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Optical Coherence Tomography Biomarkers in the Follow up of Mild Diabetic Retinopathy

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Abstract

Introduction: *Diabetic retinopathy (DR) is the leading complication of diabetes with a prevalence of 30% and if not diagnosed timely can cause important vision loss up to blindness. Systematic screening allows diagnosis of retinopathy in its early forms. Taking care of these patients by ophthalmologists is important to perform a tight control in order to prevent or delay sight threatening diabetic retinopathy. Optical Coherence Tomography (OCT) imaging provides significant biomarkers for the follow up of the initial stages of retinopathy. The purpose of this study is to assess their effectiveness in clinical practice especially in clinical pathway performed in Primary Care Setting*

Methods: *A sample of 58 consecutives patients (106 eyes) with mild diabetic retinopathy, coming from digital screening with automatic fundus cameras, were enrolled in this observational study. High definition SD-OCT was performed with a tomographic scan of 6X 6 mm centered to the fovea. We assessed quantitative biomarkers such Central Subfield Thickness (CST) and mean cube volume (MV) and qualitative biomarkers as the presence of intraretinal or subfoveal fluid, of microaneurysms, iperreflective foci and the integrity of Ellipsoid Zone*

Results: *The mean CST was 276,25 ± 54,76 µm (normal range 257-295), also MV was in the normal range. The prevalence rate (95% confidence interval) of borderline CST was 16,34% (9,34- 23,34%). The prevalence rate (95% confidence interval) of pathological CST was 5,76% (1,76 – 9,76%). Hyper reflective foci were the most frequent qualitative biomarkers.*

Conclusion: *SD- OCT represents the technique of choice for the detection and the follow up of diabetic maculopathy. Even in mild forms, CST and MV are crucial for monitoring macular thickness and detecting early signs of macular edema. Both quantitative and qualitative OCT biomarkers can guide more accurate follow up strategies, enhancing patient care.*

Keywords: *OCT Biomarkers, Mild Diabetic Retinopathy, Clinical Pathway.*

INTRODUCTION

Diabetic retinopathy (DR) is one of the leading causes of blindness in the middle-aged population with a prevalence of 30%.

Screening programs can significantly prevent the development of sight-threatening retinopathy in most of the at risk population (1)

Screening for diabetic retinopathy is crucial to identify referable cases that require timely full ophthalmic examination and treatment to prevent permanent vision loss. Advances in telemedicine and artificial intelligence are enhancing the screening strategies and are improving the cost-effectiveness of these programs.

ASL TO 5 is a Local Health Department of Turin Metropolitan Area, with a population of 310.315. Our diabetic center caters to 11598 patients. We employ telemedicine methods for the screening of diabetic retinopathy. Retinal images are captured by nursing staff across the four districts of ASL TO 5 using digital non-mydriatic cameras and are uploaded to a digital folder. A centralized reading center within the health department then provides reports with retinopathy grading.

Integrated care pathways are structured multidisciplinary plans detailing essential steps in managing patients with specific clinical problems. In 2019, ASL TO5 implemented a multidisciplinary care pathway that included diabetologists and ophthalmologists, targeting the management of patients who tested positive in the screening. Patients with retinopathy that is more severe than mild are considered positive. Typically individuals with mild DR do not enter this clinical pathway and continue to monitor for ophthalmic complications with annual screenings. The importance of a close follow-up at earlier stages has been assessed to prevent disease progression (2).

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Optical Coherence Tomography (OCT) has been widely utilized tool in clinical and research settings for the past two decades. It enables high-resolution, non-invasive imaging of the posterior segment allowing for the assessment of retinal thickness and morphology. OCT is crucial for diagnosing and monitoring diabetic macular edema (DME), but SD- OCT biomarkers are also instrumental in tracking the progression of early diabetic retinopathy (2,7,8,9).

This retrospective study aimed to evaluate SD OCT monitoring in patients with mild DR. The objective was to identify structural abnormalities at the early stages of diabetic retinopathy that require closer monitoring to ensure that patients needing therapy are not overlooked. In our clinical practice such patients typically continue with only annual retinography screenings. Some authors (10) have recommended adding OCT to routine screenings. However this study advocates for incorporating OCT into clinical pathways from the earliest stages of diabetic retinopathy.

MATERIALS AND METHODS

ASL TO 5 implemented an integrated care pathway focused on diabetic retinopathy. The clinical pathway includes systematic screening of the diabetic population using digital fundus cameras and subsequent follow up for patients diagnosed with retinopathy.

We conducted a retrospective analysis on a sample of 58 consecutive patients identified with mild diabetic retinopathy, in at last one eye, during a comprehensive screening by our health organization. Screening was performed using digital non-mydriatic cameras and the images were uploaded to a digital folder. A team of three general ophthalmologists provides reports with retinopathy grading at a single reading center within the local health department.

The sample size was determined based on the anticipated outcome of the primary endpoints of the study : the prevalence of borderline and pathological central subfield thickness (CST) with a 95% confidence interval. The required sample was calculated using an online calculator designed for observational clinical studies.

The study was approved by the Local Ethics Committee (identifier no. 213/2024) and adhered to the tenets of the Declaration of Helsinky and Good Clinical Practice Guidelines.

Participants included adult patients (aged 18 years or older) with type I and II diabetes; other forms of diabetes (gestational, secondary) were excluded. These individuals were enrolled for DR screening during their annual visit to the diabetic center between October 2023 and December 2023. Additional data on smoking, alcohol consumption and the presence of comorbidities (systemic hypertension, dyslipidemia, history of coronary disease/stroke), were also collected and are available in our digital folder.

One hundred and six eyes from the 58 patients with mild retinopathy were further examined using spectral domain OCT (SD-OCT) to assess the presence of qualitative or quantitative biomarkers. The classification of diabetic retinopathy was conducted by specialist clinicians according to the International Clinical Diabetic Retinopathy severity scale (3)

All SD-OCT images were acquired with a high resolution 6X6 mm scan centered on the fovea using the " raster scan and/ or radial scan " modalities and using the macular cube (512 X 128) protocol (Fig. I).

All images obtained were reviewed for quality. Images with a signal strength index of ≤ 6 were excluded.

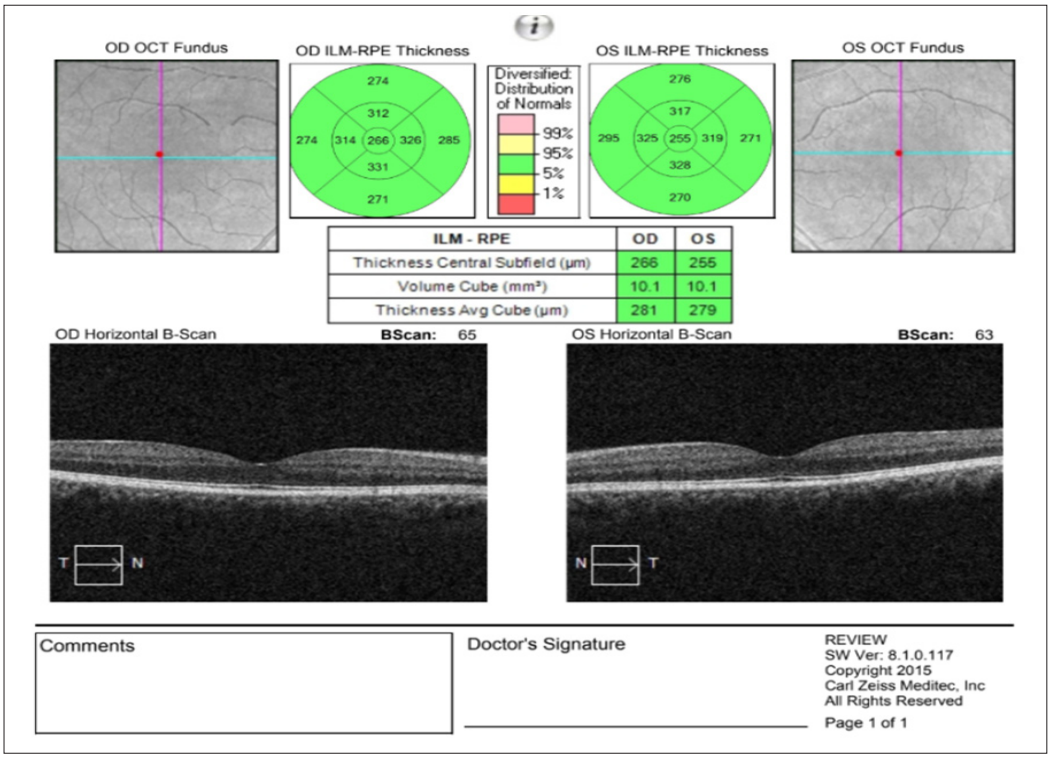

Fig I. OCT Imaging radial scan using the macular cube (512X 128) protocol

Quantitative Measurements and Biomarkers

Normative Retinal Early Treatment Diabetic Retinopathy Study (ETDRS) maps, provided in every SD-OCT, yielded quantitative biomarkers such as CST and macular cube volume (MV). The normal range for CST within the 1 mm diameter ring was set at 220 – 295 μm ; borderline range was considered to be 295 – 350 μm and pathological was defined as more than 350 μm. The normal range for MV was considered 9,26 – 10,62 mm_3 (4,5).

Furthermore we assessed the prevalence of borderline and pathological CST in the sample with a 95% confidence interval

All patients exhibiting borderline or pathological CST were referred for comprehensive ophthalmological examination including measurement of best corrected visual acuity (BCVA) using ETDRS chart and slit lamp biomicroscopy for the clinical diagnosis of macular edema.

Qualitative Biomarkers

Several morphological parameters were evaluated including the presence of hyper-reflective foci (HRF), retinal microaneurysms and hemorrhages, intraretinal and subretinal fluid and the integrity of the ellipsoid zone.

HRFs were manually counted in each scan. To ensure accurate differentiation from microaneurysms and microhemorrhages only retinal spots with reflectivity similar to that of the nerve fiber layer were included in the analysis. These spots could appear in any of the inner or outer retinal layers and lacked back-shadowing. An arbitrary cutoff of 10 HRFs per eye was established to indicate their presence.(6-7)

Microaneurysms and retinal hemorrhages were identified as larger intraretinal spots causing back shadowing, tipically located in the inner retinal layers (Fig II)

Intraretinal fluid was noted for the presence of cysts of any size in the nuclear and ganglion cell layers.

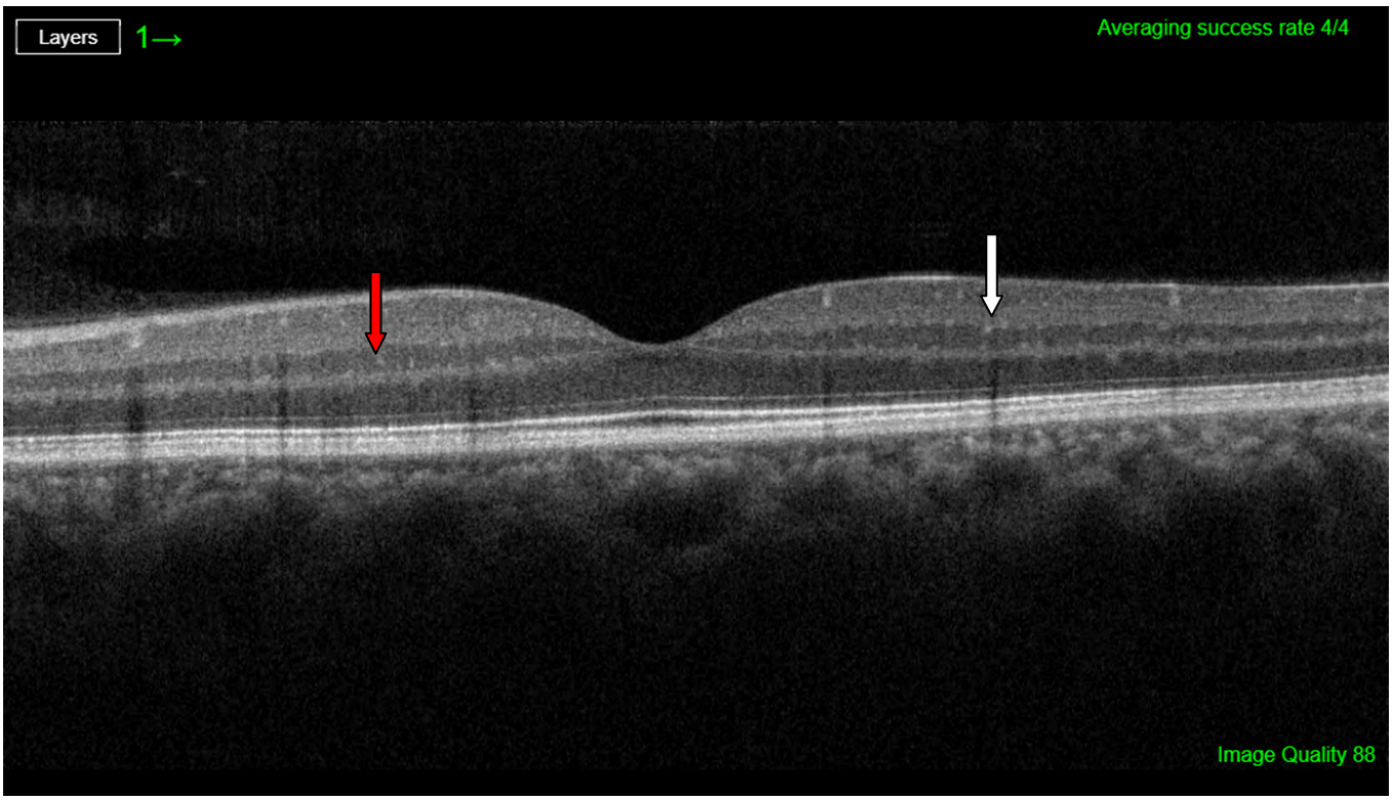

Fig II. Hyper reflective foci (red arrow) and micraneurysms (white arrow).

HRFs are smaller than microaneurysms and don't cause back shadowing on OCT imaging

The ellipsoid zone (EZ) at the fovea was categorized as disrupted if it was not perfectly discernible but still partially visible.

All qualitative biomarkers were graded by two general ophthalmologists

RESULTS

The demographic characteristics of the study sample are presented in Table 1. The average age was 64,40 ± 13,01 years. Thirteen (22,41%) subjects had type I diabetes and 45 (77,59 %) type II diabetes. The mean HBA1c value, an indicator of glycemic control was 6,91 ± 0,90. The mean duration of the disease was 19,28 ± 12,73 years. HbA_{1c} levels and disease duration are primary long-term risk factors for diabetic complications and mortality, particularly regarding microvascular involvement. Systemic hypertension was present in 32 (55,17%) patients, the smoking status was recorded for 12 individuals, 6 (10,34 %) were current smokers and 6 (10,34%) were ex-smokers. Six (10,34 %) subjects reported alcohol consumption.

Table 1. Subject characteristics

Age (years)±SD	64,40 ± 13,01
Gender	39 (67%) M 19 (33%) F
Type of diabetes (number of patients)	Type 1 : 13 (22,41%) Type 2 : 45 (77,59 %)
Disease duration (years) ± SD	19,28 ± 12,73
HbA1c (%) ±SD	6,91 ± 0,90

Screening data from the Asl T0 5 Health Institute are reported in Table 2. In 2023 the Metabolism and Diabetes Unit at ASL TO 5 managed 6113 diabetic patients. Of these, 1618 underwent fundus photography using a non mydriatic fundus imaging system. Mild non proliferative retinopathy (NPDR) was diagnosed in 262 patients (16,2 %). The prevalence of NPDR in the ASL TO 5 diabetic population is lower than that reported in the literature, likely due to the effectiveness of a long-standing massive screening program initiated in 2003, which allows the early detection and management of disease stages. At these stages, diabetologists can improve glycemic control to reduce the risk of sight threatening retinopathy.

Table 2. Diabetic Retinopathy Grading in subjects screened on 2023

		Percentage (%)
Number of subjects screened for retinopathy on 2023	1618	26,5 %
Not DR patients	1314	81,2%
Mild NPDR patients	262	16,2 %
Moderate NPDR patients	38	2,3 %
Severe NPDR or proliferative DR	4	0,2 %

Total patients with diabetes followed by Diabetic Center of ASL To5 on 2023 : 6113

A total of 106 eyes with mild non-proliferative diabetic retinopathy were included in a retrospective analysis.

The mean CST was 276,25 ± 54,76 µm (range 228 – 596). The mean MV was 10,21 ± 0,59 mm_3 (range 8,7 – 11,4)

The prevalence rate (95% confidence interval) of borderline CST was 16,34 % (9,34 – 23,34%), which corresponds to 17 out of 106 eyes. The prevalence rate (95% confidence interval) of pathological CST was 5,76 % (1,76 - 9,76 %) affecting 6 out of 106 eyes.

Patients with borderline or pathological CST underwent comprehensive ophthalmological examination. The mean (± SD) BCVA measured with ETDRS charts for patients with borderline and pathological CST was logMAR 0,1 ± 0,05 and logMAR 0,30 ±0,10 respectively.

Patients with pathological CST were referred to the ophthalmological surgery unit of our health institute for treatment with intravitreal injections.

Eight patients underwent cataract surgery (13 eyes).

Table 3 shows quantitative OCT biomarkers

Table 3. Overview of the quantitative OCT biomarkers (106 eyes)

CST (normal range 257 – 295) (µm)	276,25 ± 54,76 range 228 - 596
MV (normal range 9,26 – 10,63) (mm_3)	10,21 ± 0,59 range 8,7 – 11,4
borderline (range 295 -350 µm) CST prevalence (95% confidence interval)	16,34 % (9,34 % – 23,34%),
pathological (> 350 µm) CST prevalence (95% confidence interval)	5,76 % (1,76 % - 9,76 %)

Four qualitative parameters were evaluated in 106 eyes. HRFs were detected in 61 eyes (57,54 %), microaneurysms and retinal hemorrhages in 29 eyes (27,35%), intraretinal fluid in 18 eyes (16,98%) and disrupted EZ in 10 eyes (9,43%)

Table 4 shows qualitative OCT biomarkers

Table 4. Overview of qualitative OCT biomarkers (106 eyes)

Eyes with presence of HRF (> 10 per eye)	61	57,54 %
Eyes with presence of retinal microaneurysm and retinal hemorrhages	29	27,35%
Eyes with presence of intraretinal fluid	18	16,98 %
Eyes with EZ disrupted	10	9,43 %

DISCUSSION

Currently SD- OCT represents the technique of choice for the detection and the follow up of diabetic maculopathy.

SD-OCT offers both quantitative and qualitative biomarkers in a non invasive and repeatable manner. For instance CST is extensively utilized in both clinical trials and practice. This examination is less commonly employed in the follow up of early stage of diabetic retinopathy.

In fact, for patients with mild diabetic retinopathy, many guidelines recommended an annual examination using fundus camera. This approach may overlook patients with early macular edema.

The primary cause of increased retinal thickness is intra- and subretinal fluid. Edema occurs as a result of breakdown of blood–retinal barrier and extravasation of lipids into the intraretinal space. CST can be easily measured on SD-OCT and is invaluable in assessing the degree of DME

Several groups have proposed classifications for DME that combine both quantitative and qualitative OCT measurements (6). Early DME is defined by the presence of small intraretinal cysts and an increase in CST and/or MV of less than 30% above maximum normal values (6). This stage of maculopathy often corresponds to a good visual acuity

In our sample the mean CST was 276 µm, which is still within the normal range. Nonetheless the prevalence rate (95% confidence interval) of borderline CST was 16,34 % (9,34 – 23,34 %). These patients require closer follow up than the current guidelines suggest. Particularly for those undergoing cataract surgery, early DME can pose a problem. At this stage of the disease ophthalmologists are less concerned, as the therapy of choice is to optimize metabolic control as best as possible, a field in which diabetologist is mainly involved and responsible.

Pathological CST was 5,76 % (1,76 - 9,76%). In these instances ophthalmological intervention is necessary, even though these individuals may not experience any decline in vision. Without OCT imaging these patients would have been missed. A subsequent clinical examination confirmed a lower BCVA due to macular edema.

However, close follow-up and early intervention are crucial for preventing disease progression and delaying or preventing sight threatening diabetic retinopathy. Optimal patient care requires tight collaboration between diabetologists and ophthalmologists, especially in the earlier stages of diabetic complications. In our health institutes in Turin this collaboration has been achieved through an integrated clinical pathway implemented in a primary care setting. The main tool facilitating this process has been a digital folder used by clinicians involved, allowing each specialist evaluate the overall progression of the disease and its complications.

HRFs may be observed in OCT imaging of both patients with type I and II diabetes, even without clinically significant diabetic macular edema or visual impairment. Several Authors (7-8) consider HRFs as useful markers for the diagnosis and follow-up in the early stages of diabetic retinopathy.

In our sample HRFs occurred in 59 out of 106 eyes, suggesting an inflammatory response causing an increase in vascular permeability (breakdown of the blood retinal barrier). It was postulated by several authors that the origin of HRSs is from activated microglia (8). Activation of microglial cells is often associated with perivasculitis and the release of inflammatory mediators such as VEGF which in turn can cause macular edema.

Another important OCT biomarker is the integrity of Ellipsoid Zone. The state of the outer retinal layers directly indicates the health of the retinal photoreceptors and retinal pigment epithelium. Eyes with an intact IS/OS junction typically experienced better visual gains post treatment. The IS/OS junction can be graded as completely continuous, partly disrupted or completely disrupted. Visual acuity has shown a positive correlation with the survival rate of the EZ (9). In our analysis the EZ was partly and more rarely completely disrupted in 10 eyes (9,43 %), this occurrence was always in eyes with intraretinal or subfoveal fluid. However the presence of DME was not always associated with a disrupted EZ. This feature is predictive of improvements in visual acuity after treatment.

Strengths and Limitations

The strength of this study lies in its retrospective analysis facilitated by the use of a digital folder shared between ophthalmologists and diabetologists. This integration allows for a comparative glance at OCT data, retinopathy screening data, metabolic control data and comorbidities. Multispecialty Data comparison is essential in an integrated care pathway and particularly crucial in the management of diabetic retinopathy.

A limitation of the current study is the sample size required for achieving a given maximum length of a confidence interval calculated using formulas from classical sampling theory. In the future, we intend to expand the sample size and initiate a prospective analysis, also to correlate OCT biomarkers with visual outcomes.

Additionally implementing an Intraclass Correlation Coefficient (ICC) between readers in the evaluation of qualitative biomarkers might improve inter-grader agreement and the reliability of their assessments.

CONCLUSION

OCT biomarkers can be useful for the diagnosis and follow-up in the early stages of diabetic retinopathy. SD- OCT already represents the technique of choice for the detection and the follow up of diabetic maculopathy. Even in mild forms, CST and MV are crucial for monitoring macular thickness and detecting early signs of macular edema. HRFs were the most frequently observed biomarkers in our sample indicating

an inflammatory response. Additionally the status of EZ is predictive of visual improvement following treatment. Both quantitative and qualitative OCT biomarkers can guide more accurate follow up strategies, ultimately enhancing patient care.

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