Longitudinal Study of Diabetic Retinopathy and Correlation of Renal Insufficiency with OCT and OCTA Abnormality

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BACKGROUND AND AIMS

Diabetes mellitus (DM) is the most common cause of vision loss in the working population and one of the most feared consequences of DM. Vision loss in DM most commonly occurs as diabetic retinopathy (DR),[1] which is characterized by a combination of metabolic syndrome-induced retinal and optic nerve vascular disease and microaneurysms, leading to ischemia, hemorrhage, edema, and neurodegeneration. Given retina is one of the most metabolically active part of the body, it's no surprise that DR is highly correlated with end-organ damage, peripheral neuropathy, and cognitive decline.[2,3] DR is graded as 5 stages, from no vasculopathy (grade 0) to non-proliferative DR (grades 1-3), and proliferative DR (grade 4).[4] Important unmet needs in the field include the lack of good early diagnostic and prognostic biomarkers of DR *prior* to the development of vision loss. In this study, we analyze over 450 DM and control eyes using >100 ophthalmic parameters per eye and assay longitudinal visual outcomes 4-7 years later.

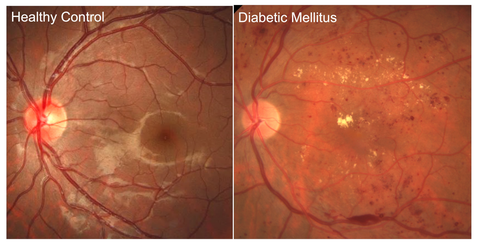

Figure 1. Representative color fundus imaging of healthy and diabetic left eyes. Compared with control eye, DM eye has innumerable retinal microhemorrhages, yellowish exudates, macular edema, and narrowed arterioles –classic ophthalmic imaging findings of diabetic retinopathy.

METHODS

We performed a case-control study of over 130 patients with DM (313 eyes) and 67 controls (95 eyes) with clinical assessment of DR grade (confirmed by retina specialist) and optical coherence tomography (OCT) and angiography (OCTA) at Byers Eye Institute, Stanford University, between December 2017 and October 2018. We used custom scripts to extract patient demography, past medical history, and all relevant clinical and laboratory between 2014 and 2022 (85% with multiple follow-up measurements over 4-7 years) using the Stanford IRIS Registry ((Intelligent Research in Sight) database, the nation's first comprehensive eye disease clinical registry. All macular and peripapillary OCT and 3 x 3 mm superficial capillary plexus OCTA (AngioPlex, Zeiss) were analyzed using automated segmentation (OCT) and custom MATLAB script that removed large vessels and created an annulus for region of interest.[5] We measured over 100 ophthalmic imaging parameters per eye, including OCT retinal fiber layer and macular ganglion cell complex thickness, total macular thickness, and 6 OCTA vessel parameters: vessel area density, vessel skeletal (length) index, vessel complexity, vessel diameter, vessel perimetric index, and flow impairment for each of the regions of interest: annulus, 4 peripapillary quadrants (like retinal nerve fiber layer), 6 Garway-Heath map sectors, 6 macular sectors (like macular ganglion cell complex), and 4 macular cross quadrants (correspond to visual field representation of the macula).

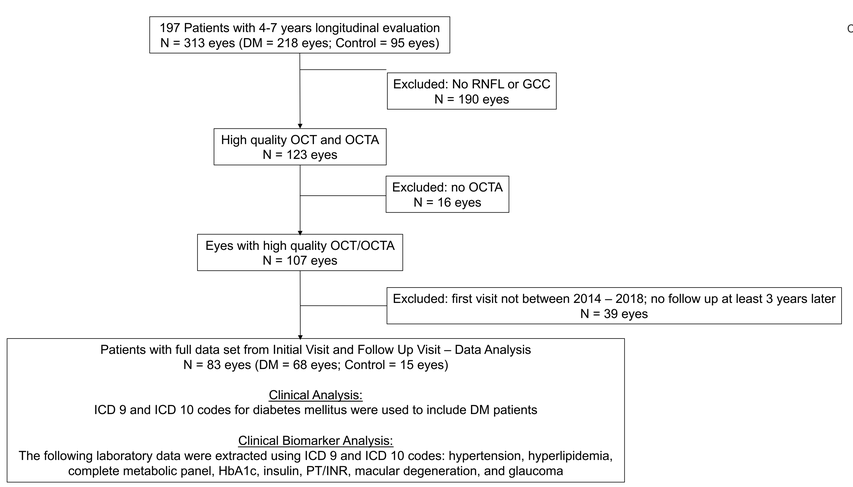

Figure 2. Flowchart of ophthalmic imaging analysis in patients with diabetic mellitus.

RESULTS

VISUAL ACUITY RELATIVELY STABLE AFTER 4-7 YEAR FOLLOW UP

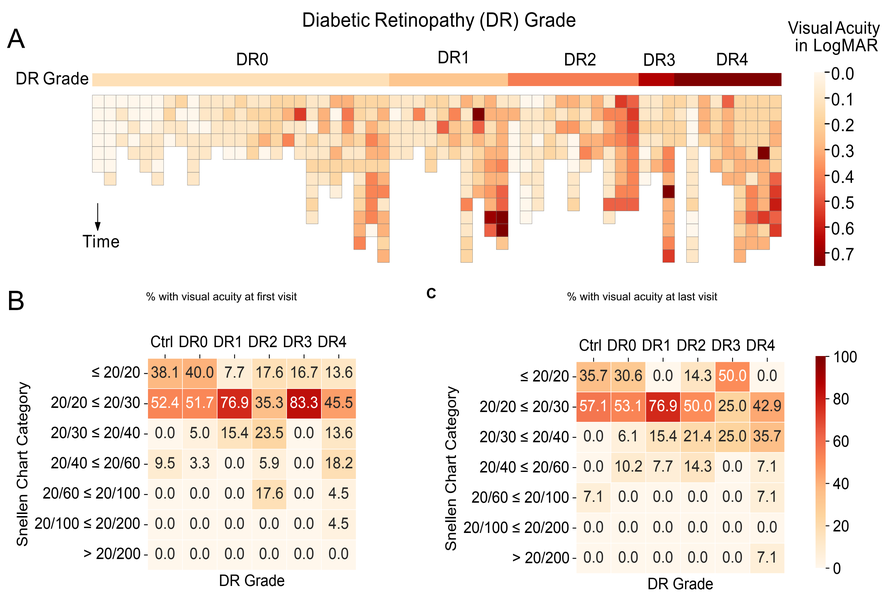

Figure 3. A. Heatmap illustrating visual acuity of individuals within each diabetic retinopathy grade over time. Subjects are arranged by average LogMAR within each DR grade and darker colors are used to indicate a worsening of visual acuity. The pattern indicates an association between severity of DR grades and visual acuity: DR0 subjects have fewer cases of LogMAR > 0.50 as compared to other DR grades. **B.** Percentage (%) of subjects with different categories of visual acuity by Snellen chart at first clinic visit (baseline) and **C.** last clinic visit (follow-up at least 4-7 years after baseline).

HYPERGLYCEMIA AND RENAL FAILURE CORRELATED WITH WORSE RETINOPATHY

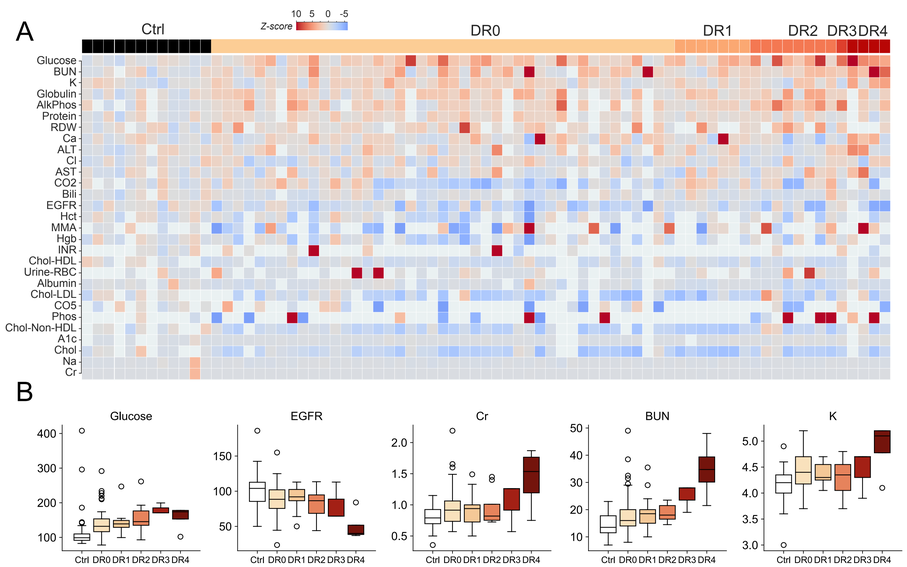

Figure 4. A. Heatmap illustrating 45,221 data points of clinical blood tests of healthy controls (Ctrl) and individuals with different diabetic retinopathy grades (DR0-4). Higher A1c and renal function tests are more common in patients with moderate to severe DR. (DR 2: moderate DR. DR3: severe non-proliferative DR. DR 4: severe proliferative DR with neovascularization.) Values are standardized by the distribution of the control group. **B.** Boxplots illustrating the unstandardized blood test values of glucose, EGFR, Cr, BUN and K. Glucose, Cr, BUN and K show an increasing trend with DM severity, while EGFR decreases. The axis for Cr is restricted at 2.5 for presentation purposes: one DR4 patient had a Cr reading of 7.0.

MICROVASCULAR DROPOUT AROUND OPTIC DISC BUT NOT MACULA CORRELATED WITH NEURODEGENERATION

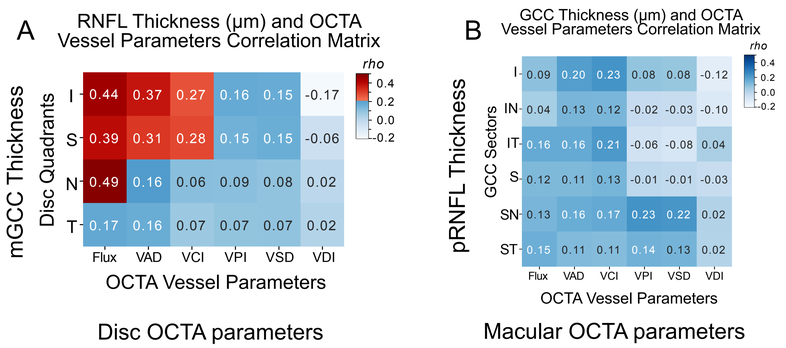

Figure 5. Spearman's *rho* correlation matrix of OCT vs. OCTA measurements in DM eyes revealed significant correlation of OCTA vascular flux, vessel area density, and vessel complexity index with OCT thickness of optic nerve unmyelinated axons due to neurodegeneration but not with inner retinal macular ganglion cell complex, where macular edema often occurs. **A.** Optic disc peripapillary retinal fiber layer (pRNFL) quadrants thickness vs. 6 peripapillary microvascular parameters (I: inferior, S: superior, N: nasal, T: temporal). **B.** Macular ganglion cell complex sector thickness vs. 6 macular OCTA measurements (IN: inferonasal, IT: inferotemporal, SN: superonasal, ST: superotemporal sectors). Red: statistical significance after Bonferroni correction for multiple comparisons, blue: non-significance. The gradient of color illustrates correlation strength.

SUMMARY AND CONCLUSIONS

We performed a case-control retrospective study of 197 adults and 313 eyes of patients with diabetes mellitus and healthy controls and analyzed 45,221 data points of clinical blood laboratory values and over 100 ophthalmic functional and structural parameters per eye, including optic disc and macular retinal microvascular measurements and found:

1. Longitudinal evaluation over 4-7 years revealed that the majority of patients followed at the Stanford Eye Clinic have relatively stable visual acuity.
2. Elevated hyperglycemia and evidence of renal failure are more common in those with moderate to severe diabetic retinopathy.
3. Optic disc and macular thickness on OCT and vascular parameters on OCTA correlated with severity of diabetic retinopathy and can be found even in those without clinical evidence of diabetic retinopathy based on examination and fundus color imaging (grade DR0).
4. The severity of diabetic retinopathy is graded by evidence of vasculopathy. Vascular analysis using OCTA of the most vulnerable layer of the retina (superficial capillary plexus) revealed significant correlation of neurodegeneration of the unmyelinated optic nerve axon with 3 vascular parameters (vessel flux, vessel area density, and vessel complexity index) in the superior and inferior peripapillary quadrants – the areas most significantly affected in DM.

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