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

ROFYDA O. FATHALLAH, M.Sc.; HUSSEIN Sh. EL MARKABI, M.D.; RASHA A. THABET, M.D. and MARIAM AL-FEKY, M.D., F.R.C.S. (Glasgow)

The Departments of Ophthalmology\* and Pediatrics\*\*, Faculty of Medicine, Ain Shams University

#### 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 metaanalysis 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<sup>2</sup>), 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 towered a lower SCP vessel densities in the whole retina and Parafoveal area (MD=–0.96, 95% CI=[–1.38, -0.55],  $I_2^2=32\%$ , value =0.23 and MD=–0.87, 95% CI=[–1.20, -0.53], I =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

*Correspondence to:* Dr. Rofyda O. Fathallah, E-Mail: roa.fathallah@gmail.com

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 (OC-TA), 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 maculopathyANDand children.

The "related articles" function was used to expand the search from each relevant study iden-

tified. 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 fulltext 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.

#### 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-value: Level of significance: p>0.05: Nonsignificant. p0.05: Significant. p0.01: H ghly 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 articled underwent full-text review as shown (Fig. 1). Seven studies finally met our inclusion criteria.



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

(A)

(B)

# 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.

Study ID	Study design	Sample size (n)	Female/male (n)	Age (y) Mean ± SD	Age of onset (y) Mean ± SD	Duration of diabetes (y) Mean ± SD	HbA1c, %, Mean ± SD
Goiebiewska et al., 2017	Cross-sectional	T1D: 94 (188 eyes) Control: 36 (60 eyes)	_	T1D: 15.3±2.1, Control: 13.6±1.8	8.9±3.8	6.4±3.3	8.2±1.3
Demir et al., 2020	Cross-sectional	T1D: 55 (110 eyes) Control: 42 (84 eyes)	T1D: 30/25 Control: 23/19	T1D: 12.3±3.2, Control: 11.7±2.8	-	3.2±2.6	8.9±2.0
Onoe et al., 2019	Retrospective study	T1D: 29 (58 eyes) Control: 24 (48 eyes)	T1D: 15/14 Control: 8/16	T1D: 16.1±8.7, Control: 13.8±7.0	6.4±3.5	9.7±8.3	8.9±2.0
Li et al., 2019	Case-control	T1D: 47 (94 eyes) Control: 44 (88 eyes)	T1D: 28/19 Control: 24/20	T1D: 11.1±2.9, Control: 10.2±2.2	6.8±3.4	4.3±2.8	8.1±2.4
Inanc et al., 2019	Cross-sectional	T1D: 60 (60 eyes) Control: 57 (57 eyes)	T1D: 33/27 Control: 37/20	T1D: 13.81±3.06 Control: 14.12±2.80	-	6.5±3.8	6.4±1.1
Kara et al., 2019	Cross-sectional	T1D: 60 (120 eyes) Control: 59 (118 eyes)	T1D: 38/22 Control: 35/24	T1D: 13.79±1.7 Control: 13.40±2.90	-	4.9 (1.5-12.8)	9.8±1.9
*Mameli et al., 2019	Cross-sectional	T1D: 53 (106 eyes) Control: 48 (96 eyes)	T1D: 30/23 Control: 26/22	T1D: 15.5 (12.4; 19.4), Control: 13.7 (11.8-18.9)	_	6.0 (3.3; 10.3)	7.6 (6.9; 8.1)

		DM		Co	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD 1	Total V	Veight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl	_
Demir et al. 2020	0.29	0.1	110	0.28	0.11	84	18.0%	0.01 [-0.02, 0.04]		
Gołębiewska et al. 2017	0.231	0.1	188	0.24	0.078	60	27.4%	-0.01 [-0.03, 0.02]		
nanc et al. 2019	0.28	0.11	60	0.27	0.13	57	8.5%	0.01 [-0.03, 0.05]		
Kara et al. 2019	0.28	0.1	60	0.27	0.11	59	11.4%	0.01 [-0.03, 0.05]		
i et al. 2019.	0.245	0.099	94	0.236	0.102	88	19.1%	0.01 [-0.02, 0.04]		
Dhoe et al. 2019	0.29	0.09	58	0.25	0.08	48	15.5%	0.04 [0.01, 0.07]		
otal (95% CI)			570			396 1	00.0%	0.01 [-0.00, 0.02]	•	
Heterogeneity: Chi <sup>2</sup> = 5.6 Test for overall effect: Z =	2, df = 5 ( 1.42 (P	(P = 0.34 = 0.16)	+), 1 -	1170					-0.05 -0.025 0 0.025 0.05 Favours [DM] Favours [control]	
leterogeneity: Chi <sup>2</sup> = 5.6 fest for overall effect: Z =	2, df = 5 ( 1.42 (P	(P = 0.34 = 0.16)	+ <i>j</i> ,	1170	Contr			Mean Difference	-0.05 -0.025 0 0.025 0.05 Favours [DM] Favours [control]	
leterogeneity: Chi <sup>2</sup> = 5.6; est for overall effect: Z = Study or Subgroup	2, df = 5 ( : 1.42 (P : Mean	(P = 0.34 = 0.16) DM SD	Tota	l Mear	Contro Si	ol D Toti	al Wei	Mean Difference ight IV, Fixed, 95%	-0.05 -0.025 0 0.025 0.05 Favours [DM] Favours [control] Mean Difference CI IV, Fixed, 95% CI	
leterogeneity: Chi <sup>2</sup> = 5.6; fest for overall effect: Z = Study or Subgroup inanc et al. 2019	2, df = 5 ( : 1.42 (P : Mean 2.11	P = 0.34 = 0.16) DM SD 0.44	Tota 60	Mean 1.9	Contro SI	ol D Toti 7 5	al Wei 7 23.	Mean Difference ight IV, Fixed, 95% .1% 0.21 (0.06, 0.36	-0.05 -0.025 0 0.025 0.05 Favours [DM] Favours [control] Mean Difference Cl IV, Fixed, 95% Cl 	
leterogeneity: Chi <sup>2</sup> = 5.6; est for overall effect: Z = <u>Study or Subgroup</u> inanc et al. 2019 Kara et al. 2019	2, df = 5 ( 1.42 (P Mean 2.11 2.04	P = 0.34 = 0.16) DM SD 0.44 0.4	Tota 60 120	I Mean 1.9 1.97	Contro SI 0.3 0.4	ol D Toti 7 5 3 11	al Wei 7 23. 8 44.	Mean Difference ight IV, Fixed, 95% .1% 0.21 (0.06, 0.36 .9% 0.07 [-0.04, 0.18	Outright Stress St	
leterogeneity: Chi <sup>2</sup> = 5.6; Test for overall effect: Z = Study or Subgroup inanc et al. 2019 Kara et al. 2019 Li et al. 2019	<u>Mean</u> 2. df = 5 ( 1.42 (P <u>1.42 (P</u> 2.11 2.04 1.953	P = 0.34 = 0.16) DM SD 0.44 0.4 0.441	Tota 60 120 94	I Mean 1.9 1.97 1.896	Contro 0.3 0.4 0.41	ol D Toti 7 5 3 11 9 8	al Wei 7 23. 8 44. 8 32.	Mean Difference   ight IV, Fixed, 95%   .1% 0.21 [0.06, 0.36   .9% 0.07 [-0.04, 0.18   .0% 0.06 [-0.07, 0.18	-0.05 -0.025 0 0.025 0.05 Favours [DM] Favours [control] Mean Difference Cl IV, Fixed, 95% Cl IV, Fixed, 95% Cl	
feterogeneity: Chi <sup>2</sup> = 5.6; Test for overall effect: Z = Study or Subgroup inanc et al. 2019 Kara et al. 2019 Li et al. 2019 Total (95% CI)	<u>Mean</u> 2. df = 5 ( 1.42 (P 2.11 2.11 2.04 1.953	P = 0.34 = 0.16) DM SD 0.44 0.44 0.441	Tota 60 120 94 274	I Mean 1.97 1.896	Contro 0.3 0.4 0.41	ol D Toti 7 5 3 11 9 8 26	al Wei 7 23. 8 44. 8 32. 3 100.	Mean Difference   ight IV, Fixed, 95%   .1% 0.21 [0.06, 0.36   .9% 0.07 [-0.04, 0.18   .0% 0.06 [-0.07, 0.18   .0% 0.10 [0.03, 0.17	-0.05 -0.025 0.05 Favours [DM] Favours [control] Mean Difference Cl IV, Fixed, 95% Cl 	
Heterogeneity: Chi <sup>2</sup> = 5.6; Fest for overall effect: Z = <u>Study or Subgroup</u> inanc et al. 2019 Kara et al. 2019 Li et al. 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 5	<u>Mean</u> 2.142 (P 2.142 (P 2.11 2.04 1.953 2.91, df	P = 0.34 = 0.16) DM 0.44 0.44 0.441 = 2 (P =	Tota 60 120 94 274 = 0.23)	I Mean 1.97 1.97 1.89€ ;  ² = 31	Contro 0.3 0.4 0.41	ol D Toti 7 5 3 11 9 8 26	al Wei 7 23. 8 44. 8 32. 3 100.	Mean Difference   ight IV, Fixed, 95%   .1% 0.21 [0.06, 0.36   .9% 0.07 [-0.04, 0.18   .0% 0.06 [-0.07, 0.18   .0% 0.10 [0.03, 0.17	All of the second secon	

Fig. (2): Result of meta-analysis for diabetic patients versus healthy controls regarding (A) FAZ area (mm<sup>2</sup>) 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, Nonflow area (mm<sup>2</sup>), 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], I<sup>2</sup>=15%, value=0.28) (Fig. 3-A), While it didn't favor any arm regarding Acircularity index, and Non-flow area (mm<sup>2</sup>) (MD=0.02, 95%CI=[-0.03, 0.07], I<sup>2</sup>=90%, value=0.002 and MD=0.03, 95%CI=[0.00, 0.05], I<sup>2</sup>=18%, value =0.27, respectively) (Fig. 3-B,C).

		DM		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
inanc et al. 2019	54.97	4.57	60	57.12	3.29	57	29.8%	-2.15 [-3.59, -0.71]	-8-
Kara et al. 2019	55.76	3.81	120	56.96	3.56	118	70.2%	-1.20 [-2.14, -0.26]	
Total (95% CI)			180			175	100.0%	-1.48 [-2.27, -0.70]	•
Heterogeneity: Chi <sup>2</sup> =	1.18, df	= 1 (P	= 0.28)	;  2 = 15	%				
Test for overall effect:	Z = 3.70	(P = (	).0002)						Favours [DM] Favours [control]

	DM Control				ontrol	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
inanc et al. 2019	1.08	0.09	60	1.03	0.08	57	45.2%	0.05 [0.02, 0.08]	Ð
Kara et al. 2019	1.09	0.02	120	1.09	0.02	118	54.8%	0.00 [-0.01, 0.01]	Ψ
Total (95% CI)			180			175	100.0%	0.02 [-0.03, 0.07]	+
Heterogeneity: Tau <sup>2</sup> =	0.00; C	1j² = 9.	.84, df :	= 1 (P =	0.002	);  ² = 9	0%	-	
Test for overall effect:	Z = 0.91	(P = (	).36)		Favours [DM] Favours [control]				

(B)

		DM		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
inanc et al. 2019	0.5	0.12	60	0.49	0.11	57	38.6%	0.01 [-0.03, 0.05]	-0-
Kara et al. 2019	0.49	0.13	120	0.45	0.13	118	61.4%	0.04 [0.01, 0.07]	-8-
Total (95% CI)			180			175	100.0%	0.03 [0.00, 0.05]	•
Heterogeneity: Chi2 =	1.22, df	= 1 (P	= 0.27)	;  2 = 18	%				
Test for overall effect:	Z = 2.15	(P = (	0.03)						-0.2 -0.1 0 0.1 0.2 Favours [DM] Favours [control]

Fig. (3): Result of meta-analysis for diabetic patients versus healthy controls regarding (A) Foveal density (%), (B) Acircularity index and (C) Non-flow area (mm<sup>2</sup>). 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 (%):

Gołębiewska 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 Gołębiewska 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],  $I^2=32\%$ , value=0.23 and MD= -0.87, 95%CI=[-1.20, -0.53],  $I^2=0\%$ , 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],  $I^2=50\%$ , value =0.09) (Fig. 4-C).

		DM		Ç	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Gołębiewska et al. 2017	51.98	2.43	188	52.45	2.74	60	28.5%	-0.47 [-1.25, 0.31]	
inanc et al. 2019	50.43	3.14	60	51.16	2.82	57	14.7%	-0.73 [-1.81, 0.35]	
Kara et al. 2019	50.42	2.2	120	51.69	2.12	118	56.8%	-1.27 [-1.82, -0.72]	
Total (95% Cl)			368			235	100.0%	-0.96 [-1.38, -0.55]	•
Heterogeneity: Chi <sup>2</sup> = 2.93	, df = 2	(P = 0.	23);  2	= 32%					-2 -1 0 1 2
Test for overall effect: Z =	4.56 (P	< 0.00	001)						Favours [DM] Favours [control]

(A)

		DM	_	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Demir et al. 2020	50.1	3.2	110	50.7	2.5	84	17.4%	-0.60 [-1.40, 0.20]	
Gołębiewska et al. 2017	53.8	2.54	188	54.41	2.62	60	19.6%	-0.61 [-1.37, 0.15]	
inanc et al. 2019	52.96	3.44	60	54.18	2.78	57	8.8%	-1.22 [-2.35, -0.09]	
Kara et al. 2019	52.98	3.28	120	53.94	3.01	118	17.5%	-0.96 [-1.76, -0.16]	
mameli et al. 2019	57	2	106	58	2	96	36.7%	-1.00 [-1.55, -0.45]	
Total (95% CI)			584			415	100.0%	-0.87 [-1.20, -0.53]	•
Heterogeneity: Chi2 = 1.52	2, df = 4	(P = 0	.82);  2	= 0%					
Test for overall effect: Z =	5.07 (P	< 0.00	001)						Favours [DM] Favours [control]

(B)

		DM		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Demir et al. 2020	18.4	5.7	110	18.5	5.8	84	18.9%	-0.10 [-1.73, 1.53]	
Gołębiewska et al. 2017	32.51	5.26	188	32.48	5.33	60	21.2%	0.03 [-1.51, 1.57]	
inanc et al. 2019	20.5	5.71	60	20.72	6.14	57	10.9%	-0.22 [-2.37, 1.93]	
Kara et al. 2019	21.05	6.88	120	23.13	6.9	118	16.5%	-2.08 [-3.83, -0.33]	
mameli et al. 2019	32	5	106	31	4	96	32.6%	1.00 [-0.24, 2.24]	+
Total (95% CI)			584			415	100.0%	-0.05 [-0.76, 0.66]	<b>•</b>
Heterogeneity: Chi <sup>2</sup> = 7.9/	4, df = 4	(P = 0	.09); l²	= 50%				<del>.</del>	
Test for overall effect: Z =	0.15 (P	= 0.88	)						Favours [DM] Favours [control]

Fig. (4): 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.

(C)

# 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 Mameli 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], I<sup>2</sup>=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], I<sup>2</sup> =69%, value=0.04 and MD=0.02, 95%CI=[-1.41,1.45], I<sup>2</sup>=70%, value=0.009, respectively) (Fig. 5-B,C).



		DM		c	ontrol	Г <u> </u>	0.00	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Gołębiewska et al. 2017	58.57	1.94	188	58.57	5.03	60	35.4%	0.00 [-1.30, 1.30]	
inanc et al. 2019	52.32	5.24	60	53.36	4.66	57	28.3%	-1.04 [-2.83, 0.75]	
Kara et al. 2019	53.79	5	120	56.11	4.76	118	36.3%	-2.32 [-3.56, -1.08]	
Total (95% CI)			368			235	100.0%	-1.14 [-2.61, 0.34]	-
Heterogeneity: Tau <sup>2</sup> = 1.1/	6; Chi <sup>2</sup> =	6.42,	df = 2 (	(P = 0.0	4);  2 =	69%			
Test for overall effect: Z =	1.51 (P	= 0.13	)						Favours [DM] Favours [control]

(B)

(A)

		DM		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Demir et al. 2020	34.5	6.3	110	34.5	7.2	84	19.0%	0.00 [-1.94, 1.94]	
Gołębiewska et al. 2017	32.37	6.17	188	31.75	3.96	60	23.2%	0.62 [-0.71, 1.95]	
inanc et al. 2019	38.29	6.55	60	39.24	6.66	57	16.0%	-0.95 [-3.35, 1.45]	
Kara et al. 2019	37.94	7.55	120	40.17	7.59	118	19.1%	-2.23 [-4.15, -0.31]	
mameli et al. 2019	33	1	106	31	7	96	22.7%	2.00 [0.59, 3.41]	
Total (95% CI)			584			415	100.0%	0.02 [-1.41, 1.45]	+
Heterogeneity: Tau <sup>2</sup> = 1.84	4; Chi <sup>2</sup> =	13.56	, df = 4	(P = 0.	009);	² = 70%			
Test for overall effect: Z =	0.03 (P	= 0.98	)						Favours [DM] Favours [control]

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 Mantel-Haenszel method.

(C)

(C)

# 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],  $I^2=0\%$ , 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],  $I^2=0\%$ ,

value=0.62) (Fig. 6-B). In DCP vessel densities in the whole retina, after excluding Gorębiewska et al., [28] pooled estimate favored DM group (MD=-1.91, 95%CI=[-2.93, -0.89],  $I^2 = 24\%$ , 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],  $I^2 = 51\%$ , 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 (%).

#### Discussion

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 3dimensional 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 Once 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 categorized 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. Golebiewska 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 Once 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.

#### 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 0.39mm<sup>2</sup> in FA and 0.42mm<sup>2</sup> 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.

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# استخدام التصوير البصرى المقطعى التماسكى للأوعية الدموية فى الكشف المبكر عن التغيرات فى الأوعية الدموية الدقيقة لدى الأطفال المصابين بداء السكرى : دراسة تحليلية و مراجعة منهجية

مقدمة : يعتبر داء السكرى من النوع ١ هو الأكثر شيوعاً بين الأطفال والشباب البالغين الذى يحدث نتيجة خلل فى إفراز الأنسولين أو تأثير الأنسولين على خلايا الجسم.

وعادة ما تشمل المضاعفات لهذا المرض التأثير على الأوعية الدموية الدقيقة وخاصة البصرية مما يؤدى إلى الاصابة باعتلال الشبكية السكرى الذى يعتبر من أخطر وأكثر المضاعفات حدوثاً فى الاطفال والمراهقين المصابين بداء السكرى من النوع ١ ويعتبر السبب الرئيسى للاصابة بالعمى فى هؤلاء المرضى.

عيون مرضى السكرى تظهر تدهور فى الأوعية الدموية الدقيقة فى منطقة (macula) حتى قبل تطور اعتلال الشبكية السكرى، وفى مواجهة هذا فإن OCTA هو أداة فحص مفيدة للكشف المبكر عن اضطرابات الدورة الد موية الد قيقة فى المرضى الذين يعانون من النوع الأول من السكرى قبل تطور اعتلال الشبكية السكرى.

هدف البحث : تهدف هذه الدراسة إلى تقييم ما إذا كان من الممكن اكتشاف التغيرات المبكرة في الأوعية الدموية الدقيقة في شبكية العين في عيون مرضى السكري مع عدم وجود علامات سريرية لمرض DR باستخدام OCTC في الأطفال.

نتائج البحث : كنتيجة لهذه الدراسة التحليلية فإن التصوير المقطعي البصري للأوعية الدموية (OCTA) يتيح التقييم الكمي للأوعية الدموية الدقيقة لعيون مرضى السكري.

بشكل عام، نستنتج أن OCTA هى أداة فحص صالحة L DR فى مجتمع الأطفال والتى تتيح التقييم الكمى للأوعية الدموية الدقيقة للعيون المصابة بداء السكرى. لقد أظهرت القدرة على أكتشاف التغيرات المبكرة فى محيط FAZ و SCP و DCP فى العين دون وجود دليل إكلينيكى على DR. كما يكتشف أيضاً التغيرات التدريجية فى قطر FAZ وكثافة الأوعية مع تفاقم المرض.