**Prevalence of focal inner, middle and combined retinal thinning in different stages of diabetic retinopathy using optical coherence tomography and its relationship with systemic and ocular parameters**

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**ABSTRACT**

**Purpose**: To determine the prevalence of focal inner, middle and combined inner and middle retinal thinning (FIRT, FMRT, and FCRT, respectively) in different stages of diabetic retinopathy (DR) using optical coherence tomography (OCT) and to assess the relationship between such findings with ocular or systemic parameters.

**Methods**: A cross-sectional, masked, comparative and consecutive study consisting of healthy subjects and diabetic patients with different stages of DR. Forty-nine horizontal macular scans of each eye were obtained using Spectral Domain—OCT (SD-OCT) and analyzed for the presence of FIRT, FMRT or FCRT and any relationship with systemic or ocular parameters.

**Results**: 380 eyes of 190 patients were examined. Although some diabetic patients without DR demonstrated focal retinal thinning (FRT), more prevalent and more severe FRT were observed in eyes with advanced DR, in comparison with the eyes of healthy subjects. Analysis revealed statistically significant positive correlation among FIRT, FMRT and FCRT. FRT was associated with coronary artery disease (CAD) and DR stages, positively correlated with diabetic duration, glycated hemoglobin levels and serum creatinine, and negatively correlated with visual acuity, estimated glomerular filtration rate, and choroidal thickness. No relationship was observed with age, gender, race, capillary blood glucose test (BGT), fast BGT, height, weight, diabetic type, systemic arterial hypertension, dyslipidemia, body mass index, axial length of the eye, systolic and diastolic blood pressure or macular central subfield thickness.

**Conclusion**: FRT occurs in all stages of DR and is increasingly prevalent with the severity of DR. Inner, middle and combined FRT is positively correlated. Patients with long diabetes duration, poor glucose control, renal dysfunction, or CAD are more susceptible to development of FRT that can lead to visual dysfunction.

**Introduction**

The study of the retinal microvasculature is of great importance because of its role in various retinal diseases that cause visual loss, including retinal vascular occlusion and diabetic retinopathy (DR).[1-3] One of the leading causes of blindness in the world,DR is known to cause inner retinal neurodegeneration (RND)[4] and damage to the macular microvasculature. The vascular mechanisms leading to disruption and dysfunction of the neurosensory retina include thickening of the basement membrane,[5] platelet aggregation,[6] leukocyte activation and adherence,[7] or some combination of the above. During this process tissue perfusion is compromised, causing ischemia at various levels of severity that leads to the production of vascular endothelial growth factor (VEGF).[8]

Dye based fluorescein angiography (FA) has been used for more than 50 years to study the retinal microvasculature, producing a wealth of knowledge about the normal and diseased retina[9]. However, only the superficial retinal capillary plexus (SCP) is well visualized using this ancillary modality and abnormalities in the intermediate (ICP) and deep retinal capillary plexus (DCP) are not optimally evaluated.[10]

While the SCP provides the main blood supply to the retinal nerve fiber layer (RNFL) and the ganglion cell layer (GCL), the ICP and DCP nourish the inner plexiform layer (IPL), the inner nuclear layer (INL), and the outer nuclear layer (ONL).[11, 12]. Disturbance of blood flow in these plexuses can lead to ischemia. SCP hypoperfusion clinically manifests in the acute phase as a cotton-wool spot (CWS) [13] illustrated as focal thickening and hyperreflectivity of the inner retinal layers with spectral domain optical coherence tomography (SD OCT).[14] Hypoperfusion of the DCP causes infarction of the INL and is acutely illustrated as a band of INL hyper- reflectivity with SD OCT referred to as paracentral acute middle maculopathy or PAMM.[15] Both CWS and PAMM lesions leave a legacy of thinning of the inner and middle retina respectively due to infarction and cell death.[1, 15].

Yu et al. in 2014, using multimodal imaging, described the presence of either focal inner retinal thinning (FIRT) or focal middle retinal thinning (FMRT) in diabetic patients and attributed these pathoanatomical findings to SCP and DCP ischemia respectively and demonstrated that both abnormalities disrupt visual function.[1] The prevalence of such findings in the diabetic population however, and its relationship with the severity of DR, is still unknown.

The purpose of this study was to ascertain the prevalence of focal inner and middle retinal thinning in different stages of DR using SD-OCT and to correlate the relationship of these findings with the severity of systemic and retinal disease.

**Methods**

 This observational, cross-sectional, consecutive, masked and comparative study was performed in accordance with the principles of the Declaration of Helsinki, approved by the Institutional Review Board Ethics Committee of our institution and informed consent was obtained from all patients prior to enrollment.

 The inclusion criteria included Type 1 and 2 diabetic patients without diabetic macular edema (DME) with best-corrected visual acuity (BCVA) better than or equal to 20/200 and healthy volunteer controls with BCVA of 20/20 on the Snellen chart. The exclusion criteria were: history of macular laser or pars plana vitrectomy, intraocular pressure greater than 21 mmHg, presence of cystoid macular edema (CME) or DME or any evidence of significant media opacity (e.g. cataract or vitreous hemorrhage) or any macular disorder including vitreous-macular traction syndrome, epiretinal membrane, macular hole, retinal vein occlusion, retinal infection, retinal dystrophy, or age related macular degeneration (e.g. macular drusen, macular choroidal neovascularization or macular atrophy).

 Two hundred and five (245) patients including healthy subjects were initially included in the study, and each was examined for the presence of one or more exclusion criteria. Of these 245 patients, 55 were excluded including 24 with DME, 4 with VMT syndrome, 8 with epiretinal membrane, 2 with lamellar macular hole, 14 with a history macular laser photocoagulation, 2 with glaucoma, and 1 with vitreous hemorrhage in both eyes.

 The 190 patients who remained in the study were given a questionnaire to determine age, gender, race, type and duration of diabetes, and presence of systemic disease including systemic arterial hypertension (SAH), dyslipidemia, and coronary artery disease (CAD). Their medical records were evaluated and medication and surgical history was ascertained. Blood pressure, weight and, height were then measured and body mass index was calculated. Finally, a blood test was requested for each patient to measure fasting blood glucose (FBG) and glycosylated hemoglobin or A1C. Capillary blood glucose (CBG) was performed in the enrollment visit. Serum creatinine was also measured for the purpose of calculating the estimated glomerular filtration rate (eGFR).[16]

All participants underwent an ophthalmologic examination consisting of BCVA using the Snellen chart at 4 meters, anterior segment slit-lamp examination, intraocular pressure measured by Goldmann applanation tonometry, and dilated biomicroscopic retinal examination with a 78-diopter lens. Ancillary testing included SD-OCT (Spectralis®, Heidelberg Engineering, Heidelberg, Germany) and biometry (IOL Master 500, Carl Zeiss Meditec AG, Jena, Germany) for axial length.

The patients were classified by severity of DR (i.e. mild, moderate, and severe nonproliferative diabetic retinopathy or NPDR and proliferative diabetic retinopathy or PDR according to the International Clinical Disease Severity Scale.[17] A PDR group with panretinal photocoagulation scars was also noted. SD OCT was performed with the Spectralis system with eye-tracking dual-beam technology (Heidelberg Engineering GmbH, Heidelberg, Germany) at 870 nm wavelength, using enhanced depth imaging, automatic real-time tracking and a camera for monitoring patient fixation to ensure image centralization. The SD OCT volume set was analyzed with the Heidelberg Eye Explorer (version 1.8.6.0) using the HRA/Spectralis Viewing Module (version 5.8.3.0). Scanning protocol included a 20 x 20 degree raster dense scan composed of 49 horizontal B-scans (512 A-scans per B-scan), high-resolution mode, with a 120-μm separation (Figure 1A). Image quality was rated by the machine (ratings above 20 were considered the threshold for inclusion). The cross-sectional images were analyzed with the built-in software.

Central subfield thickness (CST) was calculated by the automated Heidelberg SD-OCT software which measures the distance between the internal limiting membrane and the retinal pigment epithelium. The CST was then obtained from the 1000-μm diameter ETDRS (Early Treatment Diabetic Retinopathy Study) inner circle grid map placed over the macula. If an eye displayed any intraretinal cysts and/or a CST value greater than 320-μm for males and 305-μm for females,[18] a diagnosis of DME was rendered and the eye was excluded.

 Choroidal thickness (CT) was measured in the central subfoveal region, and 1000-μm temporal and nasal to the fovea, using the horizontal B-scan derived from the raster protocol passing through the foveola. CT was defined as the vertical distance between the posterior edge of the RPE band and the choroidal-scleral junction. Measurements were performed manually with the caliper tool of the incorporated software with 80% zoom. All SD-OCT scans were performed in the afternoon by a masked investigator (RG).

 FRT was subjectively defined as a recognizable tissue thinning surrounded by normal retinal thickness (Figure 1). Each of the 49-horizontal macular B-scans from 380 eyes were evaluated by two masked investigators (R.C.P and M.F.A) for the presence of focal inner retinal thinning or FIRT, focal middle retinal thinning or FMRT or focal combined retinal thinning or FCRT, so 18.620 B-scans were analyzed. A third investigator (L.C.Z) was consulted when the two raters disagreed. When thinning of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) was observed, it was recorded as FIRT (Figure 1B). The presence of focal retinal thinning of the inner plexiform layer (IPL), inner nuclear layer (INL) and outer plexiform layer (OPL) was classified as FMRT (Figure 1C). The presence of both inner and middle retinal thinning at the same SD-OCT B-scan position was recorded as FCRT (Figure 1D). The retina below major retinal vessels was eliminated from this analysis due to physiologic retinal thinning.

 The macula was divided into temporal and nasal regions to determine if thinning was more prevalent in either region. A binary method was used to record the presence, recorded as 1, or absence, recorded as 0, of FIRT, FMRT and FCRT, collectively referred to as FRT, in each of the 49 B-scans in the temporal and/or nasal. In any given temporal B scan, one broad or multiple narrow bands of thinning may be identified. In either example, the score was registered as 1 (i.e. present). The same methodology was applied to the nasal macular region (Figure 1). Intergrader analysis was performed to compare the scores of the 2 readers.

 Moreover, in order to enhance factors associated with the appearance of FRT, we assigned the presence of FRT in the inner or middle retinal layer as 1 point, since there is no universal consensus as to which one is more harmful. The presence of FCRT however, was recorded as 2 points, as it involves both the inner and middle layers and thus may be more severe. In this case, considering the presence of retinal thinning as points, we did the analyses of temporal and nasal macular regions, temporal FRT and nasal FRT, respectively and all points together were assumed as total FRT.

 To determine the *relationship* between FIRT, FMRT and FCRT or temporal FRT, nasal FRT and severity of FRT (based on total FRT) with qualitative factors [i.e. gender, race, DM type, DR stages, and presence of SAH, hypothyroidism, and coronary artery disease (CAD)] and quantitative factors (age, A1C, capillary BGT, fast BGT, height, weight, body mass index, systolic and diastolic blood pressure), and ocular parameters (visual acuity, axial length, CT, CST, and macular volume), we chose the eye with the best BCVA for the analysis. However, if the BCVA was the same in both eyes, the chosen eye was randomly selected for analysis. After analyzing the data from the randomly chosen right and left eye*s,* we then proceeded to analyze the data from *total cohort*, looking for any further correlations.

***Statistical analysis***

 The collected data were analyzed using descriptive statistics. Using the Shapiro-Wilk’s W Test, a non-normal distribution was found. The kappa statistic was used to test two interraters reliability. Fisher's Exact Test and Spearman’s Rho Test were used to determine any correlation among FIRT, FMRT, and FCRT. Spearman’s Rho Test was also used to determine any correlation between FRT in the right eyes (OD) and FRT in the left eyes (OS), and used to determine any correlation between any of three FRT (FIRT, FMRT and FCRT) and systemic or ocular *quantitative* variables. Finally, Mann-Whitney’s and Kruskal Wallis’s tests was used to determine any association between FRT and systemic *qualitative* variables [e.g., coronary arterial disease (CAD) and DR stage]. The level of statistical significance was defined as *P ≤* 0.05. All analyses were performed with the software IBM SPSS Statistics, v. 15.0 (SPSS Inc, Chicago, IL. USA).

**Results**

A total of 245 patients were screened and of these 190 met criteria. One hundred and thirty-five patients (71%) had their right eye selected for study; 55 patients (29%) had their left eye selected. Of these 190 enrolled patients, the mean age and standard deviation (SD) at presentation was 59 (14), ranging from 18 to 90 years. No statistical significant difference was observed between the age of healthy subjects and diabetic patients in each stage of diabetic retinopathy, P > 0.05. Of the total sample, 65 (34%) were male and 107 (56%) were Hispanic and 15 (8%) were Caucasian and 120 (87%) exhibited Type 2 diabetes. The mean (SD) A1C of enrolled patients was 8 (1.8), ranging from 4.7 to 13.1. Patient demographics and retinal and choroidal thickness measurements are summarized in Table 1. Intergrader analysis for the assessment of temporal and nasal FIRT, FMRT and FCRT for the right and left eyes was very high and calculated to be a kappa coefficient greater than 0.90.

FIRT, FMRT and FCRT were present in all DR stages. The prevalence of these findings increased significantly in the moderate non-proliferative DR stage (Figure 2A-D). The severity of FRT (as determined by the total FRT) in the healthy and DR groups was compared and a statistically significant incremental increase in severity of thinning was observed, from diabetic patients and no DR to the pan-retinal photocoagulated proliferative DR stages (Figure 2A Table 2). Among the various FRT categories, the presence of FCRT showed the most significant difference between the DR stages and healthy subjects (Figure 2B).

FRT was most revalent in the panretinal photocoagulated proliferative DR stage with a mean (SD) number of 21.5 (31.5), P = < 0.001 and most commonly identified in advanced DR stages (Table 2). The temporal macula of both eyes was the most prevalent region of FRT (Table 2). Considering each category of FRT based on the macular region affected, the mean (SD) number of temporal FCRT of the OD and of the OS were 2.33 (8.22) and 2.13 (6.93), respectively.

*Correlations among FRT*

 Correlations between FIRT, FMRT and FCRT of randomized eye in temporal and nasal macular regions of right and left eyes were analysed. Sperman's Coeficient Correlations and P value (*r, P*) between Temporal FIRT, FMRT and FCRT of right and left eye were (0.2, 0.04), (0.4, < 0.0001) and (0.5, < 0.0001). Sperman's Coeficient Correlations and P value (*r, P*) of nasal FIRT, FMRT and FCRT between right and left eye were (0.2, 0.004), (0.07, 0.40) and (0.3, 0.001). Every category of FRT in the right eye (except nasal FMRT) correlated positively with the left eye.

 When both macular regions of both eyes were analyzed, we also found a statistically significant positive correlation among FIRT, FMRT and FCRT in almost all measurements, with the greatest correlation between FIRT and FCRT (*r* = 0.343, P < 0.0001).

 *Correlation of FRT and qualitative systemic parameters*

When eyes with best BCVA of each patient was randomly chosen to assess the relationship between total FRT and *qualitative* systemic parameters (gender, race, DM type, DR stages, SAH, hypothyroidism, and CAD), only DR stages and CAD, demonstrated a statistical significant association, P < 0.0001 and P < 0.02, respectively. Among category of FRT, FIRT and FCRT demonstrated statistical significant association with DR stages, *P* < 0.002 and *P* < 0.0001, respectively, while FMRT did not show statistical significant association, *P* = 0.08. Only FCRT presented a statistical significant association with CAD, *P* = 0.017. There was no statistically significant association between FRT and gender, race, type of DM, SAH, dyslipidemia or hypothyroidism, *P* > 0.05.

When both eyes of the same patient were used for the above mentioned analysis, total FRT showed a statistical significant association with CAD and DR stages, *P* < 0.0001 and *P* > 0.0001, respectively. Among category of FRT, only FCRT presented a statistical significant association with CAD, *P* < 0.0001. However, FIRT, FMRT, and FCRT demonstrated statistical significant association with DR stages, *P* < 0.0001, P = 0.0002, and *P* < 0.0001, respectively. There was no statistically significant association between FRT and gender, race, type of DM, SAH, dyslipidemia or hypothyroidism, *P* > 0.05.

*Correlation of FRT and quantitative systemic parameters*

Table 3 illustrates the correlations found between temporal, nasal, and total FRT or inner, middle or combined FRT and *quantitative* systemic parameters. There are statistically significant correlations between total FRT and DM duration, A1C, eGFR, and serum creatinine not only with the eyes randomly chosen, but also when all the eyes were included in the analysis. Figure 3, illustrates these correlations in Scatter-Plot graphics. However, in relation to FRT category, when all eyes were included, all categories of FRT was only significantly correlated with diabetes duration, serum creatinine, and eGFR, and just FIRT showed statistical significant correlation with A1C. When only randomly eyes chosen were analyzed, there were less correlations with quantitative systemic parameters (Figure 3).

Among diabetic patients, sixty-four eyes (23%), 80 (30%), and 132 (47%) have eGFR (mL/min) =< 60, between 60-79 and => 80, respectively. When correlating total FRT with each eGFR category only eyes of patients with eGFR =< 60 demonstrated a statistically significant negative correlation r = - 0.4, P = 0.001. Correlation between eyes of patients with eGFR (mL/min) between 60-79 and => 80 did not showed a statiscally significant difference, r = - 0.091, P = 0.4 and r = - 0.15, P = 0.08, respectively.

*Correlation between FRT and quantitative ocular parameters*

When analyzing the eyes randomly chosen, we did not found any correlation between category of FRT or total FRT with ocular parameters. However, when all the eyes were analyzed, total FRT correlated negatively with VA (r = - 0.14, *P* = 0.02). Also, both temporal and nasal total FRT correlated negatively with VA (r = - 0.12, *P* = 0.046) and (r = - 0.16, *P* = 0.008), respectively. Nevertheless, total FRT did not correlate with axial length (*r* = 0.17), subfoveal CT (*r* = 0.08), temporal CT (*r* = 0.07), nasal CT (*r* = - 0.002), CST (*r* = - 0.01) or MV (*r* = 0.19), *P* > 0.05 for all correlations, even when each macular region was evaluated separately.

When analyzing FIRT, FMRT and FCRT for all the eyes, the correlations with VA were (r = -0.045, P = 0.45), (r = - 0.132, P = 0.028), and (r = -0.074, P = 0.219), respectively. FCRT was the only that showed a negative correlation with CT, subfoveal CT (r = -0.155, P = 0.010), temporal CT (r = -0.154, P = 0.010), and nasal CT (r = -0.122, P = 0.042), even when the correlation analysis was performed without panretinal-photocoagulated PDR eyes, subfoveal CT (r = -0.136, P = 0.03), temporal CT (r = -0.143, P = 0.023), and nasal CT (r = -0.106, P = 0.092), respectively.

**Discussion**

Our study demonstrates that FRT is observed in all DR stages, even in patients with no clinical signs of DR on fundus examination when comparing with healthy subjects (Figure 2A)—a consequence of retinal diabetic neuropathy [19] or retinal microvascular thrombosis which drives retinal capillary non-perfusion and consequent tissue death and thinning. This phenomenon is mainly driven by the leukostasis mechanism.[20] Our study further demonstrates that FRT is more prevalent in severe DR stages especially in in PDR eyes with pan-retinal photocoagulation scars. A result already expected since severe stages of DR have more vascular and neural damage.

Agemy et al recently published a study using OCT angiography that demonstrated reduction in retinal capillary plexus density, resulting from microangiopathy of DR, in direct proportion to worsening DR—a finding that seems to corroborate our study’s results.[21] Moreover, it was published that flow deficit of capillary plexus cause FRT in the same site demonstrating that severe reduction in retinal capillary plexus density can be considered as synonymous with FRT. [22]

FCRT was the most prevalent category of FRT in our study, followed by FIRT, then FMRT. The data reveal positive correlations among all of these conditions. Thus, the presence of FRT in any one of the layers may signal the presence of thinning in the other layers of the macular region as well. This is because DM causes diffuse vascular thrombosis lesions induced by leukocyte adhesion molecules,[7] hypercoagulability,[23] and neuropathy abnormalities throughout the retina.[19]

One potential reason that FIRT was more prevalent than FMRT in this study could be related to the prevalence of systemic arterial hypertension (SAH) which is known to be associated with cotton wool spot (CWS) formation and subsequent FIRT.[3, 24] SAH is typically present in more than 50% of patients with DM, and contributes significantly to both microvascular and macrovascular disease.[25] Moreover, published studies have shown that SAH correlates with severity and progression of DR.[26-28]. In our study 80.7% of DM patients presented with a history of concomitant SAH, although no statistically significant association was found between SAH and any FRT category. This lack of correlation may be due to the number of patients in our study (76, 52.4%) who had NPDR with a duration of DM less than 10 years, and/or to the number of women in our study—both factors found to be associated with a lower prevalence of FIRT. [29]

Considering retinal diabetic neuropathy (RDN) as another cause of FRT was the reason why we have adopted the term retinal thinning instead of retinal plexus ischemia. RDN seems to be a result of inner neuroretinal degeneration and consequent inner retina thinning a condition that occurs even in the absence of retinal microangiopathy.[4] However, the studies published have only demonstrated diffuse inner retinal layer thinning,[19] instead of FRT as demonstrated by Yu et al.[1] and it is why we think that the FRT is more related to capillary plexus ischemia.

It was demonstrated that damage to inner retinal layer can lead to FRT that causes visual dysfunction.[1] The variability of VA, particularly in the earlier stages of DR, makes it very difficult to conclusively identify VA’s potential correlations with macular ischemia. The majority of patients in our study sample presented with early DR.[30] Some published studies using OCTA[31] and FA,[30] have demonstrated a weak correlation between macular ischemia and VA. Similarly, our study did not find a strong correlation with FRT and VA.

Unexpectedly, however, our results, evaluating only SD OCT tomograms, definitively implicated FMRT as the responsible correlative factor with VA. Moreover, our findings corroborate the results of Bénédicte Dupas et al, who, using the OCTA methodology, also showed significant reduction of VA when there is a capillary loss of DCP, but not in the SCP.[32] It is important to note that our study did not evaluate the presence or extent of macular ischemia, nor the prevalence or frequency of FRT affecting only the foveal avascular zone.

Usui et al have postulated that the reason VA appears to be more deleterious in the presence of DCPi than SCPi involves amacrine and horizontal cells forming highly interdependent neurovascular units with capillaries in the intermediate CP and DCP. The authors demonstrated that damage to 1 or both of these plexuses interferes with photoreceptor survival and function,[33] (presumably resulting in loss of visual function). These results, while important, are inconclusive and warrant further study.

An important study published in the 1980s noted that the presence, severity and progression of DR significantly correlated with the duration of DM, A1C level, and proteinuria. [29] We intentionally selected these variables for analysis using our OCT methodology, and our study confirmed statistically significant correlations between FRT and DM duration, A1C levels, eGFR and serum creatinine (Table 3). FRT was more prevalent in advanced stages of DR. These results strongly suggest that the above-mentioned variables influence the appearance and progression of DR by, among other mechanisms, causing ischemia that drives the release of VEGF.

 Both serum creatinine and eGFR tests are used to assess kidney function. eGFR is widely perceived to be the more accurate method. Published studies have shown that lower levels of eGFR are independently associated with higher prevalence and greater severity of DR.[34-36] Our study revealed a statistically significant positive correlation between serum creatinine and FRT. The data further showed that almost one quarter of the diabetic patients had eGFR less than 60 (mL/min) and demonstrated a statistically significant negative correlation with FRT only in this level. Patients with eGFR more than 60 (mL/min) did not showed such correlation.

These results most likely reflect the fact that diabetic nephropathy and DR share similar risk factors and pathophysiological pathways, including injury of small vessels in the retina and glomerulus from chronic hyperglycemia; oxidative stress; and concomitant hypertension.[37] However, renal dysfunction can worse retinal ischemia as well, by causing vascular endothelial dysfunction and increasing coagulation factors (D-dimer, fibrinogen, Factor VII, and especially Factor VIII and von Willebrand) that even aggravate with the advance of renal injury, which can explain the ischemia followed by cell death and consequent tissue thinning.[38] Some mechanisms can explain the relationship of lower eGFR and higher levels of haemostatic factors. Renal dysfunction, results in impaired excretory function and a reduction in the removal of procoagulant substances.[39] Also, patients with renal injury have changes in the blood levels of various inflammatory cytokines.[40] that can activate procoagulant factors resulting in an increased levels of especific haemostatic factors.

In our study CAD was associated with FRT. Studies have shown an association between DR and cardiovascular disease in diabetic patients, probably because, as in the case of diabetic nephropathy, they may share common pathophysiological mechanisms.[41] Our results warrant studies in diabetic patients after coronary event to demonstrated if there is a worsening in the DR and, consequently more retinal plexus ischemias and retinal thinning due to  altered blood flow properties.

Among the limitations of our study is the subjectivity of the classification of FRT. Nevertheless, this classification subjectivity does not diminish the efficacy of our methodology, because there was high intergrader agreement, and we observed correlations between right and left eyes, both of which are similarly affected by diabetes in each individual. Another fact that attenuates the subjective classification bias is our study’s inherent underestimation of the prevalence of FIRT and FMRT: only tissue thinning severe enough to be recognized in the B-scan was recorded; subtle or microscopic FRT went unrecorded because it could not be identified using actual SD-OCT technology.

Another concern of our study was the small number in another group comprised of patients with PDR; however, the potential bias posed by this limitation in number may have been partially offset by the high prevalence of FRT in this group. Finally, despite the fact that a large proportion of enrolled patients presented with SAH, the entire study sample reflected a reliable representation of society, as concomitance of the two diseases is common.[42]

In conclusion, FRT occurs in all stages of DR and is increasingly prevalent with the severity of DR. The presence of FIRT, FMRT and FCRT is positively correlated. Patients with long duration diabetes, renal dysfunction, poor glucose control or CAD are more susceptible to development of FRT that can lead to visual dysfunction.

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**Figures**

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**Figure 1.** A, Right eye of 55-years-old male diabetic patient illustrating the 49 temporal and nasal B-scans from where the presence of inner, middle and combine focal retinal thinning, FIRT, FMRT and FCRT, respectively, was recorded. B, left eye showing in the 7th B-scan, the presence of a FIRT in the temporal macula of a 52-years-old female patient with proliferative diabetic retinopathy (DR). C, right eye of a 55-years-old male patient with mild DR demonstrating in the 11th B-scan, a FMRT lesion in the nasal macula. D, left eye of a 59-years-old female patient with severe DR exhibiting in the 47th B-scan a FCRT in the superior nasal macula.

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**Figure 2**. Box-plot of total points focal retinal thinning (FRT), FCRT, focal middle RT (FMRT), and focal inner RT (FIRT), A, B, C, and D, respectively.



**Figure 3**. Scatterplot of total focal retinal thinning (N = 277) versus; A, duration of diabetes; B, glycated hemoglobin; C, estimated glomerular filtration rate, and D, serum creatinine.

**Tables**

**Table 1**

|  |
| --- |
| **Table 1. Baseline characteristics data of included patients**  |
| Age (years), mean (SD) | 59 (14)  |
| Sex: men. N (%) | 88 (46%) |
| **Race/ethnicity. N (%)** |
|  Black/ African American | 59 (31%) |
|  Hispanic or Latin | 117 (61%) |
|  Caucasian | 15 (8%) |
| Controle N [(%), mean age (SD) years]\* | 52 [(27%), 58 (14)] |
| **DM\*\* type** |
|  Type 1 | 18 (12.4%) |
|  Type 2 | 120 (82.8%) |
| Fast BGT\*\*, mean (SD) | 153 (75) |
| Capillary BGT\*\*, mean (SD) | 158.5 (79) |
| A1C\*\* (%), mean (SD) | 8 (1.8) |
| DM\*\*, mean duration (SD) (years) (N, % ≤ 10 years)  | 12.6 (8.3) (76, 52.4%)  |
| Presence of SAH\*\* in DM patients(%) | 117 (80.7%) |
| eGFR\* mean, (SD) | 80.4 (34) |
| Presence of dyslipedemia (%) | 19 (13.1%) |
| Seric creatinine , mean (SD) | 1.27 (1.2) |
| Axial length (μm), mean (SD) | 23.12 (0.8) |
| **Blood pressure** Systolic blood pressure (mmHg), mean (SD) | 135.31 (22) |
|  Diastolic blood pressure (mmHg) mean (SD) | 81.13 (11.1) |
| Visual acuity (Snellen), mean (SD) | 0.8 (0.2) |
| Height (cm), mean (SD)  | 164.10 (9.7) |
| Weight (kg), mean (SD) | 75.46 (16) |
| Body mass index, mean (SD) | 28.7 (5.5) |
| Presence of CAD among diabetic patients\*\* | 4 (2.8%) |
| **DR classification [**N (%), mean age (SD) years] |
|  DM without DR\*\*  | 70 (48.3%), 58 (13) |
|  Mild NPDR\*  | 24 (16.6%), 63 (17) |
|  Moderate NPDR\*\*  | 19 (13.1%), 64 (10) |
|  Severe NPDR\*\*  | 6 (4.1%), 49 (15) |
|  PDR\* \*  | 5 (3.4%), 61 (5) |
|  PDR and PRP\*\*  | 14 (9.7%), 55 (13) |
| CST\*, mean (SD) | 274 (39) |
| Macular volume (mm3)ean (SD) | 8.52 (0.8) |
| CT\*\* (μm) 1000 T,\*\* central, 1000 N,\*\* mean (SD) μm | 1. (83). 274(88). 262 (88)
 |

\* No age statiscal significant difference was observed between healthy subjects and different stages of diabetic retinopathy

\*\*Legends: DM, diabetes mellitus; BGT, blood glucose test; HbA1C, glycated hemoglobin; SAH, systemic arterial hypertension; eGFR, estimated glomerular filtration rate; CAD, cardiovascular arterial disease; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; CST, central subfield thickness; CT, choroidal thickeness; T, temporal; N, nasal.

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| **Table 2. Frequency of focal retinal thinning (FRT) in healthy subjects and diabetic patients in total number (#) of eyes, per macular region and in each eye by category of FRT** |
| **Frequency of all category of FRT**  |
| **Patient** | **DR stage** | **# of eyes** | **Mean** | **Standard Deviation (SD)** | ***P*** |
| healthy subjects |  | 104 | 1.25 | 5.80 |  |
| DM |  DM without DR | 140 | 3.52 | 10.39 |  **= 0.001** |
|  Mild NPDR | 48 | 3.52 | 6.77 | **<0.001** |
|  Moderate NPDR | 38 | 15.85 | 34.13 | **<0.001** |
|  Severe NPDR | 12 | 9.27 | 11.89 | **<0.001** |
|  PDR  | 10 | 14.63 | 22.27 | **<0.001** |
|  PDR and PRP | 28 | 48.72 | 62.07 | **<0.001** |
|   |  Total | 380 | 9.6 | 26.94 |   |
| **Frequency of all category of FRT per each macular region** |
| **Patient** | **DR stage** | **# of eyes** | **Mean temporal FRT (SD)** | **Mean nasal FRT (SD)** | ***P* (temporal/Nasal)** |
| healthy subject |  | 104 | 1.0 (5.4) | 0.2 (1.1) |  |
| DM |  DM without DR | 140 | 2.1(7.9) | 1.4(4.4) | **(0.03/0.004)** |
|  Mild NPDR | 48 | 2.3(4.8) | 1.2(2.9) | **(<0.001 /0.004)** |
|  Moderate NPDR | 38 | 8.8(19.7) | 7.1(15.8) | **(<0.001 /<0.001)** |
|  Severe NPDR | 12 | 7.1(8.2) | 2.2(4.2) | **(<0.001** /**<0.001)** |
|  PDR  | 10 | 9.9(16.2) | 4.7(8.9) | (**<0.001** /**<0.001**) |
|  PDR and PRP | 28 | 30.5(33.6) | 18.3(31.2) | **(<0.001/<0.001)** |
|   |  Total | 380 | 5.9(16) | 3.7(12.3) |   |
| **Frequency of category of FRT in each DR stages** |
| **Patient** | **DR stage** | **# of eyes** | **FIRT (SD)** | **FMRT (SD)** | **FCRT (SD)** |
| healthy subject |  | 104 | 0.25 (1.2) | 0.15 (0.7) | 0.4 (2.3) |
| DM |  DM without DR | 140 | 1 (3.8) | 0.3 (0.8)\* | 1.1 (4.1)\* |
|  Mild NPDR | 48 | 0.9(2.1)\* | 0.5 (2.0) | 1.1 (2.7)\* |
|  Moderate NPDR | 38 | 2.8(6.0)\* | 1.1 (2.3)\* | 6.0 (16.5)\* |
|  Severe NPDR | 12 | 3.6(5.0)\* | 2.2 (2.6)\* | 1.7 (4.0)\* |
|  PDR  | 10 | 2.4(2.8)\* | 0.5 (1.1) | 6.0 (10.0)\* |
|  PDR and PRP | 28 | 5.0 (6.1)\* | 0.7 (2.2)\* | 21.5 (31.5)\* |
|   |  Total | 380 | 1.33(3.78) | 0.4 (1.4) | 2.8 (11.5)  |

\*p < 0.05 comparing FRT of diabetic patients with healthy subjects

**Legends**: DR, diabetic retinopathy DM, diabetes mellitus; BGT, blood glucose test; HbA1C, glycated hemoglobin; SAH, systemic arterial hypertension; eGFR, estimated glomerular filtration rate; CAD, cardiovascular arterial disease;; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; CT, choroidal thickeness; FRT, focal retinal thinning; FIRT, focal inner retinal thinning; FMRT, focal middle retinal thinning; FCRT, focal combined retinal thinning.

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| **Table 3 . Sperman's Coeficient Correlations among total FRT and category of FRT with systemic quantitative parameters**  |
| **Correlation among randomly eyes and temporal, nasal and total FRT** |
|   | **Age** | **DM\* duration** | **capillary BGT\*** | **fast BGT\*** | **A1C\*** | **eGFR\*** | **serum creatinine** | **height** | **Weight** | **BMI\*** | **SBP\*** | **DBP\*** |
| **Temporal FRT\*** | *r* | .169\* | **.289\*\*** | .018 | -.011 | **.189\*** | **.252\*\*** | **.262\*\*** | .067 | -.082 | .090 | .058 | -.071 |
| *P* | **.044** | **<0.0001** | .833 | .894 | **.024** | **.002** | **.002** | .423 | .328 | .284 | .491 | .403 |
| **Nasal FRT\*** | *r* | -.067 | .128 | .057 | -.125 | .085 | **-.171\*** | **.225\*\*** | .231\*\* | .015 | -.045 | .017 | -.131 |
| *P* | .426 | .128 | .499 | .136 | **.**314 | **.041** | **.007** | **.005** | .862 | .597 | .838 | .122 |
| **Total FRT\*** | *r* | -.143 | **.225\*\*** | .045 | -.072 | **.165\*** | **.263\*\*** | **.310\*\*** | .171\* | -.064 | .113 | .009 | -.083 |
| *P* | .088 | **.007** | .597 | .391 | **.050** | **.002** | **<0.0001** | **.041** | .448 | .179 | .918 | .325 |
| **Correlation among all eyes and temporal, nasal and total FRT**  |
|  | **Age** | **DM\* duration** | **capillary BGT\*** | **fast BGT\*** | **A1C\*** | **eGFR\*** | **serum creatinine** | **height** | **Weight** | **BMI\*** | **SBP\*** | **DBP\*** |
| **Temporal FRT\*** | *r* | .129\* | **.288\*\*** | .027 | -.003 | **.150\*** | **.285\*\*** | **.284\*\*** | .049 | -.102 | .097 | .075 | -.060 |
| *P* | **.031** | **<0.0001** | .658 | .965 | **.012** | **<0.0001** | **<0.0001** | .415 | .089 | .107 | .216 | .322 |
| **Nasal FRT\*** | *r* | -.037 | **.182\*\*** | .012 | -.091 | .062 | **.191\*\*** | **.217\*\*** | .109 | -.017 | .002 | .010 | .151\* |
| *P* | .535 | **.002** | .843 | .131 | .302 | **.001** | **<0.0001** | .070 | .777 | .967 | .870 | .**012** |
| **Total FRT\*** | *r* | -.101 | **.253\*\*** | .030 | -.055 | **.119\*** | **.296\*\*** | **.318\*\*** | .081 | -.093 | .093 | .034 | -.095 |
| *P* | .093 | **<0.0001** | .614 | .362 | **.049** | **<0.0001** | **<0.0001** | .179 | .125 | .122 | .571 | .117 |
| **Correlation among randomly chosen eyes and category of FRT** |
|  | **Age** | **DM\* duration** | **capillary BGT\*** | **fast BGT\*** | **A1C\*** | **eGFR\*** | **serum creatinine** | **height** | **Weight** | **BMI\*** | **SBP\*** | **DBP\*** |
| **FIRT\*** | *r* | -,164 | **,197\*** | ,103 | ,012 | **,252\*\*** | -,091 | **,165\*** | ,141 | ,065 | ,053 | -,039 | -,073 |
| *P* | ,051 | **,018** | ,220 | ,886 | **,002** | ,278 | **,049** | ,094 | ,440 | ,533 | ,648 | ,386 |
| **FMRT\*** | *r* | -,022 | ,122 | ,073 | -,120 | ,020 | **-,257\*\*** | **,286\*\*** | **,172\*** | -,037 | -,117 | ,041 | ,069 |
| *P* | ,793 | ,147 | ,389 | ,155 | ,812 | **,002** | **,001** | **,040** | ,662 | ,163 | ,632 | ,417 |
| **FCRT\***  | *r* | -,107 | ,156 | ,028 | -,058 | ,146 | **-,218\*\*** | **,264\*\*** | ,053 | -,091 | -,072 | ,009 | -,107 |
| *P* | ,205 | ,063 | ,736 | ,492 | ,082 | **,009** | **,001** | ,529 | ,280 | ,394 | ,915 | ,203 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Correlation among all eyes with category of FRT** |
|  | **Age** | **DM\* duration** | **capillary BGT\*** | **fast BGT\*** | **A1C\*** | **eGFR\*** | **serum creatinine** | **height** | **Weight** | **BMI\*** | **SBP\*** | **DBP\*** |
| **FIRT\*** | *r* | -.117 | **.214\*\*** | .102 | .009 | **.206\*\*** | **-.148\*** | **.211\*\*** | .081 | .004 | .028 | .029 | -.075 |
| *P* | .051 | **<0.0001** | .090 | .885 | .**001** | **.014** | **<0.0001** | .180 | .949 | .645 | .636 | .216 |
| **FMRT\*** | *r* | -.018 | **.149\*** | .025 | -.106 | -.026 | **.238\*\*** | **.253\*\*** | .082 | -.072 | .080 | .035 | -.031 |
| *P* | .761 | **.013** | .676 | .079 | .671 | **<0.0001** | **<0.0001** | .174 | .230 | .186 | .561 | .604 |
| **FCRT\***  | *r* | -.069 | **.188\*\*** | -.003 | -.032 | .095 | **.229\*\*** | **.249\*\*** | .021 | -.048 | .003 | .032 | -.102 |
| *P* | .250 | **.002** | .958 | .593 | .116 | **<0.0001** | **<0.0001** | .730 | .430 | .964 | .601 | .092 |

\*BGT, blood glucose test; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP; systolic blood pressure; DBP, diastolic blood pressure; FRT, focal retinal thinning; FIRT, focal inner retinal thinning; FMRT, focal middle retinal thinning; FCRT, focal combined retinal thinning.