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Role of optical coherence tomography angiography in early detection of retinal microvascular changes in adolescents with type 1 diabetes

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***Abstract*---**Purpose: Early detection of diabetic retinopathy can prevent progressive visual loss. Evaluate the role of Optical Coherence Tomography Angiography (OCTA) in early detection of diabetic retinopathy (DR) in type 1 diabetes (T1D) adolescents with normal

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fundus photography. Methods: Cross-sectional study included 150 eyes of 75 T1D adolescents from the Diabetes Endocrine and Metabolism Pediatric Unit, Children hospital, Cairo University. Their ages ranged from 10-18 years and diabetes duration 2 years or more. Fundus photography, OCT and OCTA were done in the diagnostic and laser unit, Ophthalmology department. Results: Twenty-eight patients (37.3%) had abnormalities in the OCTA despite normal fundus examination, photography and OCT. Diabetes duration, DKA at presentation and frequency, elevated blood pressure, limited joint mobility, elevated HbA1c and dyslipidemia had a negative correlation with OCTA measurements (foveal, parafoveal and perifoveal densities). Patients with abnormal OCTA had significantly higher mean age, higher DKA frequency, and lower height SDS (p=0.034, 0.011 and 0.001 respectively). Univariate and multivariate analysis revealed age and DKA at diabetes presentation are significant predictors for abnormal OCTA. Conclusion: OCTA can be used in early detection of diabetic retinopathy in T1D adolescents especially with risk factors (Elevated HbA1c, frequent DKA, decreased height SDS and limited joint mobility).

***Keywords*---**diabetic retinopathy, type 1 diabetes, OCT, OCTA.

Introduction

Diabetes mellitus is a chronic complex metabolic disease that necessitates ongoing medical care to reduce long-term complications, and diabetic retinopathy (DR) is one of the long-term complications that can occur as a consequence. [1] Diabetic retinopathy (DR) is a retinal microvascular complication of diabetes that can lead to progressive visual loss. DR is characterized by occlusion of the capillaries, hyperpermeability, neovascularization of the retina. [2] According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) consensus practice guidelines, it is recommended to start retinal examination either by 11 years of age or after diabetes duration of 2-5 years. [3]

According to the American Diabetes Association (2021) it is recommended for patients with T1D to have a detailed and comprehensive ophthalmological examination after 5 years of diagnosis. Initially annual examinations are done and if there is no evidence of retinopathy with proper glycemic control, subsequent screening can be done every 1-2 years. Ophthalmological examination included fundus photography, OCT and OCTA. Fluorescein angiography is the gold standard for the diagnosis of diabetic retinopathy. [4]

However, there are several limitations of the use of fluorescein angiography such as the invasive nature of the procedure, the fact it is time consuming and the occasional occurrence of side effects of fluorescein dye parenteral injection. These side effects include: nausea, pruritus, and even anaphylaxis in rare circumstances. [5]

Since the early 1990s with the invention of OCT, it has become one of the most significant ophthalmological imaging modalities. It is non-invasive and based on low-coherence interferometry. It aids clinicians in the assessment of structural change in different retinal diseases as it produces high-resolution, cross-sectional images from backscattered light. [2] OCTA can generate a 3D image of the specific capillary plexus by analyzing the decorrelation signals of erythrocyte movement inside the retinal vessels. [6] Thus, it can segment retinal vasculature into superficial and deep layers also choroidal perfusion without the use of dye injection. [7] In the present study we aim to identify clinical indicators for risk of retinopathy in adolescents with type 1 diabetes that might benefit from OCTA in those with normal fundus photography. This is especially important in limited resource settings.

Material and Methods

This is a cross sectional analytical study that included 75 patients of adolescents with type 1diabetes (T1D) who follow up at the Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU) of Children hospital at Cairo University. Duration of the study was 2 years and recruitment and assessment of patients was done over a period of 18 months. Fundus examination, photography, optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) were done for all patients in the diagnostic and laser unit, Ophthalmology department in El Kasr Al Ainy hospitals.

The study was approved by the ethical committee in the corresponding institutions and followed the Declarations of Helsinki of 1975 as revised in 2000. Informed consent was obtained from all patients. Both males and females clinically diagnosed with T1D were included in the study with age ranged from 10 to 18 years, and with diabetes duration 2 years or more. Patients with clinically detectable DR and other eye diseases as: eyelid diseases, strabismus, corneal and lens diseases that may affect OCTA results, as well as glaucoma, maculopathy, and other eye diseases that may cause fundal retinal vasculopathy were excluded. Also, patients with history of eye surgery were excluded.

Patients' Evaluation

1) Full history including demographic data, diabetes onset, presentation, duration, daily insulin requirements, type and regimen, blood glucose readings, number of attacks of hypoglycemia per month, any ophthalmological symptoms as blurred vision or floaters, family history of diabetes, hypertension, cardiac or ophthalmological diseases.
2) Thorough physical examination including: anthropometric data (height, weight, BMI with SDS, pubertal assessment using Tanner staging, detection of lipodystrophy at injection sites, limited joint mobility, blood pressure measurement (using mercury sphygmomanometer in 3 different occasions within 2 weeks) and the measurements were classified according to percentiles into normal, prehypertension and hypertension [8] and neurological examination including motor and sensory examination.
3) Laboratory tests:

- Glycosylated hemoglobin (HbA1c) the most recently done within the past 6 months, with < 7% considered as the target for optimum glycemic control. [9]
- Serum total cholesterol (TC) (the target is <200 mg/dL), triglycerides (TG) (the target is <150 mg/dL), low density lipoproteins (LDL) (the target is <100 mg/dL), high density lipoproteins (HDL) (the target is >35 mg/dL), and renal functions, thyroid profile were obtained from patients' files**.** [10]

4) Ophthalmological evaluation:

- Fundus examination & colored fundus photography using Fundus camera.
- OCT and OCTA using the following (Optovue: Model RTVue XRAvanti)
  a) OCT 3 D scan to assess macular area for macular thickness
  b) OCTA using 6x6 scan. Evaluating**:**
     - Morphology of superficial, deep retinal capillary plexuses and choriocapillaris vascular layer
     - Size & configuration of Foveal avascular zone (FAZ) in superficial & deep retinal layers

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing normally distributed data and Mann Whitney U test for independent samples for comparing not-normal data. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Univariate and multivariate logistic regression analysis models were used to test for the independent predictors of OCT abnormality. Two-sided p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

The age of the studied patients ranged from 10 to 18 (mean ± SD of 14.02 ± 2.26) years, their diabetes duration ranged from 2 to 16 (median 7 and IQR [4-9]) years. Thirty-eight (50.7%) were males, and all patients were pubertal. The majority of patients (66.7%) gave history of ketoacidosis at first presentation of diabetes. They had a mean HbA1c 9.9 ± 1.98 % and 96% had HbA1c above the target for optimum glycemic control (≥ 7 %), Total insulin dose ranged from 0.3 to 2.8 IU/kg/day. Regarding the signs of retinopathy as one of the most important complications of diabetes, none of the patients complained of blurring of vision or floaters.

Fundus examination, photography and OCT were normal in all patients. OCTA was done in the presence of an experienced ophthalmologist, who provided an initial interpretation of the OCTA results and reported abnormalities which

included: early and considerable notching of the retina, parafoveal, capillary dropouts, ischemic changes, epiretinal membrane, new vessels, exaggeration of the fovea, decreased vasculature and high reflective deposits of hard exudates in the superficial retinal layer. Twenty-Eight (37.3%) showed abnormalities in OCTA in spite of having normal fundus examination and fundus photography as shown in Table (1) and Fig (1). The mean age of patients with diabetes with abnormal OCTA was significantly higher (14.5 ± 1.96 years) than those with normal OCTA (13.74 ± 2.40 years), p=0.034. The median of height SDS -1.5(-2.2-[-1.05]) were significantly lower in patients with diabetes with abnormal OCTA compared to those with normal OCTA -0.5(-1.2-0.7) with p= 0.001. Frequency of diabetic ketoacidosis since diabetes diagnosis, and the mean ± SD basal insulin dose were significantly higher in the group with abnormal OCTA compared to the group with normal OCTA, with p-value 0.011 and 0.006 respectively as shown in Table (2).

Nineteen out of 28 patients with abnormal OCTA (67.9%) had limited joint mobility compared to 19 out of 47 (40.4%) of patients with normal OCTA, with p-value 0.022 as shown in Table (2). No statistically significant difference was found between the two groups regarding development of other complications of diabetes as peripheral neuropathy, dyslipidemia, or complications of insulin injection as lipohypertropthy. Also, no statistically significant difference regarding the development of other autoimmune diseases that are commonly associated with diabetes as celiac disease and autoimmune thyroid disorders.

On using univariate analysis to study the associations between the studied variables and the results of OCTA, the following variables achieve statistical significance (age, diabetes presentation, SBP and DBP percentiles) with p-value (0.021, 0.032, 0.008 and 0.010) respectively. This denotes that with increasing age, DKA as initial presentation and increasing SBP and DBP percentiles, there is increased risk of development of diabetic retinopathy.

On using multivariate analysis, it is shown that with every year the child ages, the risk of development of DR increases by 1.5 times. The measurements of the OCTA for both eyes were shown in tables (3,4). It shows that diabetes duration, DKA at presentation, as well as frequency, irregular dietary habits, elevated blood pressure, lipodystrophy, limited joint mobility, elevated HbA1c and impaired lipid profile (cholesterol, triglycerides, and LDL) had a negative correlation with image density, foveal, parafoveal and perifoveal densities in OCTA.

Discussion

Adolescence is a crucial time for reinforcing proper glycemic control and screening for early signs of diabetic retinopathy. Improved glycemic control will lead to regression of retinopathy. [11] Comparing patients showing abnormalities in OCTA with those without abnormalities, revealed significantly older age with stunted growth and significantly more frequent attacks of diabetic ketoacidosis (DKA) in patients with abnormal OCTA. This denotes that poor glycemic control that affects linear growth, also recurrent admission with frequent attacks of DKA is associated with increased risk of diabetic retinopathy.

The mean diabetes duration of patients with abnormal OCTA was 7.65 ± 3.59 (range 3-15), compared to 6.56 ± 3.61(range 2-16) in those with normal OCTA, but difference did not reach statistical significance. Patient's age and pubertal status appear to be strong risk factors for development of DR regardless of the diabetes duration. Minimum duration with abnormal findings in the present study was 2 years, and no abnormalities were detectable in patients with long duration up to 16 years.

This finding was inconsistent with an earlier study that was conducted by Ng et al (2019) including children with T1D between 12 and 18 years of age, registered with the regional DR screening program and were evaluated from 2012 to 2013 in United Kingdom. It showed that age at diagnosis of diabetes and diabetes duration were both significant factors in relation to retinopathy. [12]

Table (1): Demographic Characteristics of diabetic patients with OCTA abnormalities

	Age in years	Sex	Diabetes duration in years	Diabetes presentation	DKA frequency	Total insulin dose (IU/Kg/day)	Basal insulin dose (IU/kg/day)	SMBG (times per day)	Wt (SDS)	Ht (SDS)	BMI (SDS)	Limited joint mobility	Frequency of hypoglycemia/month	HbA1c	Target (<7%)	TC	Target (<200 mg/dL)	TGs	Target (<150 mg/dL)	LDL	Target (<100 mg/dL)
1	14.19	M	11	DKA	12	1.4	0.4	0	-0.9	-1.4	-0.4	Yes	3	12	Outside	192	Within	113	Within	83	Within
2	13.7	F	4	DKA	16	1	0.36	0	0.1	-1.4	1.1	Yes	1	13.7	Outside	96	Within	94	Within	100	Outside
3	11.8	M	4	DKA	17	1.7	0.32	0	0.1	-1.5	1.2	No	4	8.4	Outside	145	Within	165	Outside	60	Within
4	17.82	M	10	DKA	1	0.9	0.3	1	1.1	-1.1	1.6	Yes	0	11.5	Outside	176	Within	68	Within	100	Outside
5	18	M	13	DKA	4	1.7	0.53	0	0.7	-1.4	1.4	Yes	0	11.5	Outside	199	Within	103	Within	57	Within
6	18	F	9	DKA	1	1.2	0.5	2	-0.7	-1.8	0.5	Yes	0	15.3	Outside	192	Within	93	Within	166	Outside
7	15.65	F	9	DKA	1	1.9	0.44	3	-2	-2.2	-0.4	Yes	8	12	Outside	155	Within	75	Within	95	Within
8	13	M	8	DKA	1	0.7	0.46	2	-0.9	-2.7	0.7	Yes	0.25	12	Outside	195	Within	135	Within	63	Within
9	13.3	F	9	DKA	10	1.67	0.6	2	0.1	-1.5	1.1	No	0	9.6	Outside	188	Within	157	Outside	113	Outside
10	12.4	M	7	Hyperglycemia	15	1.8	0.46	1	-1.9	-2.5	-1	Yes	0.25	8.4	Outside	162	Within	134	Within	95.2	Within
11	13.35	M	10.5	DKA	1	1	0.5	2	-0.7	-1.3	0	No	0	8.3	Outside	225	Outside	89	Within	161	Outside
12	18	M	15	DKA	13	0.3	0.28	2	0.9	-1.4	1.5	Yes	0	8	Outside	168	Within	105	Within	105	Outside
13	11.59	M	3	DKA	2	1	0.25	5	-1	-1.7	-0.2	No	0	8	Outside	151	Within	90	Within	88	Within
14	14.97	F	4	DKA	1	1.5	0.4	4	-0.5	0.7	-0.8	No	3	7.8	Outside	167	Within	68	Within	103	Outside
15	13.92	F	9	DKA	1	1.25	0.54	2	-0.8	-3.5	1.1	No	0	11	Outside	142	Within	89	Within	90	Within
16	15.85	F	12	Hyperglycemia	18	1.3	0.51	4	2	-0.4	2.3	No	4	10.6	Outside	270	Outside	240	Outside	149	Outside
17	13.4	F	5	DKA	10	0.9	0.4	3	0.3	-1.6	1.3	Yes	0	8.5	Outside	189	Within	69	Within	92	Within
18	13.46	M	13	DKA	12	1.25	0.42	0	-2.6	-4.3	0.8	Yes	0	12.4	Outside	199	Within	94	Within	137	Outside
19	13.74	M	5	DKA	6	1.22	0.52	2	-0.2	-1.5	0.8	Yes	0	11.3	Outside	176	Within	109	Within	142	Outside
20	15.57	M	3.8	Hyperglycemia	1	1.1	0.29	2	-0.3	-2.2	1	Yes	0	13.67	Outside	104	Within	65	Within	99	Within
21	14.42	M	4	DKA	0	1.17	0.3	2	-0.7	0.7	-1.8	Yes	0	9.6	Outside	124	Within	86	Within	61	Within
22	14.48	M	5	Hyperglycemia	0	0.55	0.43	0	-1.3	-2.3	-0.6	Yes	0	11.1	Outside	237	Outside	190	Outside	151	Outside
23	16.1	F	3	DKA	0	0.69	0.51	0	0	-1	0.9	Yes	0	10	Outside	134	Within	80	Within	92	Within
24	13.14	F	13	Hyperglycemia	3	0.7	0.17	3	1.6	0.8	1.8	No	0	8	Outside	134	Within	86	Within	81	Within
25	13.91	M	3	DKA	1	0.78	0.5	2	-1.2	-2.2	-0.2	Yes	0	9.6	Outside	173	Within	91	Within	92.8	Within
26	12.16	M	8	Hyperglycemia	0	0.9	0.24	2	1.5	1.7	1.3	No	0	10.1	Outside	133	Within	42	Within	48	Within
27	17.51	M	8	DKA	1	1.4	0.37	2	0.3	-0.2	0.4	Yes	0	11.1	Outside	138	Within	126	Within	115	Outside
28	12.64	F	6	DKA	18	0.9	0.44	6	-0.6	-2.1	0.3	Yes	2	9.6	Outside	266	Outside	111	Within	178	Outside

M: Male, **F:** Female; **DKA:** Diabetic ketoacidosis; **SMBG:** Self-Monitoring of blood glucose; **SMBG:** Self-Monitoring of blood glucose; **Wt:** Weight, **Ht:** Height, **BMI:** Body mass index; **TC:** Total cholesterol, **TGs:** Triglycerides, **LDL:** Low density lipoprotein

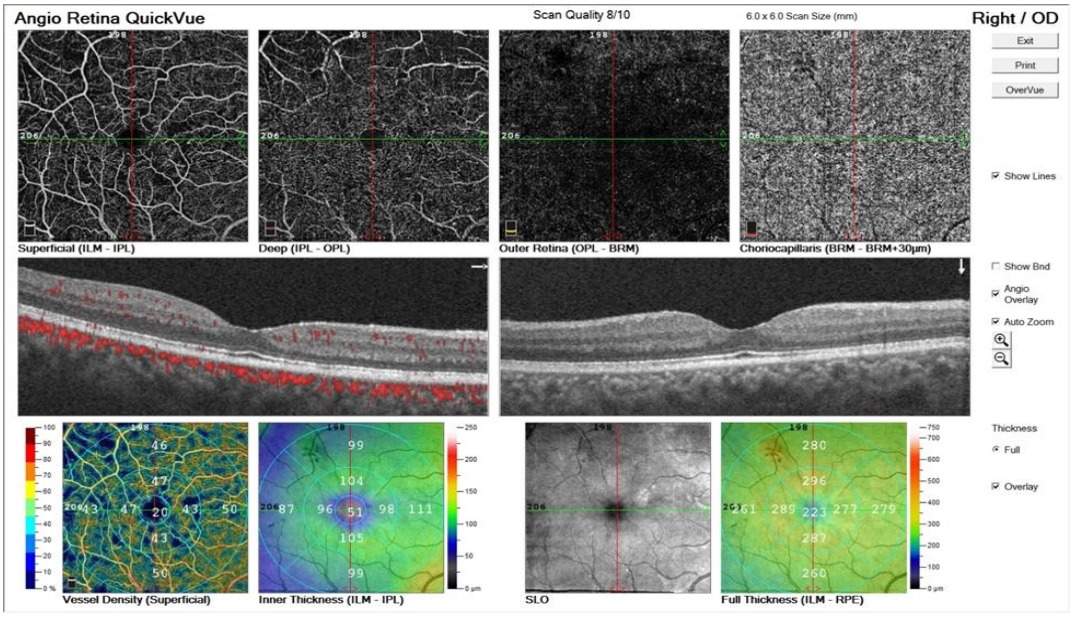

Figure 1: B scan OCT of the patient number 18 with no abnormality detected while OCTA showing capillary dropouts in the superficial and deep retinal layers with no abnormality detected in the perfusion of the choriocapillaris

Table (2): Comparison between patients with normal and abnormal OCTA regarding demographics and diabetes relevant variables

	Normal OCTA (n= 47)	Abnormal OCTA (n= 28)	
	Value	Value	p-value
Sex • Males • Females	 21(44.7%) *** 26(55.3%) ***	 17(60.7%)*** 11(39.3%)***	0.179
Age (years)	13.74 ± 2.4 (10-18)*	14.5 ± 1.96 (12-18)*	0.034
Weight SDS	0 (-0.7-0.8)**	-0.4 (-0.9-0.3)**	0.116
Height SDS	-0.5 (-1.2-0.7)**	-1.5 (-2.2-[-1.05])**	0.001
Body mass index SDS	0.45 (-0.2-0.9)**	0.8 (-0.2-1.25)**	0.417
Waist circumference (cm)	74.26 ± 9.36 (60-100)*	75.75 ± 7.56 (63-101)*	0.278
Diabetes duration(years)	6.56 ± 3.61 (2-16)*	7.65 ± 3.59 (3-15)*	0.135
DKA as initial presentation of diabetes	28(59.6%)***	22(78.6%)***	0.091
Diabetic ketoacidosis frequency since diagnosis	1 (0-2)**	1.5 (1-12)**	0.011

Total insulin dose (IU/Kg/day)	1.23 ± 0.45 (0.4-2.8)*	1.13 ± 0.39 (0.3-1.9)*	0.436
Basal insulin • Intermediate • Long acting	 16(34%)*** 31(66%)***	 15(53.6%)*** 13(46.4%)***	0.097
Basal IU dose (IU/kg/day)	0.4 ± 0.1 (0.2-0.6)*	0.41 ± 0.12 (0.2-0.7)*	0.006
Bolus insulin • Short acting • Rapid acting analogue	 31(66%)*** 16(34%)***	 20(71.4%)*** 8(28.6%)***	0.623
Frequency of self-monitoring of blood glucose	2 (1-3)**	2 (0.5-2.5)**	0.228
Frequency of hypoglycemia per month	0 (0-2)**	0 (0-0.63)**	0.989
Irregular dietary habits	18(38.3%)***	14(50%)***	0.322
Exercise habits • None • Aerobic • Anaerobic	 30(63.8%)*** 15(31.9%)*** 2(4.3%)***	 18(64.3%)*** 10(35.6%)*** 2(2.7%)***	0.530

*Data is represented by range, mean, and standard deviation.
** Data is represented by median and inter quartile range (IQR).
***Data is represented by number of cases and percent.

In the present study, diabetes duration showed negative correlation with only one of studied parameters, namely foveal density (Superficial layer); however, age showed no correlation with any of the studied parameters. Negative correlation indicates decreased density with increased risk of retinopathy. Similar results were found in studies conducted by Kara et al (2020) and Demir et al (2020) as they showed significant negative correlation of diabetes duration with foveal density deep layer and mean foveal density superficial layer and parafoveal density deep layer respectively. [13,14]

In our study, patients had diabetic ketoacidosis attacks since diagnosis of median 1(0.5-3). Comparing between both groups regarding DKA at first presentation and the results of OCTA, it was found that in the group of patients with abnormal OCTA who presented with diabetic ketoacidosis represent (78.6%) compared to (59.6%) in the group with normal OCTA, but difference did not reach statistical significance. Furthermore, DKA frequency since diagnosis showed a negative correlation with foveal density deep layer which indicates a risk of diabetic retinopathy.

Our results were similar to a cross-sectional hospital based descriptive study conducted by Shibeshi et al (2016), which included children aged between 9 and 17 years. The prevalence of DR was determined by fundus photography of each eye. It showed that all of the patients with retinopathy presented with DKA at initial diagnosis. [15]

Table 3: Correlation between the studied variables and the OCTA measurements in the right eye

		Image density		Foveal density		Parafoveal density		Parafoveal density	
		Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer
Age (years)	R	-0.170	0.175	-0.199	-0.027	-0.136	0.067	-0.152	0.127
	p	0.145	0.134	0.087	0.817	0.246	0.570	0.194	0.276
	N	75	75	75	75	75	75	75	75
Diabetes duration (years)	R	-0.215	0.095	-0.319	-0.164	-0.164	0.026	-0.168	0.045
	p	0.064	0.419	0.005	0.160	0.161	0.824	0.149	0.703
	N	75	75	75	75	75	75	75	75
Diabetes presentation (DKA)	R	0.129	0.097	0.031	-0.078	0.071	-0.030	0.146	0.041
	p	0.271	0.409	0.794	0.507	0.547	0.798	0.210	0.730
	N	75	75	75	75	75	75	75	75
Frequency of DKA since diagnosis	R	0.030	0.060	-0.217	-0.308	0.003	-0.067	0.101	-0.006
	p	0.797	0.608	0.061	0.007	0.979	0.566	0.388	0.958
	N	75	75	75	75	75	75	75	75
Total insulin dose (IU/kg/day)	R	-0.065	0.054	-0.137	-0.056	-0.087	-0.141	-0.028	-0.053
	p	0.577	0.643	0.241	0.631	0.456	0.229	0.810	0.654
	N	75	75	75	75	75	75	75	75
Basal insulin dose (IU/kg/day)	R	0.148	0.047	-0.001	-0.011	0.126	0.084	0.148	0.031
	p	0.204	0.688	0.993	0.923	0.283	0.476	0.204	0.794
	N	75	75	75	75	75	75	75	75
Frequency of glucose self-monitoring	R	0.187	-0.094	0.069	-0.060	0.113	-0.029	0.157	-0.075
	p	0.108	0.420	0.556	0.608	0.335	0.808	0.179	0.522
	n	75	75	75	75	75	75	75	75
Irregular dietary	R	-0.221	-0.144	-0.187	-0.161	-0.159	-0.0	-0.178	-0.10

		Image density		Foveal density		Parafoveal density		Parafoveal density	
		Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer
habits							97		5
	p	0.057	0.216	0.107	0.169	0.174	0.407	0.128	0.372
	n	75	75	75	75	75	75	75	75
BP state (normal-PreHTN-HTN)	R	0.009	0.059	-0.251	-0.237	-0.010	0.059	0.076	0.001
	p	0.938	0.613	0.030	0.041	0.930	0.614	0.518	0.996
	n	75	75	75	75	75	75	75	75
HbA1c	R	-0.212	-0.094	0.038	0.097	-0.247	-0.058	-0.214	-0.155
	p	0.067	0.422	0.745	0.410	0.033	0.619	0.065	0.185
	n	75	75	75	75	75	75	75	75
Cholesterol	R	-0.089	0.027	-0.255	-0.172	-0.070	0.070	-0.039	-0.029
	p	0.446	0.820	0.027	0.141	0.550	0.549	0.737	0.804
	n	75	75	75	75	75	75	75	75
TGs	R	-0.029	0.074	-0.167	-0.088	0.036	0.084	0.007	0.028
	p	0.804	0.527	0.153	0.455	0.758	0.474	0.952	0.811
	n	75	75	75	75	75	75	75	75
LDL	R	-0.089	0.040	-0.036	-0.118	-0.104	-0.051	-0.045	0.061
	p	0.446	0.732	0.758	0.313	0.372	0.665	0.699	0.605
	n	75	75	75	75	75	75	75	75
HbA1c (Target)	R	-0.160	0.108	0.042	0.119	-0.179	0.102	-0.154	0.097
	p	0.169	0.354	0.718	0.307	0.124	0.383	0.187	0.406
	n	75	75	75	75	75	75	75	75
Cholesterol (Target)	R	-0.068	-0.082	-0.117	-0.110	-0.023	-0.046	-0.053	-0.065
	p	0.562	0.482	0.318	0.349	0.847	0.694	0.649	0.578
	n	75	75	75	75	75	75	75	75
TGs (Target)	R	0.155	0.165	-0.062	0.040	0.163	0.2	0.155	0.17

		Image density		Foveal density		Parafoveal density		Parafoveal density	
		Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer
							03		2
	p	0.183	0.157	0.600	0.735	0.162	0.081	0.183	0.141
	n	75	75	75	75	75	75	75	75
LDL (Target)	R	-0.055	0.082	-0.068	-0.104	-0.056	-0.006	-0.009	0.085
	p	0.639	0.487	0.562	0.374	0.635	0.956	0.938	0.470
	n	75	75	75	75	75	75	75	75

*R (correlation coefficient) *p (p value) *n (number of patients)

Table 4: Correlation between the variables and the OCTA measurements in the left eye

		Image density		Foveal density		Parafoveal density		Perifoveal density	
		Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer
Age (years)	R	-0.068	0.023	-0.221	-0.131	-0.027	0.034	-0.035	0.018
	p	0.560	0.843	0.057	0.262	0.817	0.769	0.764	0.879
	n	75	75	75	75	75	75	75	75
Diabetes duration (years)	R	0.019	0.020	-0.217	-0.148	0.036	-0.027	0.023	0.044
	p	0.871	0.866	0.062	0.206	0.761	0.815	0.843	0.708
	n	75	75	75	75	75	75	75	75
DKA at presentation	R	0.116	-0.083	-0.055	-0.145	0.019	-0.108	0.108	-0.076
	p	0.320	0.479	0.640	0.214	0.872	0.357	0.357	0.515
	n	75	75	75	75	75	75	75	75
Frequency of DKA since diagnosis	R	-0.122	-0.042	-0.227	-0.119	-0.131	-0.064	-0.140	-0.042
	p	0.299	0.720	0.050	0.308	0.262	0.584	0.232	0.721
	n	75	75	75	75	75	75	75	75
Total insulin dose	R	0.096	0.212	-0.122	-0.07	0.099	0.112	0.141	0.210

		Image density		Foveal density		Parafoveal density		Perifoveal density	
		Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer
(IU/kg/day)					7				
	p	0.412	0.068	0.296	0.513	0.398	0.337	0.228	0.071
	n	75	75	75	75	75	75	75	75
Basal insulin dose (IU/kg/day)	R	0.147	-0.007	-0.016	0.064	0.068	0.101	0.153	-0.011
	p	0.209	0.953	0.891	0.582	0.562	0.389	0.191	0.925
	n	75	75	75	75	75	75	75	75
Frequency of glucose self-monitoring	R	0.162	0.004	0.075	0.020	0.060	0.003	0.191	-0.013
	p	0.165	0.974	0.524	0.867	0.606	0.980	0.101	0.910
	n	75	75	75	75	75	75	75	75
Irregular dietary habits	R	-0.264	-0.131	-0.318	-0.240	-0.176	-0.001	-0.294	-0.120
	p	0.022	0.261	0.005	0.038	0.132	0.996	0.010	0.304
	n	75	75	75	75	75	75	75	75
	p	0.943	0.837	0.174	0.564	0.406	0.870	0.697	0.775
	n	75	75	75	75	75	75	75	75
BP state (normal-PreHTN-HTN)	R	-0.036	-0.037	-0.288	-0.266	-0.139	0.008	0.030	-0.070
	p	0.760	0.755	0.012	0.021	0.233	0.945	0.800	0.553
	n	75	75	75	75	75	75	75	75
HbA1c	R	-0.201	0.093	-0.027	0.061	-0.260	0.163	-0.215	0.080
	p	0.083	0.426	0.818	0.601	0.024	0.163	0.064	0.493
	n	75	75	75	75	75	75	75	75
Cholesterol	R	-0.215	-0.152	-0.272	-0.238	-0.204	-0.059	-0.202	-0.131
	p	0.064	0.194	0.018	0.040	0.079	0.615	0.082	0.263
	n	75	75	75	75	75	75	75	75
TGs	R	-0.267	-0.276	-0.212	-0.155	-0.184	-0.206	-0.259	-0.262
	p	0.021	0.017	0.068	0.183	0.114	0.077	0.025	0.023

		Image density		Foveal density		Parafoveal density		Perifoveal density	
		Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer	Superficial layer	Deep layer
	n	75	75	75	75	75	75	75	75
LDL	R	-0.117	-0.150	-0.076	-0.077	-0.237	-0.092	-0.089	-0.131
	p	0.316	0.200	0.515	0.513	0.041	0.431	0.448	0.264
	n	75	75	75	75	75	75	75	75
HbA1c (Target)	R	-0.212	0.173	0.035	0.072	-0.259	0.179	-0.209	0.141
	p	0.068	0.138	0.768	0.538	0.025	0.124	0.072	0.226
	n	75	75	75	75	75	75	75	75
Cholesterol (Target)	R	-0.186	-0.304	-0.105	-0.078	-0.123	-0.257	-0.130	-0.280
	p	0.111	0.008	0.370	0.506	0.292	0.026	0.268	0.015
	n	75	75	75	75	75	75	75	75
TGs (Target)	R	-0.130	-0.177	-0.061	0.037	-0.153	-0.112	-0.122	-0.183
	p	0.267	0.128	0.605	0.753	0.191	0.339	0.296	0.116
	n	75	75	75	75	75	75	75	75
LDL (Target)	R	-0.116	-0.250	-0.139	-0.102	-0.210	-0.183	-0.106	-0.223
	p	0.322	0.030	0.234	0.383	0.070	0.117	0.368	0.054
	n	75	75	75	75	75	75	75	75

*R (correlation coefficient) *p (p value) *n (number of patients)

Total insulin doses in IU/kg/day and types of insulin used were comparable in both groups but the mean (±SD) basal insulin requirements were significantly higher in those with abnormal compared to normal OCTA (0.41 ± 0.12) compared to (0.40 ± 0.1) IU/kg/day, respectively. Higher basal insulin requirements were probably related to older age and more advanced pubertal status in those with findings suggestive of retinopathy.

The median height SDS of patients with diabetes with abnormalities in OCTA was significantly less than in those with normal findings, -1.5 (-2.2- [-1.05]) compared to -0.5(-1.2-0.7) respectively. This supports that retinopathy is related to poor glycemic control which hinders linear growth as well. Delayed linear growth and short stature can therefore be considered a clinical sign of risk for developing retinopathy. All other anthropometric parameters studied (weight, BMI and waist

circumference) were comparable in both groups.Both systolic and diastolic blood pressures were comparable between the 2 groups.

However, the blood pressure status being prehypertensive or hypertensive had a negative correlation with foveal density superficial and deep layers. Mean SBP had a negative correlation with foveal density superficial layer; and mean DBP and DBP percentiles had a negative correlation with both superficial and deep foveal layers. This emphasizes the importance of measuring the blood pressure for any patient with diabetes. As it is one of the important risk factors for development of diabetic retinopathy. Our results were in agreement with a study conducted by Dost et al (2017), which showed that BP levels were higher in patients positive for DR, although significantly only for DBP. [16]

The presence of lipohypertrophy at the insulin injection sites was comparable between the 2 groups. Also, limited joint mobility was found in a total of 38 patients out of the 75 (50.67%), and was significantly more frequent in patients with abnormalities in the OCTA (67.9%) compared to those with normal OCTA. Limited joint mobility can be considered also a clinical sign indicating risk of developing retinopathy.

Also, the presence of limited joint mobility showed a negative correlation with image density deep layer, parafoveal density deep layer and perifoveal density deep layer. In addition, the presence of lipohypertrophy at the insulin injection sites showed a negative correlation with image density superficial layer, parafoveal density superficial layer and perifoveal density superficial layer which indicates increased risk of diabetic retinopathy.

Our study agreed with a study conducted by Shadhan et al (2016), on 150 patients with T1D, their age ranges from 4.5 - 19 years, with duration ranges from 2-18 years. It showed that there was a significant association between the presence of eye complications and limited joint mobility. [17] The mean HbA1c of patients with diabetes with normal OCTA was 9.64 ± 1.94%, while the mean HbA1C in percent of patients with diabetes with abnormal OCTA was 10.46 ± 1.96 %. Results showed numerically higher HbA1c in the group with abnormal OCTA but not reaching statistical significance. This indicates that risk of development of retinopathy increases with poor glycemic control.

Our findings were similar to the study conducted by Ng et al (2019) which showed significantly higher mean HbA1c in patients with retinopathy compared to those with no retinal changes. [12] It is important to note that glycosylated hemoglobin (HbA1c) has been the sole surrogate marker for optimal glycemic control and predicting diabetic complications. However, its accuracy for reflecting an individual's glycemic control is limited because it does not provide detailed information such as glycemic variability, acute excursion of glucose change, or severity of hypo- or hyperglycemia. Therefore, a patient's glycemic status can vary between excellent, fair, and poor, even among individuals with similar HbA1c. These findings suggest that poor glycemic control is not the sole risk for developing retinopathy. It is also explained by glucose variability and by the HbA1c at onset and over the past years which were not included in this study

because of lack of frequent SMBG to detect variability and lack of regular HbA1c testing.

Our study showed that cholesterol had a negative correlation with foveal density superficial and deep layers. Cholesterol level (being in target) had a negative correlation with image density deep, parafoveal density deep and perifoveal density deep. This was similar to the study conducted by Kumar et al (2020), which showed cholesterol was found to be high in 30 (15%) patients. Prevalence of retinopathy was 60%, in patients having high total cholesterol levels. [18] DR was graded as per the ETDRS guidelines.

According to our study, triglycerides had a negative correlation with image density superficial layer, image density deep layer, perifoveal density superficial layer and perifoveal density deep layer. Similarly keel et al (2016), showed a trend towards participants with DR displaying a higher triglyceride level but without reaching statistical significance. [19] In our study, LDL had a negative correlation with parafoveal density superficial layer. LDL (being in target) had a negative correlation with image density deep layer which was similar to a study conducted by Rathsman et al (2020) that found **a** significant association between increased LDL levels and risk of retinopathy. [20]

Although fundus examination, photography and OCT were normal, OCTA showed findings in 28(37.3%) of the patients. So, OCTA can be considered a valuable sensitive tool for detection of early DR changes. Delayed linear growth and short stature, presence of lipodystrophy as well as limited joint mobility are indicators of unsatisfactory glycemic control and can be considered clinical signs of risk for developing retinopathy.

Conclusion

OCTA can be used in early detection of diabetic retinopathy in T1D adolescents especially with risk factors (Elevated HbA1c, frequent DKA, decreased height SDS and limited joint mobility).

Limitations of the study

- This is a Cross sectional study, and longitudinal follow up is needed to prove that OCTA abnormalities indicate retinopathy development and progression.
- Comparison with adolescents without diabetes as well as comparison with patients with optimum HbA1c wasn't done.
- Relation to long term glycemic control since diagnosis wasn't investigated.
- Relation to other microvascular complications like microalbuminuria and nephropathy wasn't done.

Declaration of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest

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