design sample size, age, gender, duration of diabetes, HbA1c, % along with microvascular change outcomes that were reported consistently across the included studies.

**Data synthesis and analysis:**

Statistical analysis was performed using Review Manager (version 5.3). We calculated the pooled Mean difference (MD) and 95% confidence intervals (CIs) for all outcomes using the Mantel-Haenszel method.

**Records identified through database searching**

(n=217)

Full-text articles excluded, with reasons (n=26)
1: Review
2: Conference abstract
3: Not type 1 diabetes
8: Not pediatric population
1: Not diabetic patients
3: Duplicates
1: Case report
1: Autoimmune thyroiditis population
6: Data could not be included in the analysis

**Records after duplicates removed**

(n=191)

**Records screened**

(n=191)

Full-text articles assessed for eligibility

(n=33)

Studies included in qualitative synthesis

(n=7)

Studies included in quantitative synthesis (meta-analysis) (n=7)

**Records excluded (n=158)**

1: Book chapter
8: Case report
15: Duplicates
127: Not diabetic patients
1: Not OTC
1: Not pediatric patients
5: Review

**Testing for heterogeneity:**

The extent of heterogeneity was estimated with the I^2 measure which describes the percentage of variation across studies that is due to heterogeneity, according to Cochrane handbook about guidelines for conducting meta-analysis, I^2 value below 50% means low heterogeneity so we used 50% as a cut off point for heterogeneity.

**Pooled estimates:**

In case of I^2 value below 50%, we used fixed effect model while in I^2 value above 50%, we used random effect model to pool the data.

**Examination of publication bias:**

Due to the low number of the included studies, we didn't performed assessment of the publication bias

\[ p > 0.05: \text{Non-significant.} \quad p < 0.05: \text{Significant.} \quad p < 0.01: \text{Highly significant.} \]

**Results**

We obtained 136 articles from PubMed, 17 articles from Scopus, 6 articles from Cochrane library and 58 from web of science. 27 duplicated articles were removed using Endnote X8 program (Thompson Reuter, USA), 191 articles manually underwent titles and abstracts screening and 33 article underwent full-text review as shown (Fig. 1). Seven studies finally met our inclusion criteria.

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**Fig. (1): PRISMA flow diagram showing process of studies selection.**
Included studies characteristics:

We identified seven studies that evaluated retinal microvascular change in pediatric patients using OCTA with a total 708 cases with 1228 eyes. Mean age of patients across the studies ranged between 11 and 15 years. All studies had a prospective design except Onoe et al., that was retrospective. Summary of the rest of studies characteristics are shown in Table (1).

Table (1): Included studies characteristics.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Sample size (n)</th>
<th>Female/male (n)</th>
<th>Age (y) Mean ± SD</th>
<th>Age of onset (y) Mean ± SD</th>
<th>Duration of diabetes (y) Mean ± SD</th>
<th>HbA1c, %, Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gońbięńska et al., 2017</td>
<td>Cross-sectional</td>
<td>T1D: 94 (188 eyes)</td>
<td>–</td>
<td>T1D: 15.3±2.1, Control: 13.6±1.8</td>
<td>8.9±3.8</td>
<td>6.4±3.3</td>
<td>8.2±1.3</td>
</tr>
<tr>
<td>Demir et al., 2020</td>
<td>Cross-sectional</td>
<td>T1D: 55 (110 eyes)</td>
<td>T1D: 30/25</td>
<td>T1D: 12.3±3.2, Control: 11.7±2.8</td>
<td>–</td>
<td>3.2±2.6</td>
<td>8.9±2.0</td>
</tr>
<tr>
<td>Onoe et al., 2019</td>
<td>Retrospective study</td>
<td>T1D: 29 (58 eyes)</td>
<td>T1D: 15/14</td>
<td>T1D: 16.1±8.7, Control: 13.8±7.0</td>
<td>6.4±3.5</td>
<td>9.7±8.3</td>
<td>8.9±2.0</td>
</tr>
<tr>
<td>Li et al., 2019</td>
<td>Case-control</td>
<td>T1D: 47 (94 eyes)</td>
<td>T1D: 28/19</td>
<td>T1D: 11.1±2.9, Control: 10.2±2.2</td>
<td>6.8±3.4</td>
<td>4.3±2.8</td>
<td>8.1±2.4</td>
</tr>
<tr>
<td>Inanc et al., 2019</td>
<td>Cross-sectional</td>
<td>T1D: 60 (60 eyes)</td>
<td>T1D: 33/27</td>
<td>T1D: 13.8±3.06, Control: 14.12±2.80</td>
<td>–</td>
<td>6.5±3.8</td>
<td>6.4±1.1</td>
</tr>
<tr>
<td>Kara et al., 2019</td>
<td>Cross-sectional</td>
<td>T1D: 60 (120 eyes)</td>
<td>T1D: 38/22</td>
<td>T1D: 13.79±1.7, Control: 13.40±2.90</td>
<td>–</td>
<td>4.9 (1.5-12.8)</td>
<td>9.8±1.9</td>
</tr>
<tr>
<td>*Mameli et al., 2019</td>
<td>Cross-sectional</td>
<td>T1D: 53 (106 eyes)</td>
<td>T1D: 30/23</td>
<td>T1D: 15.5, (12.4; 19.4), Control: 13.7 (11.8-18.9)</td>
<td>–</td>
<td>6.0 (3.3; 10.3)</td>
<td>7.6 (6.9; 8.1)</td>
</tr>
</tbody>
</table>

Fig. (2): Result of meta-analysis for diabetic patients versus healthy controls regarding (A) FAZ area (mm$^2$) and (B) FAZ perimeter (mm). The vertical line indicates that there is no difference between the two treatment groups. Pooled odds ratios calculated from fixed effects model with the Mantel-Haenszel method.
**Non-flow parameters:**

Three parameters [Acircularity index, Non-flow area (mm²), SCP and Foveal density (%)] were evaluated by two studies (Inanc et al., 2019, Kara et al., 2019) with a total of 355 eyes. Effect estimate favored DM group in term of Foveal density (%) (MD=–1.48, 95%CI=[–2.27, –0.70], I²=15%, value=0.28) (Fig. 3-A), While it didn't favor any arm regarding Acircularity index, and Non-flow area (mm²) (MD=0.02, 95%CI=[–0.03, 0.07], I²=90%, value=0.002 and MD=0.03, 95%CI=[0.00, 0.05], I²=18%, value =0.27, respectively) (Fig. 3-B,C).

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**Fig. (3):** Result of meta-analysis for diabetic patients versus healthy controls regarding (A) Foveal density (%), (B) Acircularity index and (C) Non-flow area (mm²). The vertical line indicates that there is no difference between the two treatment groups. Pooled odds ratios calculated from fixed effects model for Foveal density and Non-flow area and from random effects model for Acircularity index with the Mantel-Haenszel method.
Vessel density, SCP flow (%):

Gołąbiewska et al., 2017, Inanc et al., 2019 and Kara et al., 2019 evaluated SCP vessel densities in the whole retina with a total of 603 eyes while Gołąbiewska et al., 2017, Demir et al., 2020, Inanc et al., 2019, Kara et al., 2019 and Mameli et al., 2019 evaluated SCP vessel densities in Fovea and Parafoveal area with a total of 999 eyes. Effect estimate favored DM group regarding SCP vessel densities in the whole retina and Parafoveal area (decreased vessel densities) (MD=–0.96, 95%CI=[–1.38, –0.55], I²=32%, value=0.23 and MD=–0.87, 95%CI=[–1.20, –0.53], I²=0%, value=0.82, respectively) (Fig. 4-A,B). Effect estimate of SCP vessel densities in the Fovea didn’t favor any arm (MD=–0.05, 95%CI=[–0.76, 0.66], I²=50%, value =0.09) (Fig. 4-C).

![Result of meta-analysis for diabetic patients versus healthy controls regarding (A) SCP vessel densities in the whole retina (%), (B) SCP vessel densities in Parafoveal area (%) and (C) SCP vessel densities in Fovea (%). The vertical line indicates that there is no difference between the two treatment groups. Pooled odds ratios calculated from fixed effects model with the Mantel-Haenszel method.](image-url)
Vessel density, DCP flow (%):

Goiebiewska et al., [28], Inanc et al., [33] and Kara et al., [30] evaluated DCP vessel densities in the whole retina with a total of 603 eyes while Goiebiewska et al., [28], Demir et al., [9@9], Inanc et al., [33] Kara et al., [30] and Mammeli et al., [31] evaluated DCP vessel densities in Fovea and Parafoveal area with a total of 999 eyes. Effect estimate favored DM group regarding DCP vessel densities in Parafoveal area (decreased vessel densities) (MD=–1.02, 95%CI=[–1.35, –0.70], I²=8%, value =0.35) (Fig. 5-A). Effect estimate of DCP vessel densities in the whole retina and Fovea didn't favor any arm (MD=–1.85, 95%CI=[–3.06, –0.64], I²=69%, value=0.04 and MD=0.02, 95%CI=[–1.41, 1.45], I²=70%, value=0.009, respectively) (Fig. 5-B,C).

![Fig. (5): Result of meta-analysis for diabetic patients versus healthy controls regarding (A) DCP vessel densities in Parafoveal area (%), (B) DCP vessel densities in the whole retina (%) and (C) DCP vessel densities in Fovea (%). The vertical line indicates that there is no difference between the two treatment groups. Pooled odds ratios calculated from fixed effects model for DCP vessel densities in Parafoveal area (%) and from random effects model for DCP vessel densities in the whole retina (%) and Fovea with the Mantel-Haenszel method.](image-url)
Sensitivity analysis:

In FAZ perimeter, after excluding Inanc et al., [33], pooled estimate didn’t favor any arms with no heterogeneity (MD=0.06, 95%CI=[–0.02, 0.15], I²=0%, value=0.88) (Figure 6A). In SCP vessel densities in the Fovea, after excluding Kara et al., [30], there was no heterogeneity across the remaining studies but still pooled estimate didn’t favor any arms (MD=0.35, 95%CI=[–0.43, 1.12], I²=0%, value=0.62) (Fig. 6-B). In DCP vessel densities in the whole retina, after excluding Golębiowska et al., [28] pooled estimate favored DM group (MD=–1.91, 95%CI=[–2.93, –0.89], I²=24%, value=0.25) (Fig. 6-C). In DCP vessel densities in the Fovea, after excluding mameli et al., 2019, still there was high heterogeneity and the pooled estimate didn’t favor any arm (MD=–0.51, 95%CI = [–1.83, 0.80], I²=51%, value =0.11) (Fig. 6-D).

Fig. (6): Result of sensitivity analysis regarding (A) FAZ perimeter (mm), (B) SCP vessel densities in Fovea (%), (C) DCP vessel densities in whole retina (%) and (D) DCP vessel densities in Fovea (%).
Diabetes mellitus (DM) has become a worldwide epidemic in recent decades and poses a great challenge to health care systems [11]. It is estimated that 366 million people worldwide have diabetes, with 20-40 million people having type 1 DM. The prevalence of type 1 DM among children showed a dramatic increase [12].

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes [13]. Due to the long lifespan of pediatric diabetic patients, nearly all children diagnosed with DM will show evolution to DR. A study estimated that if DM developed at the age of 7, DR would occur at 17 to 34 years of age, with 35% of the cases showing proliferative changes [14].

So it is important to screen diabetic children for diabetic retinopathy to identify cases as early as possible to provide them with the comprehensive treatment they need [15]. Changes in retinal blood vessel morphology and retinal blood flow have been reported in DR. The screening tools focus on detecting very early changes in blood vessels [16].

Fluorescence Angiography (FA) is often regarded as the gold standard tool in DR diagnosis and classification. The state and blood circulation of retinal vessels can be accurately understood by observing the state of fluorescein in blood circulation [17].

Retinopathy manifests as dotted fluorescence, capillary filling defects, papillary ectasia and fluorescence leakage [18].

But FA requires an intravenous dye injection and can cause significant discomfort and stress, particularly in children. On the contrary, optical coherence tomography angiography (OCTA), a minimally invasive modality that can be performed in a short time without dye injection, provides 3-dimensional maps of macular perfusion and appears to be a promising method to detect early microcirculation disorders [19].

Hence, the current meta-analysis was conducted to review the literature to determine if OCTA can detect early retinal microvascular changes in diabetic eyes with no clinical signs of DR in type 1 diabetic pediatric patients.

One of the main outcomes of this meta-analysis is the assessment of FAZ. Changes in the FAZ are now viewed as an important tool in the screening and treatment of DR. The FAZ parameters of patients with diabetes showed a direct correlation with non-perfused capillaries [20].

Therefore, in this meta-analysis we evaluated the ability of OCTA to observe the changes in various FAZ parameters.

However, we did not find a significant difference in FAZ diameter between diabetic patients and healthy controls. There is a concern that the FAZ area is not sensitive enough to detect early DR as there is a great variation in FAZ size across the population with normal vision [21].

Unlike the FAZ area, the FAZ border may show changes that reflect early DR. Usually, in the healthy population; the FAZ area has a circular or elliptical shape, while in diabetic patients it becomes more acircular [22].

The reason behind this alteration in the FAZ boundaries is attributed to vascular changes in this area, such as altered blood flow [23].

This is consistent with the findings; diabetic patients have higher FAZ perimeter, in addition to low foveal density, which confirms that the change in FAZ boundaries occurs before the enlargement of the FAZ. It is worth noting that among the studies that estimated the FAZ diameter, only Onoe et al., showed significant enlargement of the FAZ area [24]. This is because the diabetes duration was much longer than in other studies (9.7 years).

Another potential marker for early DR is estimation of vessel densities (VD) across the retina. Studies in the literature showed capillary plexus impairment in patients with type 1 diabetes mellitus with no signs of DR [25].

This meta-analysis compared OCTA measurements of superficial (SCP) and deep capillary plexus (DCP) in various retinal regions. Evaluated studies found a decrease in vessel densities in SCP in the retina, except in the fovea and a decrease in vessel densities in DCP in parafoveal area only.

This is an interesting finding as it indicates that OCTA can provide quantitative assessment of early microvascular changes before other diabetic complications become visible by other screening procedures. Moreover, there are ongoing updates on OCTA to further stratify SCP and DCP into more layers that may be affected in very early phases of DR [26].

According to the American Academy of Ophthalmology, the duration of diabetes has a direct link to the development of DR. They even cate-
OCTA to Detect Microvascular Changes in DM

This meta-analysis included 42 patients who were examined using both OCTA and FA. There was a good agreement in the readings using both tools; the FAZ area was 0.39mm² in FA and 0.42mm² in OCTA. The micro-aneurysm count was 14 in FA and 13 in OCTA. Additionally, the examiners favored OCTA for the assessment of the FAZ, but FA was favored for the assessment of micro-aneurysms [36].

Also, recent statistics showed FA procedures were performed less often after the introduction of OCTA technology. The ease, speed, and safety of the optical coherence tomography angiography procedure in everyday clinical practice have facilitated more optical coherence tomography angiography applications compared to fluorescein angiography in recent years [37].

Obtained data from this systematic review and meta-analysis suggest that OCTA might be a valid tool in the assessment of early DR in the pediatric population. The early parameters detected in diabetic patients are FAZ perimeters and SCP and DCP. The FAZ area may not be sensitive enough in patients with short diabetes duration. The duration of diabetes is a determining factor for DR. Further studies are needed to compare the performance of OCTA in patients with various durations of diabetes.

Conclusion:

OCTA enables quantitative evaluation of the microvasculature of diabetic eyes. It has demonstrated the ability to detect early changes in FAZ perimeter and SCP and DCP in the eyes without clinical evidence of DR. It has also been shown to detect progressive changes in the FAZ diameter, and vascular perfusion density, with worsening severity of disease. Additional studies with larger sample size are needed to validate our findings.

References


rized the screening program according to disease duration, i.e., children with diabetes for more than 5 years should undergo fundus examination once a year [27]. Hence, the importance of OCTA as a non-invasive screening tool.

This meta-analysis had a wide range of disease duration between 3.2 and 9.7 years, with most studies around 4 to 6 years. Some studies showed a correlation between the disease duration in diabetic patients and OCTA measured parameters. Golębiowska et al., (Duration=6.4 years) reported a negative correlation between the diabetes duration and parafoveal DCP VD [28]. In Demir et al., (Duration=3.2 years), the diabetes duration was significantly correlated with FAZ diameter, and VD in the macular region [29]. In Kara et al., (Duration=4.9 years), there was a negative correlation between the diabetes duration and the capillary densities [30]. In Mameli et al (Duration=6.0 years), more microvascular abnormalities were detected on OCTA in a patient with longer diabetes duration and poor diabetes control [31].

On the other hand, in Demir et al., (Duration =3.2 years), there was no significant correlation between diabetes duration and VD in the disc region [29]. Li et al., (Duration=4.3 years) did not find a significant correlation between diabetes duration and FAZ diameter or VD [32]. Inanc et al., (Duration=6.5 years) reported that diabetes duration was not significantly correlated with microvascular structures of the macular region [33]. In Onoe et al., (Duration=9.7 years), there was no evidence of DR in diabetic patients despite it starting at an early age [24]. This was attributed to good diabetes control.

Those findings are consistent with previously published systematic reviews that evaluated the role of OCTA in DR.

Johannesen et al., [34] compared healthy controls to adult cases with non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. The results suggested that the FAZ area is larger in patients with diabetes, and it was the largest in proliferative diabetic retinopathy cases.

Another meta-analysis revealed that, as compared to the healthy control group, the diabetic group had enlarged areas and increased FAZ perimeters as well as decreased perfusion density in both SCP and DCP [35].

On the same line, OCTA had comparable measurements to FA.


