Early Detection of Microvascular Impairments With Optical Coherence Tomography Angiography in Diabetic Patients Without Clinical Retinopathy: A Meta-analysis

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• PURPOSE: To evaluate microvascular impairments with optical coherence tomography angiography (OCTA) in the eyes of diabetic patients with no diabetic retinopathy (NDR).

• DESIGN: Systematic review and meta-analysis.

• METHODS: The PubMed and Embase databases were comprehensively searched to identify studies comparing the microvascular changes between diabetic eyes without clinical retinopathy and healthy controls using OCTA. Data of interest were extracted and analyzed by Review Manager V.5.3 and Stata V.14.0. The weighted mean differences and their 95% confidence intervals were used to assess the strength of the association.

• RESULTS: Forty-five cross-sectional studies involving 2241 diabetic and 1861 healthy eyes were ultimately included. OCTA unambiguously revealed that compared with the healthy control group, the NDR group manifested enlarged areas and increased perimeters of the foveal avascular zone, with decreased perfusion density (PD) in both superficial and deep capillary plexus of the macula (except parafoveal PD of the inner retina and foveal PD) and reduced radial peripapillary capillary PD. In addition, subgroup analyses according to the type of diabetes mellitus indicated that most of those differences became nonsignificant (except parafoveal PD in the deep capillary plexus) in type 1 diabetes mellitus, while in type 2 diabetes mellitus they remained statistically significant.

• CONCLUSION: Our results suggested that retinal microvascular impairments might have occurred antecedent to clinically visible diabetic retinopathy and could be detected early by OCTA. However, those manifestations could be inconsistent according to the types of diabetes mellitus. (Am J Ophthalmol 2021;222:226–237. © 2020 Elsevier Inc. All rights reserved.)

DIABETIC RETINOPATHY (DR) IS THE MOST COMMON microvascular complication of diabetes mellitus (DM) and one of the leading causes of acquired visual loss worldwide, affecting approximately 35% of diabetic patients.[1] Previous data from animal models and human populations have shown that retinal vascular alterations and impairment of autoregulation occur in the very early stages of DR.[2,3] Histopathologic evidence has also revealed that changes in retinal capillaries precede clinically visible retinal signs such as microaneurysms.[4,5] The retinal structure and vision have already been affected once the lesions become clinically visible. Fortunately, those patients would achieve benefits for the retina by prompt and intensive treatment.[6] Therefore, the detection and quantification of early biomarkers of preclinical retinopathy in diabetic patients could allow a better understanding of the pathogenesis of DR, the prediction of the development of DR at an early stage, and early intervention to ultimately delay or even prevent advanced retinopathy.

At present, the mildest form of DR is defined as the presence of only microaneurysms during mydriatic fundus examination. However, whether pathologic changes occur and what kind of changes could have occurred in the fundus (including the retina and choroid) of diabetic patients before reaching the minimum clinical diagnostic criteria for DR are ambiguous. Compared to fluorescein angiography (FA), optical coherence tomography angiography (OCTA) is a noninvasive imaging technique that allows stratified visualization and objective quantitation of retinal and choroidal blood flow, and it can be used for the early follow-up and evaluation of diabetic patients. In addition to observing some clinically undetectable microaneurysms,[7,8] many studies have reported some "real" preclinical changes observed by OCTA that did not fit the definition of DR and predated the occurrence of microaneurysms or hemorrhage, such as enlargement and deformation of the foveal avascular zone (FAZ) and decrease in retinal perfusion density.[9–11] However, several

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comparative studies did not find any OCTA changes between the DM groups and control groups.[12–14]

Owing to the lack of a meta-analysis of this topic, we collected evidence from observational comparative studies of OCTA for diabetic eyes with no diabetic retinopathy (NDR) to explore whether there are DM-related preclinical retinal and choroidal microvascular changes and to provide a basis for early diagnosis and prompt treatment as well as deepening the understanding of DR pathogenesis.

METHODS

THIS META-ANALYSIS WAS PERFORMED STRICTLY IN ACCORDance with the guidelines presented by the Meta-Analysis of Observational Studies statement.[15]

• **SEARCH STRATEGY:** The PubMed and Embase databases were comprehensively searched by 2 independent reviewers (B.L.Z. and Y.Y.C.) to identify potentially relevant studies for this analysis. As there was no universal terminology for diabetic eyes without retinopathy, the detailed search criteria were (diabetic[Title/Abstract] OR diabetes [Title/Abstract] OR "diabetes mellitus"[MeSH Terms]) AND ("optical coherence tomography angiography"[Title/Abstract] OR "OCT angiography"[Title/Abstract]) OR OCTA[Title/Abstract] OR "angio-OCT"[Title/Abstract]). The literature search was limited to articles published in peer-reviewed journals before April 2020. The references of included studies using the bibliographic database were also reviewed. In addition, we searched the gray literature and unpublished data.

• **INCLUSION AND EXCLUSION CRITERIA:** The inclusion criteria were as follows: (1) OCTA studies focused on diabetic patients without retinopathy or contained the preclinical stage of DR, (2) observational comparative studies, and (3) OCTA measurements reported as the mean and standard deviation (SD).

The exclusion criteria were as follows: (1) patients with ocular or systematic diseases that may significantly affect the retina or choroid, such as choroidal neovascularization and systemic lupus erythematosus (except well-controlled hypertension); (2) diabetic eyes without retinopathy mixed with other stages of DR; (3) insufficient data to estimate a weighted mean difference (WMD); (4) studies with significantly unreliable data on FAZ measurements (deviation from the normal range by more than 10 times in the control group); (5) review articles or technical notes; (6) animal studies or cadaver subjects; (7) duplicate study populations or redundant publications.

• **DATA EXTRACTION AND ASSESSMENT OF METHODOLOGICAL QUALITY:** Data of interest extraction and the methodological quality assessment were accomplished by 2 reviewers (B.L.Z. and Y.Y.C.) independently. Discrepancies were resolved by discussion with a third reviewer (Y.X.C.) when necessary. The corresponding authors of relevant articles were contacted when the requisite information was unavailable.

After removing the duplicates using NoteExpress V.3.2.0.7535 (Aiqinhailezhi Technology, Beijing, China), the 2 reviewers (B.L.Z. and Y.Y.C.) read the titles and abstracts to filter the unrelated studies and then reviewed the full texts of the remaining studies to identify those that met the inclusion criteria and failed the exclusion criteria. The following characteristics of the included studies were recorded: the first author, year of publication, design, country or region, sample size, mean age, type and duration of DM, OCTA device used, and details of OCTA scans. When outcomes were available in different sizes of scans in the same study (eg, macular scans of 3×3 mm and 6×6 mm), we chose the smaller scan for better resolution.

The quality of cross-sectional studies included in this meta-analysis was evaluated using the criteria recommended by the Agency for Healthcare Research and Quality (AHRQ) to assess risk of bias.[16]

• **STATISTICAL ANALYSIS:** Review Manager V.5.3 (Cochrane Collaboration, Oxford, United Kingdom) and Stata V.14.0 (StataCorp, College Station, Texas, USA) were used to perform statistical analyses. In this meta-analysis, continuous variables extracted as the mean values and SDs were estimated by WMDs and their 95% confidence intervals (CIs). The χ^2 test and I^2 statistic were used to assess the statistical heterogeneity, and the random-effect model was applied because of anticipated high levels of heterogeneity. Subgroup analyses were planned (unless the number of studies was insufficient), based on the types of DM and OCTA devices. Publication bias was assessed by Egger's linear regression test and $P < .05$ was considered to indicate statistical significance of bias.

RESULTS

• **STUDY CHARACTERISTICS:** The Figure illustrates the flowchart of the study selection. A total of 1,003 potentially relevant articles were identified from our search strategies across all databases and systematic review reference lists. After removal of duplicates using NoteExpress software and screening of titles and abstracts, 63 studies remained, and the full texts were assessed. Then, 18 of them were excluded for various reasons, yielding 45 cross-sectional studies involving 2,241 diabetic and 1,861 healthy eyes ultimately eligible for the quantitative synthesis.[8–11,13,14,17–55] Notably, 6 studies were excluded for some significantly unreliable FAZ data, such as area in hundreds of square millimeters or square microns.[56–61] Despite the possible

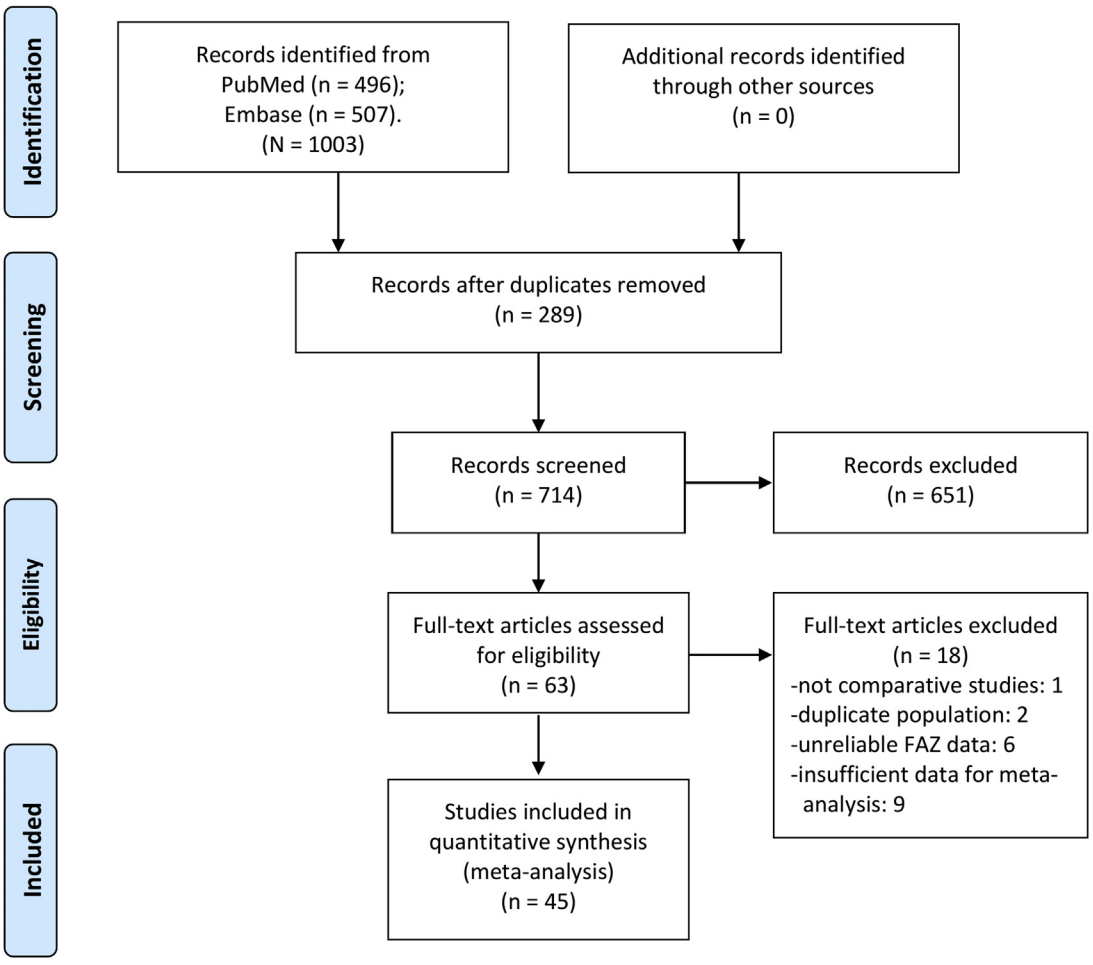

FIGURE 1. Flowchart of the study selection. FAZ = foveal avascular zone.

duplicate populations of some authors, such as Cao and associates,[8,51] Li and associates,[49,52] and Liu and associates,[35,53] we extracted different outcome variables. All studies included were published between 2015 and 2020, and their main characteristics are presented in Table 1.

• **TERMINOLOGY:** Since the terms of outcomes varied among studies and different types of OCTA devices, the terminology was standardized in this meta-analysis. For instance, vessel density (VD) represents both the ratio of blood flow area to the total area of the scan using Optovue and the ratio of blood flow length to the total area using the Zeiss device. The latter was called vessel length density (VLD) more often. Consequently, we named the area ratio "perfusion density" (PD).

Acircularity index (AI) was the ratio of the FAZ perimeter to the perimeter of a circle with an area equal to that of the FAZ mathematically.[62]

Foveal density-300 (FD-300) was the PD 300 μm around the FAZ.

Vessel tortuosity (VT) was the ratio of actual branch length to the straight length between branch nodes.

The subregion of the macula also sometimes varied for the measurements of PD. Mostly, the foveal zone was defined as the area of the small circle with a diameter of 1 mm, the parafoveal zone was defined as the annular region between 2 circles with diameters of 1 and 3 mm, and the perifoveal zone was defined as the annular region of diameters of 3 and 6 mm.

• **SUMMARY MEASURES:** The outcomes of primary quantitative synthesis are summarized in Table 2. For FAZ parameters, the areas in the superficial capillary plexus (SCP), deep capillary plexus (DCP), inner retinal layer, and perimeter significantly enlarged in the NDR groups compared with those in the control groups ($P < .05$ for all, Supplemental Figures S1-S3; Supplemental Material available at AJO.com), while only AI showed no significant difference ($P > .05$, Supplemental Figure S4; Supplemental Material available at AJO.com). Because the FAZ borderline in the SCP covers the borderline in the DCP during the OCTA inner retina scan, we merged the FAZ area in the SCP and inner retina together as the FAZ area of the mixed layer to facilitate further subgroup analyses.

TABLE 1. Characteristics of Included Studies

Author, Year	No. of Eyes		Location	Type of DM	Mean Duration (Years)	OCTA Device	Scan Size[a] (mm)	Outcome Variables
	DM	HC						
Choi[17]	55	48	South Korea	2	17.9	Zeiss	M 6	FAZ
Dai[18]	16	16	USA	Mixed	2.1	Zeiss	M 6	FAZ
Fleissig[19]	20/32	28	USA	1/2	30.3/12.3	Zeiss	M 3	FAZ/MPD
Onoe[9]	58	48	Japan	1	9.7	Optovue	M 3	FAZ/MPD
Sacconi[13]	12	12	Italy	1	35	Zeiss	M 3	FAZ/MPD
Yang Jyan[47]	292	80	China	2	15.1	Optovue	M 3	MPD/RPD
							O 4.5	
Cao[51]	60	60	China	2	8.7	Optovue	O 4.5	RPD
Conti[20]	31	37	USA	Unclear	Unclear	Optovue	M 3	FAZ/MPD
Czako[21]	31	92	Hungary	Mixed	17.72	Optovue	M 3	FAZ/MPD
Hsiao[22]	19	10	Taiwan	Unclear	8.7	Optovue	M 3	MPD
Inanc[11]	60	57	Turkey	1	6.54	Optovue	M 6	FAZ/MPD
Li Z[52]	54	52	China	2	6.17	Optovue	O 4.5	RPD
Liu[53]	23	26	China	Unclear	3	Optovue	O 4.5	RPD
Mastropasqua[23]	25	25	Italy	Unclear	5.4	Zeiss	M 5.5	MPD/VLD
Meshi[24]	60	45	USA	Mixed	9.23	Optovue	M 3	FAZ/PD
Palochak[25]	26	21	USA	Mixed	9.3	Optovue	M 3	MPD
Rosen	36	40	USA	Mixed	Unclear	Optovue	M 3	FAZ
Sacconi[27]	34	27	Italy	1	12	Zeiss	M 3	FAZ/MPD
Shin[54]	40	50	South Korea	2	6.2	Zeiss	O 6	RPD
Sousa[28]	24	24	Portugal	1	13.6	Optovue	M 6	FAZ/MPD
Tan F[29]	90	86	China	2	5.47	Optovue	M 3	MPD
Yang[30]	56	43	China	Unclear	Unclear	Optovue	M 3	MPD
Zeng[31]	66	62	China	2	8.65	Optovue	M 6	MPD/RPD
							O 4.5	
Zhu[32]	34	35	China	2	7.74	Optovue	M 3	FAZ/MPD/VLD/VT
Cao[8]	71	67	China	2	6.6	Optovue	M 6	FAZ/MPD
Hwang[33]	16	39	USA	Mixed	15.7	Optovue	M 3	FAZ/MPD
Kim[48]	80	75	South Korea	2	8.3	Zeiss	M 3/6	FAZ/MPD
Lee DH[10]	74	34	South Korea	2	3.1	Topcon	M 3	FAZ/MPD
Lee H[14]	31	30	South Korea	2	9.6	Zeiss	M 3	FAZ/MPD/VT
Lei[34]	35	59	China	Unclear	Unclear	Zeiss	M 3	MPD/VLD
Li Z[49]	44	40	China	2	6.64	Optovue	M 3/6	FAZ/MPD
Liu[35]	31	31	China	Unclear	Unclear	Optovue	M 3	FAZ/MPD
Scarinci[55]	20	23	Italy	1	16.6	Optovue	M 3	FAZ/MPD
Vujosevic[50]	59	34	Italy	Mixed	10.5	Topcon	M 3	MPD/VLD/RPD
							O 4.5	
Yasin[36]	39	40	USA	Unclear	Unclear	Prototype	M 3	FAZ
Carnevali[37]	25	25	Italy	1	11	Zeiss	M 3	FAZ/MPD
Dimitrova[38]	29	33	Japan	2	7.37	Optovue	M 3	FAZ/MPD
Golebiewska[39]	188	60	Poland	1	6.4	Optovue	M 3	FAZ/MPD
Goudot[40]	34	40	France	Mixed	4.8	Optovue	M 3	FAZ/MPD
Mastropasqua[41]	15	20	Italy	2	Unclear	Optovue	M 3	FAZ/MPD
Nesper[42]	45	44	USA	Mixed	11	Optovue	M 3	FAZ/MPD
Di[43]	53	85	China	Unclear	Unclear	Optovue	M 3	FAZ
Salz[44]	13	11	USA	Mixed	Unclear	Prototype	M 3/6	FAZ
De Carlo[45]	61	28	USA	Mixed	Unclear	Optovue	M 3	FAZ
Takase[46]	24	19	Japan	Unclear	6.1	Optovue	M 3	FAZ

DM = diabetes mellitus; FAZ = foveal avascular zone, relevant outcome variables including area, perimeter, acircularity index; HC = healthy control; MPD = macular perfusion density, relevant outcome variables including capillary perfusion density, foveal density-300, and foveal/parafoveal/perifoveal/whole image perfusion density; OCTA = optical coherence tomography angiography; RPD = radial peripapillary capillary perfusion density; VLD = vessel length density; VT = vessel tortuosity.

[a]M indicates macular scan; O indicates optic nerve head scan; the number represents the side length of the scan.

TABLE 2. Differences in Optical Coherence Tomography Angiography Measurements Between Diabetic Patients Without Clinically Visible Retinopathy and Healthy Controls

Outcome Variables	No. of Studies	No. of Eyes		Weighted Mean Difference (95% Confidence Interval)	*P* Value	I^2 Test (%)	Egger's Test
		DM	HC				
FAZ area							
Mixed	34	1688	1361	0.03 [0.02, 0.05] mm^2	<.0001	66	0.292
Inner retina	15	781	583	0.03 [0.01, 0.05] mm^2	.0007	45	0.856
SCP	19	907	778	0.03 [0.01, 0.05] mm^2	.003	75	0.21
DCP	13	528	462	0.07 [0.03, 0.12] mm^2	.0004	79	0.881
FAZ perimeter	8	340	339	0.19 [0.12, 0.27] mm	<.0001	38	0.442
FAZ AI	7	275	273	0.02 [0.00, 0.04]	.05	62	0.78
Macular perfusion density							
Whole-image							
SCP	14	979	662	−1.99 [−2.76, −1.22] %	<.00001	88	0.266
DCP	10	562	397	−1.70 [−2.67, −0.74] %	.0005	86	0.066
CC	4	183	172	−1.01 [−2.21, 0.20] %	.1	95	0.408
Foveal							
SCP	5	596	249	−0.77 [−1.69, 0.14] %	.1	13	0.729
DCP	4	304	169	−1.02 [−3.57, 1.52] %	.43	82	0.869
Parafoveal							
Inner retina	4	127	127	−0.47 [−1.73, 0.79] %	.47	57	0.974
SCP	21	1162	882	−2.27 [−3.22, −1.32] %	<.00001	90	0.988
DCP	18	863	655	−2.19 [−2.97, −1.41] %	<.00001	79	0.004
CC	4	102	101	0.23 [−0.23, 0.70] %	.33	0	0.581
Perifoveal							
SCP	5	274	258	−2.56 [−4.65, −0.46] %	.02	91	0.839
DCP	4	194	183	−3.57 [−5.89, −1.26] %	.002	77	0.153
FD-300	6	551	318	−1.60 [−2.90, −0.29] %	.02	78	0.762
Capillary perfusion density							
SCP	4	202	187	−2.59 [−4.62, −0.55] %	.01	77	0.585
DCP	4	202	187	−2.90 [−3.96, −1.83] %	<.00001	0	0.619
VLD SCP	4	153	153	−0.75 [−1.88, 0.38] mm^{-1}	.19	90	0.429
Vessel tortuosity							
SCP	3	77	77	0.00 [−0.00, 0.00]	.67	0	0.968
DCP	3	77	77	−0.00 [−0.00, 0.00]	.99	0	0.699
Radial peripapillary capillary perfusion density							
Whole-image	3	406	192	−2.56 [−4.65, −0.47] %	.02	95	0.371
Peripapillary	5	248	232	−2.27 [−3.56, −0.97] %	.0006	84	0.89

AI = acircularity index; CC = choriocapillary; DCP = deep capillary plexus; DM = diabetes mellitus; FAZ = foveal avascular zone; FD-300 = foveal density-300; HC = healthy control; OCTA = optical coherence tomography angiography; SCP = superficial capillary plexus; VLD = vessel length density.

For macular PD, compared with that in the control eyes, PD of the whole-image, parafoveal, perifoveal region and capillary perfusion density (CPD) in both SCP and DCP all decreased in NDR ($P < .05$ for all, Supplemental Figures S5-S8; Supplemental Material available at AJO.com). FD-300 also declined ($P < .05$, Supplemental Figure S9; Supplemental Material available at AJO.com), while foveal PD (SCP and DCP, both $P > .05$, Supplemental Figures S10 and S11; Supplemental Material available at AJO.com) and parafoveal PD of the inner retina ($P = .47$, Supplemental Figure S12; Supplemental Material available at AJO.com) did not change significantly. Unlike the retina, the choroid seemed to be more stable as there was no significant difference in choriocapillary PD between the 2 groups (parafoveal and whole-image, both $P > .05$, Supplemental Figures S6, C, and S13; Supplemental Material available at AJO.com).

For other OCTA metrics, no significant difference was found in vessel length density of SCP or vessel tortuosity ($P > .05$ for all, Supplemental Figures S14 and S15; Supplemental Material available at AJO.com). However, regardless of the whole-image or peripapillary scans, the radial peripapillary CPD dropped significantly in the NDR group compared with the control group (both $P > .05$, Supplemental Figure S16; Supplemental Material available at AJO.com).

TABLE 3. Sensitivity Analysis Results of the Meta-analysis

Author, Year	Outcome Variables	Exclusion	Weighted Mean Difference (95% Confidence Interval)	*P* Value	I^2 Test (%)
Yang[30]	Whole-image PD in CC	Before	−1.01 [−2.21, 0.20] %	.1	95
		After	−0.49 [−0.85, −0.14] %	.007	0
Li Z[49]	Foveal PD in DCP	Before	−1.02 [−3.57, 1.52] %	.43	82
		After	0.42 [−0.63, 1.46] %	.44	0
Carnevali[37]	Parafoveal PD in inner retina	Before	−0.47 [−1.73, 0.79] %	.47	57
		After	−0.98 [−2.04, 0.08] %	.07	0
Kim[48]	Perifoveal PD in SCP	Before	−2.56 [−4.65, −0.46] %	.02	91
		After	−1.42 [−2.26, −0.57] %	.001	37
Inanc[11]	Perifoveal PD in DCP	Before	−3.57 [−5.89, −1.26] %	.002	77
		After	−4.62 [−6.32, −2.91] %	<.00001	38
Lei[34]	Vessel length density in SCP	Before	−0.75 [−1.88, 0.38] mm^{-1}	.19	90
		After	−0.26 [−0.89, 0.38] mm^{-1}	.43	49
Cao[51]	Whole-image RPD	Before	−2.56 [−4.65, −0.47] %	.02	95
		After	−1.56 [−2.22, −0.90] %	<.00001	0
Cao[51]	Peripapillary RPD	Before	−2.27 [−3.56, −0.97] %	.0006	84
		After	−1.70 [−2.32, −1.08] %	<.00001	0

CC = choriocapillary; DCP = deep capillary plexus; PD = perfusion density; RPD: radial peripapillary capillary perfusion density; SCP: superficial capillary plexus.

• **ADDITIONAL ANALYSES:** Owing to the high heterogeneity, sensitivity analyses were undertaken by removing 1 study that caused high heterogeneity in each of the direct comparisons (Table 3). For whole-image PD in the choriocapillary, Yang and associates[30] contributed the most to the heterogeneity, and its removal made the difference significant (from WMD: -1.01%, 95% CI: -2.21% to 0.20%, $P = .1$, $I^2 = 95\%$ to WMD: -0.49%, 95% CI: -0.85% to -0.14%, $P = .007$, $I^2 = 0\%$; Supplemental Figure S13). Li and associates[49] was the source of heterogeneity for foveal PD in DCP. Excluding this study eliminated the heterogeneity and changed the result direction, but the difference was still nonsignificant (from WMD: -1.02%, 95% CI: -3.57% to 1.52%, $P = .43$, $I^2 = 82\%$ to WMD: 0.42%, 95% CI: -0.63% to 1.46%, $P = .44$, $I^2 = 0\%$; Supplemental Figure S11). The other 5 studies induced heterogeneity in 6 comparisons, but their omission did not change the results (Supplemental Figures S7, S12, and S16).

Since the sources of the heterogeneity in many comparisons were not found with sensitivity analyses, we planned subgroup analyses. After thorough review of the characteristics of the included studies, 2 subgroup analyses were performed: the type of DM and OCTA devices (Table 4). The results revealed that after subgroup analyses, in most type 1 diabetes mellitus (T1DM) groups the differences between diabetic eyes and healthy eyes became nonsignificant, and the heterogeneity diminished. In contrast, except for FD-300, type 2 diabetes mellitus (T2DM) groups maintained significant differences in FAZ and PD parameters compared to the controls (Supplemental Figures S17-S24; Supplemental Material available at AJO.com). The tests for subgroup differences revealed substantial heterogeneities between T1DM and T2DM in FAZ area of the mixed layer and in DCP ($I^2 = 80.1\%$ and 72.2%, respectively), whole-image MPD, and foveal and parafoveal PD in SCP ($I^2 = 77.8\%$, 63.1%, and 90.5%, respectively). For OCTA devices, the Optovue seemed to be the source of heterogeneity in more comparisons, whereas no consensus trend was detected among different devices (Supplemental Figures S25-S28; Supplemental Material available at AJO.com). To further explore whether those differences between the types of DM were influenced by the variation of duration, we conducted another subgroup analysis of DM type after grouping the included studies by mean duration of diabetes. Four out of 5 subgroup analyses showed that the differences were nonsignificant between T1DM groups and controls while they became significant for T2DM (Table 5, Supplemental Figures S29-S31; Supplemental Material available at AJO.com). Substantial heterogeneities between subgroups were detected in FAZ area of the mixed layer over 10 years ($I^2 = 91.8\%$) and whole-image MPD in SCP and DCP for mean duration no more than 10 years ($I^2 = 69.9\%$ and 62.6%, respectively).

• **PUBLICATION BIAS AND RISK OF BIAS:** Egger's tests showed that there was no publication bias in most of the comparisons ($P \geq .05$), except the analysis of the parafoveal PD in DCP ($P = .004$, Table 2). In addition, we evaluated the risk of bias by using the quality assessments recommended by AHRQ. Most of the eligible studies were of low risk of bias (Supplemental Table; Supplemental Material available at AJO.com).

TABLE 4. Main Outcomes of Subgroup Analysis According to the Type of Diabetes Mellitus and Optical Coherence Tomography Angiography Device

Outcome Variables	Parameters	Total	Type of DM			OCTA Device		
			Type 1	Type 2	Mixed or Unclear	Optovue	Zeiss	Topcon
FAZ area mixed	No. of studies	34	9	11	14	22	9	1
	WMD (mm^2)	0.03	0.00	0.04	0.05	0.03	0.03	0.06
	95% CI (mm^2)	[0.02, 0.05]	[−0.02, 0.02]	[0.01, 0.06]	[0.02, 0.07]	[0.01, 0.04]	[0.00, 0.06]	[0.02, 0.10]
	P value	<.0001	.79	.002	<.0001	.002	.05	.005
	I^2 test (%)	66	41	62	65	67	64	–
FAZ area in DCP	No. of studies	13	4	5	4	4	7	1
	WMD (mm^2)	0.07	0.03	0.11	0.07	0.05	0.08	0.21
	95% CI (mm^2)	[0.03, 0.12]	[−0.02, 0.08]	[0.05, 0.18]	[−0.01, 0.14]	[−0.03, 0.13]	[0.04, 0.11]	[0.15, 0.27]
	P value	.0004	.22	.0007	.07	.21	<.0001	<.00001
	I^2 test (%)	79	0	77	84	82	23	–
FAZ perimeter	No. of studies	8	2	3	3	–	–	–
	WMD (mm)	0.19	0.11	0.17	0.28	–	–	–
	P value	<.00001	.34	.006	<.00001	–	–	–
	I^2 test (%)	38	67	43	0	–	–	–
Whole-image MPD in SCP	No. of studies	14	2	6	6	9	3	2
	WMD (%)	−1.99	−0.56	−2.04	−2.55	−2.45	−1.63	−1.03
	95% CI (%)	[−2.76, −1.22]	[−1.19, 0.07]	[−3.25, −0.83]	[−3.80, −1.30]	[−3.66, −1.24]	[−2.67, −0.58]	[−2.52, 0.45]
	P value	<.00001	.08	.001	<.0001	<.0001	.002	.17
	I^2 test (%)	88	0	93	73	91	34	73
Whole-image MPD DCP	No. of studies	11	2	6	3	8	2	1
	WMD (%)	−1.42	−0.36	−1.18	−2.62	−1.9	0.02	−0.53
	95% CI (%)	[−2.32, −0.52]	[−1.41, 0.70]	[−2.22, −0.15]	[−6.36, 1.13]	[−3.32, −0.49]	[−1.89, 1.92]	[−0.87, −0.19]
	P value	.002	.5	.03	.17	.009	.99	.002
	I^2 test (%)	87	0	88	88	90	0	–
Foveal PD in SCP	No. of studies	5	3	2	–	–	–	–
	WMD (%)	−0.77	−0.1	−1.73	–	–	–	–
	P value	.1	.85	.03	–	–	–	–
	I^2 test (%)	13	0	28	–	–	–	–

Continued on next page

TABLE 4. Main Outcomes of Subgroup Analysis According to the Type of Diabetes Mellitus and Optical Coherence Tomography Angiography Device (*Continued*)

			Type of DM			OCTA Device		
Outcome Variables	Parameters	Total	Type 1	Type 2	Mixed or Unclear	Optovue	Zeiss	Topcon
Parafoveal PD in SCP	No. of studies	21	7	7	7	17	4	–
	WMD (%)	−2.27	−0.72	−3.8	−2.35	−2.33	−1.93	–
	95% CI (%)	[−3.22, −1.32]	[−1.58, 0.13]	[−5.45, −2.15]	[−3.66, −1.04]	[−3.14, −1.51]	[−5.15, 1.30]	–
	P value	<.00001	.1	<.00001	.0004	<.00001	.24	–
	I^2 test (%)	90	75	84	77	78	97	–
Parafoveal PD in DCP	No. of studies	18	6	6	6	15	3	–
	WMD (%)	−2.19	−1.52	−2.78	−2.54	−2.46	−1.07	–
	95% CI (%)	[−2.97, −1.41]	[−2.28, −0.76]	[−5.07, −0.49]	[−4.04, −1.05]	[−3.47, −1.45]	[−1.56, −0.57]	
	P value	<.00001	<.0001	.02	.0009	<.00001	<.0001	–
	I^2 test (%)	79	51	87	82	81	0	
Perifoveal PD in SCP	No. of studies	5	2	3	–	–	–	–
	WMD (%)	−2.56	−1.17	−3.45	–	–	–	–
	P value	.02	.11	.04	–	–	–	–
	I^2 test (%)	91	57	94	–	–	–	–
Perifoveal PD in DCP	No. of studies	4	2	2	–	–	–	–
	WMD (%)	−3.57	−3.51	−3.73	–	–	–	–
	P value	.002	.17	<.0001	–	–	–	–
	I^2 test (%)	77	92	0	–	–	–	–
Foveal density-300	No. of studies	6	2	3	1	–	–	–
	WMD (%)	−1.60	−0.94	−2.04	−1.61	–	–	–
	P value	.02	.45	.08	.09	–	–	–
	I^2 test (%)	78	79	88	–	–	–	–

CI = confidence interval; DCP = deep capillary plexus; DM = diabetes mellitus; FAZ = foveal avascular zone; MPD = macular perfusion density; OCTA = optical coherence tomography angiography; PD = perfusion density; SCP = superficial capillary plexus; WMD = weighted mean difference.

TABLE 5. Outcomes of Subgroup Analysis According to the Type of Diabetes Mellitus Based on the Mean Duration

Outcome Variables	Parameters	Mean Duration ≤10 Years			Mean Duration >10 Years		
		T1DM	T2DM	Total	T1DM	T2DM	Total
FAZ area mixed	No. of studies	3	7	10	6	3	9
	WMD (mm^2)	0.01	0.03	0.03	0.00	0.08	0.03
	95% CI (mm^2)	[−0.02, 0.04]	[0.01, 0.06]	[0.01, 0.05]	[−0.03, 0.03]	[0.05, 0.12]	[−0.01, 0.06]
	P value	.44	.006	.01	.95	<.00001	.13
FAZ area in DCP	No. of studies	–	–	–	4	2	6
	WMD (mm^2)	–	–	–	0.03	0.09	0.06
	95% CI (mm^2)	–	–	–	[−0.02, 0.08]	[−0.01, 0.20]	[0.01, 0.10]
	P value	–	–	–	.22	.09	.02
Whole–image MPD in SCP	No. of studies	2	5	7	–	–	–
	WMD (%)	−0.56	−1.92	−1.49	–	–	–
	95% CI (%)	[−1.19, 0.07]	[−3.23, −0.60]	[−2.43, −0.55]	–	–	–
	P value	.08	.004	.002	–	–	–
Whole-image MPD DCP	No. of studies	2	5	7	–	–	–
	WMD (%)	−0.36	−1.66	−1.31	–	–	–
	95% CI (%)	[−1.41, 0.70]	[−2.81, −0.51]	[−2.21, −0.40]	–	–	–
	P value	.5	.005	.005	–	–	–

CI = confidence interval; DCP = deep capillary plexus; FAZ = foveal avascular zone; MPD = macular perfusion density; SCP = superficial capillary plexus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; WMD = weighted mean difference.

DISCUSSION

TO OUR KNOWLEDGE, THIS IS THE FIRST META-ANALYSIS that includes all the available data of high quality and considers all the pivotal indices of OCTA to evaluate microvascular impairment in the eyes of diabetic patients without clinically visible retinopathy. Our study found that OCTA unambiguously revealed that compared with the healthy control group, the NDR group exhibited enlarged areas and increased perimeters of FAZ, with decreased PD of the macula except the fovea and reduced radial peripapillary CPD. This suggested that retinal microvascular impairments might have occurred antecedent to clinically visible DR and could be detected early by OCTA. In addition, subgroup analyses indicated that those differences became nonsignificant and were accompanied by decreases in heterogeneities in T1DM, while T2DM remained statistically significant. This finding hinted that ophthalmologists should take different types of DM into discriminatory consideration with caution.

The FAZ is typically circular or elliptical in healthy individuals, and the area measured by FA is approximately 0.231~0.280 mm^2.[63–65] It is well known that the size of the FAZ tends to increase with the aggravation of diabetic retinopathy.[43,46] However, there is controversy over changes in FAZ in the NDR. This meta-analysis showed that FAZ expanded in all layers of OCTA scans, and the perimeter also elongated. Progressive capillary dropout is thought to be responsible for the enlargement of the FAZ area, and capillary closure can be another mechanism.[63,66] These histopathologic changes could further lead to FAZ margin deformation. Although some physicians believe that the distortion of the FAZ margin precedes enlargement,[11] the AI representing the degree of FAZ boundary deformation showed only a marginal statistical significance in our meta-analysis ($P = .05$), indicating that AI may not be a sensitive indicator for the detection of microvascular alterations in NDR.

As mentioned above, we uniformly adopted the term perfusion density rather than vessel density to express the ratio of blood flow area to the total area of the scan to avoid confusion. Accurately quantifying PD is a tremendous advantage of OCTA over FA, because the measurement can be significantly disturbed by fluorescein leakage and window defects. It is acknowledged that lesions in DR, such as the nonperfusion area, usually start from the peripheral retina,[67] and subject to the relative immaturity of ultrawide imaging technology of OCTA, previous studies have mainly focused on the macula as well as the optic nerve head (ONH). Our meta-analysis found that the PD of the NDR group was significantly lower than that of the healthy control group both in the macula and in the ONH. The presence of FAZ narrowed the vascular zone within the 1-mm-diameter circle and possibly affected the measurement of foveal perfusion density, thus resulting in a nonsignificant difference. The FD-300 eliminated this disturbance and could consequently be a better indicator for the fovea.[11] Some ophthalmologists believed that the presence of large blood vessels interfered with the detection of microvascular changes, so they measured capillary PD elaborately after excluding large vessels.[19,24,26,29,34] Further studies are needed to assess the effectiveness of this

approach. In addition, there was a view that thickening of blood vessel diameter would cloak the capillary dropout and closure in PD measurement, so the use of skeletonized images was proposed to exclude diameter interference, namely, measuring VLD.[23,32,34,50] However, our results did not support this indicator.

T1DM is commonly considered to be more aggressive than T2DM, with a higher prevalence of vision-threatening retinopathy. We obtained different results after the subgroup analysis for DM types, even though this grouping did not eliminate substantial heterogeneities completely. T1DM showed inconsistency with T2DM as well as the overall result. Those patients manifested results even more similar to those of the control group; that is, the microvascular changes were negligible. This finding was similar to Fleissig and associates' study.[19] The study simultaneously included T1DM, T2DM, and a control group in comparison and found that type 1 patients showed fewer changes in the FAZ than the type 2 group, although their duration of diabetes was longer. Of note, the duration of the selected type 1 patients reached an average of 30.3 years, which means they might belong to the "Happy Few" (as described by Sacconi and associates[13]) and therefore be of a special type in T1DM. We attempted to explore the influence of the disease duration on the diverse manifestations of T1DM and T2DM. Owing to the quantitative restriction of included studies, the further subgroup analyses could be conducted on only 5 parameters after the rough grouping of mean duration, and the inconsistence remained. Another study comparing T1DM and T2DM without a healthy control group did not find any difference in NDR stage between those 2 types of DM.[68] We hypothesize that type 1 patients tend to experience a peaceful period after prompt diagnosis and then deteriorate so rapidly to the nonproliferative stage that preclinical microvascular impairments are difficult to capture by OCTA in a timely manner. All of these require more longitudinal comparative studies of types of DM in NDR to verify whether T1DM is truly "healthier" and to explore the underlying mechanism.

Admittedly, this meta-analysis has some limitations: (1) Sensitivity analyses showed that the exclusion of studies by Yang and associates[30] and Li and associates[49] could change the results of whole-image PD in choriocapillary and foveal PD in DCP, so those 2 analyses might need to be treated with caution. (2) Even if the sensitivity analyses and subgroup analyses were performed carefully, the heterogeneities of some comparisons remained substantial, which might be related to factors such as manual measurement methods and races. (3) Owing to the lack of published data, some factors that might affect the OCTA measurements, such as axial length, signal strength index, and projection artifact removal techniques, were not analyzed. (4) NDR possibly represents a long process in which the eyes of diabetic patients develop from a relatively healthy state to the mild nonproliferative stage.[12,26,42] Thus, this meta-analysis was insufficient to explore the specific timing and process of microvascular impairments based on the cross-sectional studies included, which means that better-designed longitudinal studies are required in the future.

To conclude, this meta-analysis indicated that retinal microvascular impairments, including FAZ enlargement and decrease of perfusion density of the macula and ONH in OCTA, could have occurred before clinically visible DR. Ophthalmologists should further discriminate the possibly diverse manifestations according to the types of DM.

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