Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublisher.com/sjams/

OPEN ACCESS

Ophthalmology

Macular Thickness in Relation to Duration and Severity of Diabetes

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DOI: 10.36347/sjams.2020.v08i01.043 | **Received:** 20.12.2019 | **Accepted:** 27.12.2019 | **Published:** 26.01.2020

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Abstract **Original Research Article**

Diabetes mellitus is the leading cause of blindness in the working age group; retinal neuronal abnormalities are present in early stages of Diabetes mellitus, even before the development of clinically detectable microvascular damage. With the increasing duration of DM, these abnormalities might increase leading to alteration in retinal thickness. The study was undertaken to test the hypothesis that duration and severity of diabetes affects macular thickness even in the absence of clinically apparent macular edema. We recruited 50 diagnosed patients of type-II Diabetes mellitus (NIDDM) as cases and 100 age and sex matched non-diabetic subjects attending outpatient services of department of Ophthalmology as the control group. Complete ophthalmological examination was done and measurement of retinal thickness was obtained in nine EDTRS subfields within 3 concentric circles centered on fovea making use of spectral domain Optical coherence tomography (SD-OCT). Corresponding quantitative data (μ±SD) was compared using chi square test and one-way analysis of variance. Significantly decreased macular thickness and volume was found in diabetics in comparison to the control group in outer and inner nasal and superior quadrant. This decrease in macular thickness in the specific quadrant also significantly increased with decrease in control of disease i.e. increase in HbA1c value more than 7%. Duration of disease more than 10 years was the only factor which resulted in decreased thickness of the central fovea. Our study detected morphological changes in NIDDM patients with the help of SD-OCT signifying that neural tissue loss begins in the early stages of diabetes and warrants early neuroprotective measures to prevent the damage. SD-OCT may represent an effective tool for identifying early signs of neurodegeneration in diabetic patients.

Keywords: Diabetic retinopathy (DR), retinal neuronal abnormalities, macular thickness, optical coherence tomography (OCT), neurodegeneration.

INTRODUCTION

There has been an epidemic increase in the proportion of diabetes mellitus cases worldwide; according to an estimate by the World Health Organization (WHO), the number of diabetics will rise to about 360 million by the year 2030[1]. In these individuals with diabetes mellitus, there is always a risk for development of diabetic retinopathy (DR) which has been accepted as the leading cause of blindness in the working age group, thus increasing the economic burden [2, 3].

DR has been traditionally considered a retinal microvascular disorder characterized by retinal ischemia, increased retinal permeability, macular oedema and retinal neovascularization [4, 5]; the International classification of DR is based on these microvascular changes only. However recently, various studies have demonstrated that retinal neuronal abnormalities like retinal ganglion cell death and axonal degeneration are present even before development of clinically detectable microvascular damage. As the duration of diabetes increase, these abnormalities also increase, thus leading to variations in retinal thickness [6-10]. Detection of these retinal neuronal abnormalities at early stages might prevent neurodegeneration, thus preventing severe visual loss.

Despite widespread clinical use, there are not many studies on distribution and correlation of SD-OCT measured retinal thickness in subjects with diabetes, especially those without Diabetic retinopathy. A few studies have been undertaken regarding retinal

morphology in diabetic subjects but results have been variable and multiple reasons could be attributed. First and foremost, different OCT machines use different segmentation algorithms and software for quantitative measurement of ocular structures and thus data between different OCT machines is not interchangeable and comparable [11-13]. Besides this demographic and ethnic variations may occur in different groups of population. This study was undertaken to evaluate any significant difference in macular thickness in our population using SD-OCT in subjects with and without diabetics and to analyze influence of variables like duration and severity of disease on macular thickness. We aimed to test the hypothesis that duration and severity of diabetes affects macular thickness even in the absence of clinically apparent diabetic retinopathy changes.

MATERIAL AND METHODS

This prospective cross-sectional study was conducted in the department of Ophthalmology, BPS Government Medical College for Women, Khanpur, Sonepat, and Haryana over a period of six months (August 2017 to January 2018**)** after taking approval from the institutional ethical committee and written informed consent from patients. Diabetic patients presenting to the department of general medicine were included as cases; those with a physician diagnosis of DM and being given anti-diabetic treatment were defined as diabetic. All these patients were undertaken for complete ophthalmological examination and those with history or signs of retinal laser treatment, coexisting macular pathology or clinically significant macular edema (CSME) or any other signs of diabetic retinopathy were excluded from the study. Those who fulfilled the inclusion and exclusion criteria were included as cases (group-I); age and sex matched non-diabetic subjects attending outpatient services of department of Ophthalmology and among staff of the hospital were recruited as controls (group-II). To keep the procedure uniform, we included only one eye of each patient (either right or left), depending on media clarity.

Patient information sheet was completed making note of all demographic, clinical and laboratory parameters. The cases were further divided as per different variables; as per duration of the disease (< 10 years, sub-group-I; ≥ 10 years, sub-group-II) and as per severity of diabetes (HbA1C <7 %, group-I; HbA1C ≥7 %, group-II).

OCT examination was performed on both cases and controls using the Nidek RS-3000 Lite (Software version NAVIS EX 1.1.0.0; Nidek Co. Ltd, Gamagori, Japan) through dilated pupils of at least 5mm in diameter. The macula map analysis protocol was selected on the Nidek RS-3000 Lite SD OCT. Macular thickness was evaluated in the nine quadrants as described in the early treatment diabetic retinopathy study (EDTRS) grid comprising three concentric circles of 1, 3 and 6 mm. The quadrants were named as the central zone, inner superior-inferior-nasal-temporal and outer superior-inferior-nasal-temporal quadrants (figure-1). Internal fixation was used for all the patients and measurements were repeated till SSI of atleast 7/10 was achieved. Measurements (in micrometer) were taken for both cases and controls and corresponding data was compared using the chi-square test and one-way analysis of variance.

RESULTS

A total 50 diagnosed patients of NIDDM were recruited as cases (mean age 49.5±14.04 years) and 100 age and sex matched non-diabetic subjects as controls (mean age 32.69±14.44 years). The retinal thickness (RT) (in µ) obtained from each of the nine EDTRS subfield in each group and their mean values are given in table-1, 2, 3. Table 4 and 5 describes comparative retinal thickness and volume in nine quadrants in controls and cases with HbA1c less than and more than 7% respectively. Table 6 and 7 describes comparative retinal thickness and volume in nine quadrants in control and cases with duration less than and more than 10 years respectively.

We found significantly decreased macular thickness and volume in diabetics in comparison to the control group in outer nasal and inner nasal and superior quadrant. This decrease in macular thickness in the nasal inner quadrant also significantly increased with decrease in control of disease i.e. increase in HbA1c value more than 7%. Duration of disease more than 10 years was the only factor which resulted in decreased thickness of the central fovea. Other quadrants which showed decreased macular thickness with increased duration of disease were inner superior quadrant and those with decreased volume outer inferior and outer temporal quadrant.

Table-1: Comparative retinal thickness and volume in nine quadrants in controls and cases

Group		N	Mean	Std. Deviation	p-value
CSF(t)	Control	99	256.52	30.53	0.161
	Case	50	247.26	49.46	
SIM(t)	Control	99	334.68	34.83	
	Case	50	315.18	46.63	**0.005**
NIM(t)	Control	99	336.69	33.86	
	Case	50	315.54	46.28	**0.002**
IIM(t)	Control	99	332.79	34.33	
	Case	50	370.46	419.64	0.375
TIM(t)	Control	99	319.51	28.67	
	Case	50	305.28	70.84	0.84
SOM(t)	Control	99	330.28	303.64	
	Case	50	292.46	22.14	0.381
NOM(t)	Control	99	316.38	25.05	
	Case	50	302.52	25.01	**0.002**
IOM(t)	Control	99	289.30	28.46	
	Case	50	280.32	53.30	0.181
TOM(t)	Control	99	288.87	20.44	
	Case	50	276.44	45.65	0.202
CSF(v)	Control	99	0.20	0.03	
	Case	50	0.19	0.04	0.627
SIM(v)	Control	99	0.53	0.06	
	Case	50	0.50	0.07	**0.005**
NIM(v)	Control	99	0.53	0.05	
	Case	50	0.50	0.07	**0.002**
IIM(v)	Control	99	0.52	0.05	
	Case	50	0.49	0.13	0.39
TIM(v)	Control	99	0.50	0.04	
	Case	50	0.48	0.11	0.128
SOM(v)	Control	99	1.59	0.13	
	Case	50	1.55	0.12	0.5
NOM(v)	Control	99	1.65	0.15	
	Case	50	1.59	0.15	**0.044**
IOM(v)	Control	99	1.53	0.16	
	Case	50	1.48	0.28	0.225
TOM(v)	Control	99	1.54	0.11	
	Case	50	1.47	0.24	**0.027**

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

Table-2: Comparative retinal thickness and volume in nine quadrants in diabetics with severity of disease as variable

Group		N	Mean	Std. Deviation	p-value
CSF(t)	HbA1c < 7	23	252.39	25.04	
	HbA1c > 7	27	242.89	63.53	0.504
SIM(t)	HbA1c < 7	23	329.22	15.11	
	HbA1c > 7	27	303.22	59.85	0.0408
NIM(t)	HbA1c < 7	23	331.61	15.41	
	HbA1c > 7	27	301.85	58.42	**0.022**
IIM(t)	HbA1c < 7	23	451.57	604.23	
	HbA1c > 7	27	301.37	110.31	0.21
TIM(t)	HbA1c < 7	23	313.52	18.87	
	HbA1c > 7	27	298.26	95.10	0.453
SOM(t)	HbA1c < 7	23	296.74	15.92	
	HbA1c > 7	27	288.81	26.05	0.21
NOM(t)	HbA1c < 7	23	308.35	19.58	
	HbA1c > 7	27	297.56	28.26	0.13
IOM(t)	HbA1c < 7	23	286.87	23.26	
	HbA1c > 7	27	274.74	69.46	0.428
TOM(t)	HbA1c < 7	23	278.00	43.68	
	HbA1c > 7	27	275.11	48.05	0.826
CSF(v)	HbA1c < 7	23	0.20	0.02	
	HbA1c > 7	27	0.19	0.05	0.521
SIM(v)	HbA1c < 7	23	0.52	0.02	
	HbA1c > 7	27	0.48	0.09	**0.048**
NIM(v)	HbA1c < 7	23	0.52	0.03	
	HbA1c > 7	27	0.47	0.09	**0.019**
IIM(v)	HbA1c < 7	23	0.51	0.03	
	HbA1c > 7	27	0.47	0.17	0.297
TIM(v)	HbA1c < 7	23	0.49	0.03	
	HbA1c > 7	27	0.47	0.14	0.519
NOM(v)	HbA1c < 7	23	1.57	0.08	
	HbA1c > 7	27	1.53	0.14	0.154
SOM(v)	HbA1c < 7	23	1.62	0.15	
	HbA1c > 7	27	1.58	0.15	0.34
IOM(v)	HbA1c < 7	23	1.52	0.12	
	HbA1c > 7	27	1.45	0.36	0.341
TOM(v)	HbA1c < 7	23	1.49	0.22	
	HbA1c > 7	27	1.46	0.26	0.599

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

Table-3: Comparative retinal thickness and volume in nine quadrants in diabetics with duration of disease as variable

Group		N	Mean	Std. Deviation	p-value
CSF(t)	duration >10 yrs	28	236.57	28.28	
	duration <10 yrs	22	260.86	65.82	**0.003**
SIM(t)	duration >10 yrs	28	310.14	50.85	
	duration <10 yrs	22	321.59	40.90	**0.002**
NIM(t)	duration >10 yrs	28	309.64	49.97	
	duration <10 yrs	22	323.05	41.01	0.085
IIM(t)	duration >10 yrs	28	401.32	557.16	
	duration <10 yrs	22	331.18	94.20	0.314
TIM(t)	duration >10 yrs	28	291.04	60.82	
	duration <10 yrs	22	323.41	79.61	0.563
SOM(t)	duration >10 yrs	28	289.50	21.30	
	duration <10 yrs	22	296.23	23.09	0.109
NOM(t)	duration >10 yrs	28	299.21	22.46	
	duration <10 yrs	22	306.73	27.88	0.291
IOM(t)	duration >10 yrs	28	266.43	47.73	
	duration <10 yrs	22	298.00	55.80	0.296
TOM(t)	duration >10 yrs	28	267.00	54.81	
	duration <10 yrs	22	288.45	27.01	**0.03**
CSF(v)	duration >10 yrs	28	0.19	0.02	
	duration <10 yrs	22	0.21	0.05	0.09
SIM(v)	duration >10 yrs	28	0.49	0.08	
	duration <10 yrs	22	0.51	0.06	0.86
NIM(v)	duration >10 yrs	28	0.49	0.08	
	duration <10 yrs	22	0.51	0.07	0.349
IIM(v)	duration >10 yrs	28	0.47	0.11	
	duration <10 yrs	22	0.52	0.15	0.318
TIM(v)	duration >10 yrs	28	0.47	0.09	
	duration <10 yrs	22	0.51	0.12	0.148
SOM(v)	duration >10 yrs	28	1.53	0.11	
	duration <10 yrs	22	1.56	0.12	0.161
NOM(v)	duration >10 yrs	28	1.59	0.12	
	duration <10 yrs	22	1.60	0.18	0.654
IOM(v)	duration >10 yrs	28	1.41	0.25	
	duration <10 yrs	22	1.58	0.29	**0.036**
TOM(v)	duration >10 yrs	28	1.41	0.29	
	duration <10 yrs	22	1.55	0.11	**0.043**

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

Table-4: Comparative retinal thickness and volume in nine quadrants in control and cases with HbA1c less than 7%

Group		N	Mean	Std. Deviation	p-value
CSF(t)	Control	99	256.52	30.53	.548
	HbA1c < 7	23	252.39	25.04	
SIM(t)	Control	99	334.68	34.83	.464
	HbA1c < 7	23	329.22	15.11	
NIM(t)	Control	99	336.69	33.86	.485
	HbA1c < 7	23	331.61	15.41	
IIM(t)	Control	99	332.79	34.33	.051
	HbA1c < 7	23	451.57	604.23	
TIM(t)	Control	99	319.51	28.67	.343
	HbA1c < 7	23	313.52	18.87	
SOM(t)	Control	99	330.28	303.64	.599
	HbA1c < 7	23	296.74	15.92	
NOM(t)	Control	99	316.38	25.05	.153
	HbA1c < 7	23	308.35	19.58	
IOM(t)	Control	99	289.30	28.46	.704
	HbA1c < 7	23	286.87	23.26	
TOM(t)	Control	99	288.87	20.44	.077
	HbA1c < 7	23	278.00	43.68	
CSF(v)	Control	99	0.20	0.03	.886
	HbA1c < 7	23	0.20	0.02	
SIM(v)	Control	99	0.53	0.06	.465
	HbA1c < 7	23	0.52	0.02	
NIM(v)	Control	99	0.53	0.05	.556
	HbA1c < 7	23	0.52	0.03	
IIM(v)	Control	99	0.52	0.05	.375
	HbA1c < 7	23	0.51	0.03	
TIM(v)	Control	99	0.50	0.04	.395
	HbA1c < 7	23	0.49	0.03	
SOM(V)	Control	99	1.59	0.13	.577
	HbA1c < 7	23	1.57	0.08	
NOM(v)	Control	99	1.65	0.15	.378
	HbA1c < 7	23	1.62	0.15	
IOM(v)	Control	99	1.53	0.16	.946
	HbA1c < 7	23	1.52	0.12	
TOM(v)	Control	99	1.54	0.11	.165
	HbA1c < 7	23	1.49	0.22	

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

Table-5: Comparative retinal thickness and volume in nine quadrants in controls and cases with HbA1c more than 7%

Group		N	Mean	Std. Deviation	p-value
CSF(t)	Control	99	256.52	30.53	.117
	HbA1c >7	27	242.89	63.53	
SIM(t)	Control	99	334.68	34.83	**.001**
	HbA1c >7	27	303.22	59.85	
NIM(t)	Control	99	336.69	33.86	**.002**
	HbA1c >7	27	301.85	58.42	
IIM(t)	Control	99	332.79	34.33	.016
	HbA1c >7	27	301.37	110.31	
TIM(t)	Control	99	319.51	28.67	.055
	HbA1c >7	27	298.26	95.10	
SOM(t)	Control	99	330.28	303.64	.481
	HbA1c >7	27	288.81	26.05	
NOM(t)	Control	99	316.38	25.05	**.001**
	HbA1c >7	27	297.56	28.26	
IOM(t)	Control	99	289.30	28.46	.101
	HbA1c >7	27	274.74	69.46	
TOM(t)	Control	99	288.87	20.44	**.028**
	HbA1c >7	27	275.11	48.05	
CSF(v)	Control	99	0.20	0.03	.432
	HbA1c >7	27	0.19	0.05	
SIM(v)	Control	99	0.53	0.06	**.001**
	HbA1c >7	27	0.48	0.09	
NIM(v)	Control	99	0.53	0.05	**.000**
	HbA1c >7	27	0.47	0.09	
IIM(v)	Control	99	0.52	0.05	**.016**
	HbA1c >7	27	0.47	0.17	
TIM(v)	Control	99	0.50	0.04	.094
	HbA1c >7	27	0.47	0.14	
SOM(v)	Control	99	1.59	0.13	**.029**
	HbA1c >7	27	1.53	0.14	
NOM(v)	Control	99	1.65	0.15	**.030**
	HbA1c >7	27	1.58	0.15	
IOM(v)	Control	99	1.53	0.16	.098
	HbA1c >7	27	1.45	0.36	
TOM(v)	Control	99	1.54	0.11	**.017**
	HbA1c >7	27	1.46	0.26	

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

Table-6: Comparative retinal thickness and volume in nine quadrants in control and cases with duration less than ten years

Group		N	Mean	Std. Deviation	p-value
CSF(t)	Control	99	256.52	30.53	**.002**
	duration <10 YRS	28	236.57	28.28	
SIM(t)	Control	99	334.68	34.83	**.004**
	duration <10 YRS	28	310.14	50.85	
NIM(t)	Control	99	336.69	33.86	**.001**
	duration <10 YRS	28	309.64	49.97	
IIM(t)	Control	99	332.79	34.33	.222
	duration <10 YRS	28	401.32	557.16	
TIM(t)	Control	99	319.51	28.67	**.001**
	duration <10 YRS	28	291.04	60.82	
SOM(t)	Control	99	330.28	303.64	.480
	duration <10 YRS	28	289.50	21.30	
NOM(t)	Control	99	316.38	25.05	**.001**
	duration <10 YRS	28	299.21	22.46	
IOM(t)	Control	99	289.30	28.46	**.002**
	duration <10 YRS	28	266.43	47.73	
TOM(t)	Control	99	288.87	20.44	**.001**
	duration <10 YRS	28	267.00	54.81	
CSF(v)	Control	99	0.20	0.03	.082
	duration <10 YRS	28	0.19	0.02	
SIM(v)	Control	99	0.53	0.06	**.003**
	duration <10 YRS	28	0.49	0.08	
NIM(v)	Control	99	0.53	0.05	**.001**
	duration <10 YRS	28	0.49	0.08	
IIM(v)	Control	99	0.52	0.05	**.000**
	duration <10 YRS	28	0.47	0.11	
TIM(v)	Control	99	0.50	0.04	**.002**
	duration <10 YRS	28	0.47	0.09	
SOM(v)	Control	99	1.59	0.13	**.047**
	duration <10 YRS	28	1.53	0.11	
NOM(v)	Control	99	1.65	0.15	.049
	duration <10 YRS	28	1.59	0.12	
IOM(v)	Control	99	1.53	0.16	**.003**
	duration <10 YRS	28	1.41	0.25	
TOM(v)	Control	99	1.54	0.11	**.001**
	duration <10 YRS	28	1.41	0.29	

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

Table-7: Comparative retinal thickness and volume in nine quadrants in control and cases with duration more than 10 years

Group		N	Mean	Std. Deviation	p-value
CSF(t)	Control	99	256.52	30.53	.638
	duration .>10 yrs	22	260.86	65.82	
SIM(t)	Control	99	334.68	34.83	.125
	duration .>10 yrs	22	321.59	40.90	
NIM(t)	Control	99	336.69	33.86	.103
	duration .>10 yrs	22	323.05	41.01	
IIM(t)	Control	99	332.79	34.33	.893
	duration .>10 yrs	22	331.18	94.20	
TIM(t)	Control	99	319.51	28.67	.697
	duration .>10 yrs	22	323.41	79.61	
SOM(t)	Control	99	330.28	303.64	.601
	duration .>10 yrs	22	296.23	23.09	
NOM(t)	Control	99	316.38	25.05	.112
	duration .>10 yrs	22	306.73	27.88	
IOM(t)	Control	99	289.30	28.46	.292
	duration .>10 yrs	22	298.00	55.80	
TOM(t)	Control	99	288.87	20.44	.936
	duration .>10 yrs	22	288.45	27.01	
CSF(v)	Control	99	0.20	0.03	.360
	duration .>10 yrs	22	0.21	0.05	
SIM(v)	Control	99	0.53	0.06	.145
	duration .>10 yrs	22	0.51	0.06	
NIM(v)	Control	99	0.53	0.05	.110
	duration .>10 yrs	22	0.51	0.07	
IIM(v)	Control	99	0.52	0.05	.946
	duration .>10 yrs	22	0.52	0.15	
TIM(v)	Control	99	0.50	0.04	.746
	duration .>10 yrs	22	0.51	0.12	
SOM(v)	Control	99	1.59	0.13	.415
	duration .>10 yrs	22	1.56	0.12	
NOM(v)	Control	99	1.65	0.15	.257
	duration .>10 yrs	22	1.60	0.18	
IOM(v)	Control	99	1.53	0.16	.271
	duration .>10 yrs	22	1.58	0.29	
TOM(v)	Control	99	1.54	0.11	.656
	duration .>10 yrs	22	1.55	0.11	

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula. (t) Thickness; (v) volume.

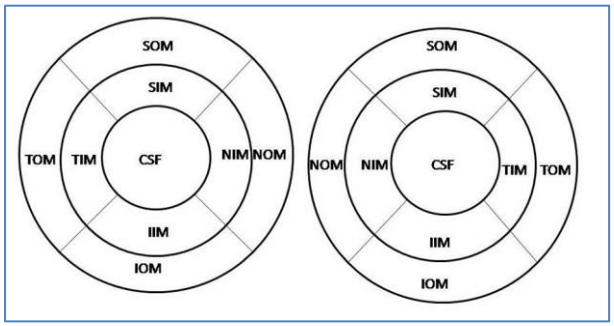

Fig-1: Representation of OCT image taken by NIDEK SD-OCT system (a) Diagramatic representation of the 3 concentric circles (b) The 9 subfields in right and left eye as per the EDTRS grid

CSF-Central subfield; SIM-Superior Inner Macula; NIM-Nasal inner macula; IIM-Inferior inner macula; TIM-Temporal inner macula; SOM-Superior outer macula; NOM-nasal outer macula; IOM-inferior outer macula; TOM-temporal outer macula.

DISCUSSION

Various microvascular changes are known to occur in retina of diabetic patients, the first recognizable vascular abnormalities being microaneurysms and dot and blot hemorrhages; as the disease progresses, more severe signs of vascular leakage set in, such as large hemorrhages, hard and soft exudates and thereafter neovascularization [14]. However while much is known about the ophthalmoscopically visible vascular abnormalities, the underlying retinal neurodegenerative changes have often been ignored. These include apoptosis of several types of retinal cells, including photoreceptors, bipolar cells, ganglion cells etc. with consequent decrease in thickness of different retinal layers. It is important to recognize these early changes since it gives time to plan preventive therapy much before development of ophthalmoscopically detectable vascular lesions [15].

We found significantly decreased retinal thickness and volume in some quadrants in diabetic patients even in the absence of clinically apparent signs of diabetic retinopathy in comparison to non-diabetic individuals. This thinning of macula even before clinical signs of diabetic retinopathy could probably correspond to an apoptotic process in the retina. Results of our study are comparable to study by Vujosevic S and Midena E and studies by Van Dijk HW *et al*. which found reduction in the inner retinal thickness in diabetics without clinically detectable retinopathy and with mild and moderate non-proliferative retinopathy without macular oedema [16-18]. This inner retinal thinning strongly suggests an early neuronal loss in DR. Van Dijik *et al*. in their study demonstrated a decrease in the inner retinal thickness in the macula suggesting initial Ganglion cell layer (GCL) loss in the pericentral areas followed by thinning of Retinal Nerve Fibre Layer (RNFL) in the peripheral macula [18,19]. Various other studies have also documented that retinal neurodegeneration may occur in DR even before the development of microvascular abnormalities [20-22]. Loss of ganglion cell bodies, neural apoptosis and glial reactivity are now considered to be the main factors for retinal neurodegeneration [23, 24]. This hypothesis regarding occurrence of neurodegeneration before vascular changes has been confirmed by various electrophysiological and psychophysical studies as well [25, 26].

In contrast to the above-mentioned studies which have reported decrease in retinal thickness, there are other studies in literature which has given conflicting views. Kashani *et al*. reported no difference in macular thickness between non-diabetic controls and diabetics with DR [27]. Hortensia Sa´nchez-Tocino *et al*. found a statistically significant difference in thickness at the foveal centre in diabetic eyes, even in the absence of ophthalmoscopic evidence of retinopathy compared with normal eyes [28]. Study by Lattenzio *et al*. and a few other studies reported thicker macula in diabetic subjects without DR than non-diabetic controls [25, 29, 30]. A probable explanation to this is an alteration in the blood retinal barrier which may facilitate an increase in vascular permeability of perifoveal and macular capillaries [31]. Another possible explanation for increased macular thickness is interstitial oedema which occurs secondary to perifoveal capillary loss in due course of DR [32]. Another metanalysis published in Cochrane database evaluated the diagnostic accuracy of OCT for detecting macular changes in DR; the study concluded that OCT can detect macular thickening earlier than clinical examination but many of these cases did not progress to CSME [33].

CCA Sng *et al*. reported thicker fovea and increased temporal outer macular thickness in diabetic participants with moderate or severe DR, even in the absence of diabetic macular oedema [34]. However in their study, duration and control of disease did not significantly affect macular thickness. We found significant association between decreases in macular thickness in the nasal inner quadrant with decrease in control of disease i.e increase in HbA1c value more than 7%. Interestingly the only factor which resulted in decreased thickness of the central fovea was duration of disease more than 10 years. Another study has reported association between increased macular thickness with higher HbA1c levels [35] and decreased macular thickness with increased duration of disease [36]. Hudson *et al*. reported that macular capillary blood flow was lower in areas of diabetic macular oedema and this reduction was more evident in the temporal compared with the nasal macula; these vascular changes may be related to the severity of DR even in the absence of diabetic macular oedema [37]. In contrast to this, we found that diabetic subjects had decreased macular thickness in the nasal quadrant and not temporal, thus rejecting the aforementioned hypothesis.

We found decreased macular thickness in our diabetic population in correlation with increase in duration and decrease in control of disease. There are certain limitations of our study; firstly it is hospital based and thus inclusion of cases and controls may have had some selection bias. Secondly, there is probability of severity of DR being a compounding factor for duration and severity of disease which has not been adjusted for in our study.

CONCLUSION

Macula has a distinct and intricate layout of the retinal structures and this makes the macula not only adaptable to high acuity vision but also vulnerable to systemic diseases. In the study, we found significantly thinner retina in diabetic subjects even in absence of clinically significant retinopathy changes. Detection of morphological changes in Diabetic patients signifies importance of early detection of neurodegenerative changes which occur before the ophthalmoscopically visible microvascular abnormalities so that neuroprotective measures to prevent the damage can be timely initiated.

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