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The Relationship of Retinal Vessel Geometric Characteristics to the Incidence and Progression of Diabetic Retinopathy

Ronald Klein, MD, MPH¹, Kristine E Lee, MS¹, Lorraine Danforth, BS¹, Michael Y. Tsai, PhD², Ronald E. Gangnon, PhD³, Stacy E. Meuer, BS¹, Tien Y. Wong, MD, PhD⁴, Carol Y. Cheung, PhD⁵, and Barbara E.K. Klein, MD, MPH¹

¹Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Madison, WI, United States.

²Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, United States.

³Population Health Sciences, University of Wisconsin-Madison, Madison, WI, United States.

⁴Ophthalmology & Visual Sciences, Duke-NUS Medical School, Singapore.

⁵Ophthalmology and Visual Sciences, The Chinese University of Hong Kong.

Abstract

Purpose—To examine the relationships of retinal vessel geometric characteristics (RVGCs) to the incidence and progression of diabetic retinopathy (DR).

Design—Observational prospective cohort study.

Participants—There were 996 persons with type 1 diabetes (T1DM) and 1370 persons with type 2 diabetes (T2DM) seen at a baseline examination. These persons were eligible for follow-up examinations at subsequent 5 year intervals. A total of 3,846 person-interval data from these follow-up examinations are the basis for the analyses.

Methods—DR and macular edema were assessed by grading of 30° stereoscopic color fundus photographs. RVGCs were assessed using the Singapore I Vessel Assessment (SIVA) program from a digitized copy of one of the field 1 fundus photographs taken at baseline and follow-up.

Main Outcome Measures—The 5-year incidence of any DR, progression of DR, incidence of proliferative diabetic retinopathy (PDR) and clinically significant macular edema (CSME) in right eyes.

Results—Incident DR occurred in 45%, progression in 32%, PDR in 10% and CSME in 5%. While adjusting for glycated hemoglobin, duration of diabetes, mean arterial blood pressure and

Correspondence to, Ronald Klein, MD, MPH, Dept. of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, 610 Walnut Street, 417 WARF, Madison, WI 53726-2336, (608) 263-7758, FAX (608) 263-0279, kleinr@epi.ophth.wisc.edu.

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Conflicts of Interest: Tien Y. Wong is a named inventor of the Singapore I Vessel Analyzer. The patent and license agreements are managed through the National University of Singapore and A*STAR. None of the other authors has any conflicts of interest to disclose.

other factors, retinal arteriolar simple tortuosity was significantly associated with the incidence of any DR (odds ratio per standard deviation increase, 95% Confidence Interval) (1.17; 1.01, 1.35). Retinal venular branching angle was significantly associated with progression of DR (1.18; 1.03, 1.36), retinal venular curvature tortuosity was significantly associated with the incidence of PDR (1.15; 1.01, 1.30) and retinal venular branching angle (1.41; 1.10, 1.82) was significantly associated with the incidence of CSME. There were no significant associations of other RVGCs with any of the DR outcomes in the full multivariate model. Inclusion of all possible RVGCs did not improve the predictive value of the models that already included retinal vessel diameter and baseline DR severity level.

Conclusions—RVGCs of the retinal venules were associated with progression of DR; however, most of the RVGCs measured from digitized fundus photographs added little to the assessment of risk of incidence and progression of DR when other risk factors were considered in type 1 and 2 diabetes.

Introduction

Persons with diabetes are at higher risk of diabetic retinopathy (DR) and also severe vision-threatening retinopathy (proliferative diabetic retinopathy [PDR] and clinically significant macular edema [CSME]), than non-diabetic persons.^{1, 2} Because an increasing number of people with diabetes are living longer, and because duration of diabetes is still an important risk factor for progression of DR, there are more people experiencing visual loss due to these severe ocular complications.^{3–5} Therefore, biomarkers that predict, precede or accompany early manifestations of retinopathy may permit early identification of those likely to experience severe visual loss and reduce that.^{6, 7}

Retinal vessel diameters and other retinal vessel geometric characteristics (RVGCs), such as tortuosity, fractal dimensions, branching angles, and length-to-diameter ratios have been suggested to represent microvascular changes prior to onset of overt DR and have been found in some studies to be associated with both retinal and systemic diabetic complications, including diabetic nephropathy and cardiovascular diseases.^{8–23} Some investigators have therefore suggested that these characteristics are biomarkers that may be useful in screening for those at increased risk of the incidence and progression of DR and systemic diabetic complications.^{8–20} However, there is limited information available about the value of RVGCs for long-term risk assessment for the development of PDR and CSME as many of the studies to date have been cross-sectional.^{8–21} Because interventions that occur early in disease are likely to reap benefits in forestalling development of more severe disease, we explored the relationships of RVGCs to those outcomes. We examine relationships of RVGCs to the incidence of any DR, the progression of DR, and the incidences of PDR and CSME in those participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). We also examine whether RVGCs provide additional predictive value for the risk of incidence and progression of DR and incidences of PDR and CSME as determined by significant incremental gains in the area under the receiver operating characteristic curve (AUC) when added to a model that includes traditional risk factors (e.g., glycated hemoglobin (HbA1c), mean arterial blood pressure, duration of diabetes, DR severity status at baseline).

Methods

Population

The WESDR study cohort was derived from the 10,135 diabetic persons living in and receiving their care in an 11-county area in southern Wisconsin from 1979 to 1980.^{24–30} There were 996 persons with type 1 diabetes and a probability sample based on duration of type 2 diabetes of 1370 persons who participated in the baseline examination.^{24, 25} There are relevant data from 3 follow-up examinations for the T1DM group and two follow-up examinations from the T2DM group. Descriptions of participation, and reasons for loss to follow-up, which is primarily due to mortality, has been previously published.^{24–30} All examinations followed similar protocols that were approved by the Institutional Human Subjects Committee of the University of Wisconsin and conformed to the tenets of the Declaration of Helsinki.

Among those with T1DM, 891 of the 996 persons seen at the first WESDR (W1) exam (1980–1982), 776 of the 903 persons seen at the second WESDR (W2) exam (1984–1986) and 651 of the 795 persons seen at the third WESDR (W3) exam (1990–1992) returned for the next follow-up examination. In the T2DM group, 987 of the 1370 persons seen at the W1 exam, and 541 of the 1007 persons seen at the W2 exam returned for the next follow-up examination. Information from each set of intervals (W1 to W2, W2 to W3 and W3 to W4) was accumulated and analyzed as person-intervals. While the period of time covered for these intervals varies from 4 to 6 years, we treat all of them the same and consider the incidence to represent a 5-year incidence rate. There were 2318 person-intervals in those with T1DM and 1528 person-intervals in those with T2DM.

Procedures and Grading Protocols

The ocular and physical characteristics included in the analyses for this investigation included measurement of blood pressure,³¹ height, weight, and HbA1c level.³² The pupils were dilated and 30 degree stereoscopic fundus photographs were taken and graded using the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocols^{33, 34} A structured interview was conducted by the examiners, including questions on smoking and specific medications for control of hyperglycemia and high blood pressure.

Proteinuria was measured using a reagent strip (Labstix, Ames, Elkhart, IN). Mean arterial blood pressure (MABP) was defined as diastolic pressure +1/3 pulse pressure.

CSME was identified from the presence of any one of the following: thickening of the retina located 500 μ m or less from the center of the macula; hard exudates with thickening of the adjacent retina 500 μ m or less from the center of the macula; or a zone of retinal thickening one disc area or larger in size, located 1 disc diameter or less from the center of the macula from the stereoscopic fundus photographs.³³

RVGCs were graded from digitized images of photographs in right eyes at the first three examinations for those with T2DM and for the first four examinations for those with T1DM. The thirty-degree retinal photographs centered on the optic nerve (one of the pair of field 1 from the standard pair taken to grade diabetic retinopathy) were evaluated using the semi-

automated computer assisted Singapore I Vessel Assessment (SIVA) software Version 3.2. Trained graders followed a SIVA protocol adapted by adding standardized procedures to reduce variability across multiple visits (standardized grid sizing and location registration across visits, etc.). Image quality and confounding conditions (pathology, image artifacts, etc.) that might affect measurements were recorded. The measurement data included fractal dimension (calculated from a skeletonized line tracing using the box-counting method and represents a “global” measure summarizing the whole branching pattern of the retinal vasculature with larger values representing a more complex pattern¹⁰); simple and curvature tortuosity; branching angle (total angle between the daughter branches); angle asymmetry (imbalance in angles off the center line); branching coefficient (width of the branch relative to trunk); asymmetry factor (the imbalance of widths between daughter branches); the junctional exponent (a combination of widths of branches relative to the trunk); and length-to-diameter ratios from digitized images. Graders were masked to measurements made at previous visits and their gradings were examined during regular quality control exercises to maintain reproducibility.

CRAE and CRVE were measured using Interactive Vessel Analysis [IVAN] software (Univ. of Wisconsin).³⁵

Definitions

All incidence and progression outcomes were defined for each sequential pair of examinations (WESDR (W)1 to W2, W2 to W3 for people with T2DM, and W1 to W2, W2 to W3, and W3 to W4 in people with T1DM). The incidence of any DR was defined by presence of DR severity level 21 or greater at follow-up among those with level 10 at the previous examination. Progression of DR was defined as a change in severity of DR from level 21 to level 37 or higher, from level 31 to 43 or higher, 37 to 47 or higher, 43 to 53 or higher, 43 to 60 or higher, 53 to 60 or higher over an interval. Incidence of PDR was defined by the presence of level 60+ at follow-up in an eye with DR level < 60 at the beginning of an interval. Incidence of CSME was defined by the presence of CSME at follow-up in eyes without CSME at the beginning of an interval.

Intervals were excluded for the following reasons: under 18 years of age at the beginning of an interval (274 in those persons with T1DM), missing data for all outcomes (203 in those with T1DM and 111 in those with T2DM), those on renal dialysis or who had undergone a renal transplant or who had pan-retinal and/or focal laser treatments (244 in those with T1DM, 25 in those with T2DM), or who had a poor quality image for SIVA evaluation (269 in those with T1DM and 425 in those with T2DM) or missing covariate data (103 in those with T1DM and 83 in those with T2DM) at the beginning of an interval were excluded from these analyses, leaving a total of 1225 person-intervals that was included for analyses in those with T1DM and 884 person-intervals that were included in those with T2DM. Differences in those included and excluded for analyses are shown in Table 1. Persons with a longer duration of diabetes, a higher HbA1c, a smaller body mass index (BMI), who had proteinuria, who were current smokers, who had PDR or CSME, who had a narrower CRAE or CRVE, who had a smaller retinal arteriolar fractal dimension, a greater retinal arteriolar tortuosity, a greater retinal arteriolar branching coefficient, or a greater retinal arteriolar

asymmetry factor, or who had a smaller retinal venular fractal dimension, a greater retinal venular simple tortuosity, a greater retinal venular branching coefficient or a greater retinal venular asymmetry factor were more likely to be excluded (Table 1). The numbers available for specific DR outcome analyses are smaller because those with the outcome of interest at the beginning of the interval are excluded. Most person-intervals remain eligible for incidence of PDR (2004 person-intervals) and incidence of CSME (1961 person-intervals). Fewer remain eligible for incidence of any DR, since there had to be no evidence of DR at the start of the interval. Only 17% (204/1225) of the person-intervals in those with T1DM and 52% (461/884) in those with T2DM are eligible for incidence of any DR. The person-intervals not eligible for incidence of DR are eligible for progression.

Statistical Analyses

Because the RVGCs were only graded in right eyes, all analyses were done using data from right eyes only. Findings from participants 18 years of age or older with T1DM and T2DM were combined in a single model with adjustment for type of diabetes. Logistic regression models were used to test for differences in baseline characteristics of those included and excluded in the cohort as well as for the associations of RVGCs with each of the outcomes. All RVGCs were standardized (subtract the population mean and divide by the standard deviation within each visit and separately for T1DM and T2DM) and treated continuously in the logistic regression model. Retinal arterioles and venules were analyzed separately and updated with each examination interval pair. For example the standardized fractal measures at W1 were analyzed with incidence/progression from W1 to W2 while the standardized fractal measures at W2 were analyzed with incidence/progression from W2 to W3, and the standardized fractal measures at W3 were analyzed with incidence/progression from W3 to W4. Each examination interval pair (W1 to W2, W2 to W3, etc) was included in a single logistic regression model with a generalized estimating equations adjustment for the multiple visits.

Base models included adjustment for duration of diabetes, age at diagnosis of diabetes, HbA1c, sex, diabetes type and MABP at the start of an exam interval (updated with each interval as done with the RVGC). Additional adjustment for the “full” model was done including CRAE in arteriole models and CRVE in venule models, proteinuria, and baseline DR severity level. The baseline DR severity levels were grouped to reflect the levels with the highest risk for each outcome. For progression of DR or incidence of CSME the DR severity was grouped as none (level 10), minimal to moderate non-proliferative diabetic retinopathy (NPDR levels 21–37), moderate to severe NPDR (levels 43–53) and PDR (level 60). Baseline DR is not relevant for incidence of any DR, because everyone must have no DR. For incident PDR, we chose to focus on the specific NPDR levels, so the baseline DR adjustment was for level 43, level 47 or level 53.

Evaluation of the additional predictive value of RVGCs was done by computing the C-statistic (change in area under the receiver operating characteristic curve (AUC)) when RVGCs are added to the full model based on traditional DR risk factors using the method described by DeLong et al.³⁶ This was evaluated by adding all RVGCs (arteriolar and venular) together in the model using principal components analyses to avoid collinearity.

Ten principal components explained >85% of the variation and were used in the prediction models.

SAS version 9 (SAS Institute Inc., Cary, North Carolina, USA) was used for all analyses.

Results

The incidence of any retinopathy across all interval visits was 44.5% (296/665), of progression of DR it was 31.6% (374/1185), of the incidence of PDR it was 10.2% (203/2004), and of CSME the incidence was 4.8% (94/1961).

Retinal arteriolar simple tortuosity was statistically significantly associated with the incidence of any DR both in the base (odds ratio per standard deviation increase, 95% Confidence Interval) (1.17; 1.02, 1.36) and full (1.17; 1.01, 1.35) models (see Table 2A). There were no other statistically significant associations of other RVGCs with incidence of any of DR in the full model (Table 2A).

Retinal venular branching angle was statistically significantly related to 2 levels of progression of DR in an eye while adjusting for in the base (1.16; 1.01, 1.33) and full (1.18; 1.03, 1.36) models (Table 2B). There were no other statistically significant associations of other RVGCs with progression of DR in the full model (Table 2B).

Retinal arteriolar fractal dimension (0.79; 0.65, 0.97), retinal venular simple tortuosity (1.17; 1.03, 1.34), retinal venular asymmetry factor (0.82; 0.69, 0.96), and retinal venular junctional exponent (1.22; 1.03, 1.44), were each statistically significantly associated with the incidence of PDR after adjustment in the base but not the full model (Table 2C). Retinal venular curvature tortuosity was statistically significantly associated with the incidence of PDR after adjustment in both the base (1.30; 1.13, 1.49) and full (1.15; 1.01, 1.30) models. There were no other statistically significant associations of other RVGCs with incidence of PDR in the full model (Table 2C).

Retinal venular curvature tortuosity (1.21; 1.01, 1.45) and retinal venular angle asymmetry (0.80; 0.64, 0.99) was statistically significantly associated with the incidence of CSME only in the base model while retinal venular branching angle was statistically significantly related to the incidence of CSME in the base (1.37; 1.07, 1.74) and in the full (1.41; 1.10, 1.82) models (Table 2D). There were no other statistically significant associations of other RVGCs with incidence of CSME in the full model (Table 2D).

Interactions between the RVGC and diabetes type were evaluated for each of the models. None were statistically significant (data not shown).

While individual RVGCs do not appear to be strongly associated with the incidence of DR outcomes, we evaluated whether all RVGC measures combined add predictive value to traditional full models. The first 10 factors from principal components were added to the full model and change in the area under the curve (AUC) was evaluated. We found no significant improvements in AUC for any outcome (Table 3). The inclusion of baseline DR level and retinal vessel diameter measurement (CRAE and CRVE) are often not included in risk

models. We re-evaluated the improvement in AUC when baseline DR and vessel diameter measurement are left out of the models, and found no significant improvement for the incidence of any DR ($p=0.06$), incidence of CSME ($p=0.09$) for progression of DR ($p=0.58$) or incidence of PDR ($p=0.37$). We further evaluated whether the RVGC measures would add predictive value in a situation where other clinical measures, such as glycosylated hemoglobin or blood pressure, was not available (as could happen in a telemedicine setting). We began with a model containing only measures available from retinal images, CRAE, CRVE and DR level. These models have a significantly lower AUC ($p < 0.001$ for all outcomes) compared to the model with the other clinical measures. For example, the AUC for incidence of PDR was 0.859 with the clinical measures without the RVGCs. The AUC for incidence of PDR with just CRAE, CRVE and DR level is 0.791. The addition of the RVGC (using the 10 principal components factors) did not significantly improve the AUC for incidence of any DR ($p=0.07$), incidence of CSME ($p=0.12$), progression of DR ($p=0.43$) or incidence of PDR ($p=0.28$).

Discussion

Adjusting for DR severity, CRAE and CRVE, and proteinuria status in addition to HbA1c level, sex, MABP, diabetes duration and type, resulted in only four statistically significant associations of RVGCs with DR outcomes measured over a 15-year period in the WESDR. When accounting for the number of models run, these associations are likely a result of chance findings. However, these may still suggest some relevant mechanisms worth considering. Most of the associations were for venular characteristics of branching and tortuosity. Venular branching angle was associated with an 18% increase in the odds of progression of DR and a 41% increase in the odds of incident CSME over a 5-year period per standard deviation higher retinal venular branching angle. The odds for incident PDR over a 5-year period were 15% higher per standard deviation of retinal venular curvature tortuosity. These associations reflect the traditional view that fundus signs of venular dilation, tortuosity and “beading”, which are reflective of diabetes severity, are predictive of progression of DR.^{37, 38} The observations are also consistent with Murray’s observations nearly 90 years ago of optimal retinal relationships of blood flow to branching angle and vessel diameters throughout the vasculature.^{39, 40} Less than optimal patterns were thought by Murray to result in increased energy needed to maximize efficient blood flow. The odds for incidence of any DR over a 5-year period was 17% higher per standard deviation of retinal arteriolar simple tortuosity.

There were no statistically significant changes in the area under the curve (AUC, assessed with C-statistic) when all of the RVGCs were added (using principal components) to any of the models that included established DR risk factors. They also do not add predictive value to a situation where only retinal image information is available, as long as CRAE and CRVE are evaluated. These data show that the RVGCs provide limited additional information about risk of progression of DR or the risk of incidence of PDR or CSME when severity of DR or retinal vessel diameters are known. Thus, suggestions that RVGCs may be useful for DR screening require verification and further studies.^{41–44}

There are few prospective cohort studies to compare our results to. In one such study, the RVGCs were related to the 1-year incidence and progression of DR in persons with T1DM and type T2DM.²¹ In that study while adjusting for age, duration of diabetes, sex, smoking status, HbA1c, hypertension, and hyperlipidemia, a relationship of venular fractal dimensions to the incidence of any DR was found. Less tortuous arterioles were also found to have more regression of DR. In a large population-based study, which included Malays with only type 2 diabetes, Cheung et al found that greater arteriolar simple tortuosity, larger venular branching coefficient, and higher arteriolar simple tortuosity predicted the incidence and progression of DR but not the incidence of PDR or ME. The lack of relationship of RVGCs to the incidence of PDR and CSME in their study was attributed to a lack of power.⁹ Unlike the WESDR, neither of the studies of Cheung and Lim et al. adjusted for the presence of DR severity when examining the relationships of RVGCs to DR outcomes.^{9, 21} In the WESDR, inclusion of RVGCs did not improve the predictive value of the models that already included the CRAE, CRVE, and baseline retinopathy severity but showed borderline improvement in models that did not include these predictors.

While there are more consistent associations of retinal vascular caliber, in particular venular caliber (summarized as CRVE) to incidence and progression of DR,^{43–45} to date, few other studies have found a consistent association of other retinal geometric measures e.g. fractal dimension with DR.^{11, 15, 20} We found a 21% decrease in the odds of incident PDR with an increase in the arteriolar fractal dimension in the base model, which was no longer statistically significant in the full model. Grauslund et al.¹⁵ showed a statistically significant inverse relation of retinal arteriolar fractal dimension with PDR in persons with T1DM. Cheung et al.^{11, 15} found a positive association between fractal dimension and early DR in young persons with T1DM (OR 3.92; 95% CI 2.02–7.61). Fractal dimension as measured using SIVA software has been inversely, directly, or, not associated with the incidence of any DR in other studies.^{10, 11, 18, 19} Most of the other studies that have examined the RVGC biomarker fractal dimension have done so in cross-sectional or case-control studies in which the antecedent consequent relationships could not be determined. These studies also did not adjust for baseline retinopathy severity. It is possible that at different stages of early DR, the fractal dimension reflects the retinal blood vessel characteristics inherent to those stages, so serves as a surrogate for severity, but is not antecedent. Longitudinal studies have mostly involved examining these relationships over a short follow-up period. Comparisons among studies are limited due to differences in the cohorts studied and the protocols used.

Strengths of our study include the use of standard protocols for measuring RVGCs and DR outcomes over several exam phases. In our study, poor focus or field definition affected the measurements of RVGCs, resulting in the exclusion of 18% of the person-intervals. Selective survival and participation may have also limited the generalizability of our findings and the ability to find associations of RVGCs with DR outcomes. Our study used digitized photographs to evaluate RVGCs using the SIVA software. Whether assessment using digital photographs and other software (e.g., VAMPIRE software, Universities of Edinburgh and Dundee, UK)⁴⁶ or whether new computer algorithms using artificial intelligence and convoluted network to segment and map the retinal vascular tree⁴⁷ may provide more precise estimates is unknown.

In conclusion, we found few associations of SIVA RVGCs measures and long-term incidence and progression of DR, PDR and CSME. Some geometrical characteristics of the retinal venules, reflecting clinical importance of the assessment of the retinal venules, were associated with progression of DR. However, most RVGCs measured from fundus photographs added little to the assessment of risk of incidence and progression of DR when other risk factors were considered.

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The relationships of retinal vessel geometric characteristics are weakly and inconsistently related to the incidence and progression of diabetic retinopathy and clinically significant macular edema.

Table 1

Distribution of characteristics for included and excluded person intervals

Characteristic	Excluded		Included		P-value
	N	mean %	N	mean %	
Diabetes type (T2DM)	1737	37.1%	2109	41.9%	0.33
Duration of Diabetes, yrs	1737	16.6±10.6	2109	14.2± 8.5	<.001
Age, yrs	1737	44.5±22.0	2109	44.9±18.1	0.24
Age at Diagnosis, yrs	1737	27.9±22.1	2109	30.7±19.8	0.24
Sex (M)	1737	47.4%	2109	47.7%	0.90
HbA1c, %	1561	10.1± 2.1	2109	9.8± 1.9	0.01
Mean Arterial Blood Pressure, mmHg	1639	96.1±13.6	2109	95.7±11.9	0.31
Body Mass Index, kg/m ²	1642	25.7± 5.5	2098	27.0± 5.4	<.001
Proteinuria Present	1589	21.5%	2109	13.7%	<.001
Current Smoker	1735	15.4%	2108	21.8%	<.001
Central Retinal Arteriolar Equivalent, μm	1296	157.8± 20.7	2109	161.5± 15.5	<.001
Central Retinal Venular Equivalent, μm	1332	239.5± 30.5	2109	244.3± 25.7	<.001
Proliferative Diabetic Retinopathy	1714	31.6%	2109	4.8%	<.001
Clinically Significant Macular Edema	1519	6.1%	2092	2.6%	<.001
Arteriole: Fractal Dimension	1165	1.18± 0.08	2109	1.23± 0.05	<.001
Arteriole: Simple Tortuosity	1165	1.103±0.029	2109	1.103±0.028	0.97
Arteriole: Curvature Tortuosity (×10−4)	1165	1.10± 0.29	2109	1.04± 0.26	<.001
Arteriole: Branching Angle, degree	1125	80.9±13.0	2104	81.6±11.1	0.07
Arteriole: Angle Asymmetry	1125	38.9±13.8	2104	39.3±12.5	0.31
Arteriole: Branching Coefficient	1125	1.57± 0.30	2104	1.54± 0.21	0.001
Arteriole: Asymmetry Factor	1125	0.76± 0.10	2104	0.74± 0.09	<.001
Arteriole: Junctional Exponent	1125	−0.57± 0.35	2104	−0.57± 0.29	0.69
Arteriole: Length-to-Diameter Ratio	806	13.96± 7.71	1770	14.30± 7.68	0.35
Venule: Fractal Dimension	1165	1.17± 0.06	2109	1.20± 0.05	<.001
Venule: Simple Tortuosity	1165	1.095±0.018	2109	1.097±0.018	0.008

Characteristic	Excluded		Included		P-value
	N	mean %	N	mean %	
Venule: Curvature Tortuosity ($\times 10^{-4}$)	1165	1.13 $\pm$ 0.25	2109	1.13 $\pm$ 0.24	0.89
Venule: Branching Angle, degree	1141	79.2 $\pm$ 11.4	2099	79.0 $\pm$ 10.8	0.55
Venule: Angle Asymmetry	1141	43.7 $\pm$ 15.0	2099	44.7 $\pm$ 13.7	0.06
Venule: Branching Coefficient	1141	1.39 $\pm$ 0.24	2099	1.36 $\pm$ 0.24	0.004
Venule: Asymmetry Factor	1141	0.66 $\pm$ 0.12	2099	0.65 $\pm$ 0.11	0.002
Venule: Junctional Exponent	1141	-0.35 $\pm$ 0.37	2099	-0.33 $\pm$ 0.33	0.06
Venule: Length-to-Diameter Ratio	917	12.65 $\pm$ 7.57	1852	12.42 $\pm$ 7.15	0.41

TABLE 2

A: Relationships of Retinal Vessel Geometric Characteristics to Incidence of Any Diabetic Retinopathy for Arterioles and Venules																	
RVGC	Arterioles				Venules				RVGC	Arterioles				Venules			
	Base Model		Full Model		Base Model		Full Model			Base Model		Full Model		Base Model		Full Model	
	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val		OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val
Fractal Dimension	1.01 (0.80,1.28)	0.91	0.97 (0.76,1.22)	0.77	0.93 (0.77,1.13)	0.49	0.92 (0.76,1.12)	0.42									
Simple Tortuosity	1.17 (1.02,1.36)	0.03	1.17 (1.01,1.35)	0.04	1.14 (0.96,1.36)	0.14	1.14 (0.95,1.35)	0.15									
Curvature Tortuosity	1.09 (0.94,1.28)	0.25	1.09 (0.93,1.27)	0.27	1.15 (0.97,1.36)	0.12	1.14 (0.96,1.35)	0.14									
Branching Angle	1.09 (0.91,1.30)	0.37	1.09 (0.91,1.31)	0.34	1.15 (0.96,1.37)	0.13	1.15 (0.96,1.38)	0.12									
Angle Asymmetry	1.08 (0.92,1.28)	0.33	1.08 (0.91,1.27)	0.38	0.92 (0.78,1.10)	0.37	0.92 (0.77,1.09)	0.33									
Branching Coefficient	0.86 (0.71,1.04)	0.11	0.90 (0.74,1.10)	0.29	1.00 (0.83,1.21)	0.99	1.00 (0.83,1.22)	0.96									
Asymmetry Factor	0.90 (0.76,1.05)	0.18	0.93 (0.79,1.10)	0.40	1.07 (0.91,1.25)	0.43	1.07 (0.91,1.27)	0.42									
Junctional Exponent	1.15 (0.96,1.38)	0.14	1.11 (0.92,1.35)	0.29	1.15 (0.96,1.37)	0.12	1.15 (0.96,1.37)	0.13									
Length-to-Diameter Ratio	1.16 (0.97,1.39)	0.10	1.18 (0.99,1.42)	0.07	1.08 (0.92,1.27)	0.34	1.09 (0.92,1.29)	0.31									

B: Relationships of Retinal Vessel Geometric Characteristics to Progression of Diabetic Retinopathy for Arterioles and Venules																	
RVGC	Arterioles				Venules				RVGC	Arterioles				Venules			
	Base Model		Full Model		Base Model		Full Model			Base Model		Full Model		Base Model		Full Model	
	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val		OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val
Fractal Dimension	0.98 (0.83,1.16)	0.84	0.98 (0.83,1.17)	0.85	1.06 (0.92,1.23)	0.40	1.05 (0.91,1.22)	0.49									
Simple Tortuosity	1.08 (0.95,1.22)	0.23	1.08 (0.95,1.22)	0.24	1.06 (0.94,1.20)	0.33	1.03 (0.91,1.16)	0.68									
Curvature Tortuosity	1.06 (0.93,1.22)	0.37	1.06 (0.92,1.21)	0.42	1.12 (0.99,1.26)	0.08	1.08 (0.95,1.22)	0.26									
Branching Angle	1.03 (0.89,1.18)	0.73	1.03 (0.89,1.19)	0.70	1.16 (1.01,1.33)	0.03	1.18 (1.03,1.36)	0.02									
Angle Asymmetry	1.04 (0.91,1.19)	0.59	1.03 (0.90,1.18)	0.69	0.96 (0.84,1.10)	0.53	0.94 (0.82,1.08)	0.38									
Branching Coefficient	0.96 (0.83,1.12)	0.64	0.98 (0.84,1.14)	0.75	0.97 (0.85,1.10)	0.59	1.00 (0.89,1.13)	0.96									
Asymmetry Factor	0.91 (0.79,1.05)	0.20	0.92 (0.80,1.07)	0.28	0.98 (0.86,1.12)	0.75	1.02 (0.89,1.16)	0.82									
Junctional Exponent	1.10 (0.96,1.27)	0.17	1.10 (0.95,1.27)	0.20	1.12 (0.97,1.28)	0.12	1.07 (0.93,1.24)	0.33									
Length-to-Diameter Ratio	0.95 (0.82,1.10)	0.49	0.95 (0.82,1.11)	0.54	1.00 (0.86,1.15)	0.95	1.02 (0.88,1.18)	0.77									

C: Relationships of Retinal Vessel Geometric Characteristics to Incidence of Proliferative Diabetic Retinopathy for Arterioles and Venules

RVGC	Arterioles						Venules					
	Base Model			Full Model			Base Model			Full Model		
	OR (95% CI)	p-val		OR (95% CI)	p-val		OR (95% CI)	p-val		OR (95% CI)	p-val	
Fractal Dimension	0.79 (0.65,0.97)	0.03		0.90 (0.71,1.14)	0.36		0.95 (0.79,1.13)	0.55		0.87 (0.72,1.06)	0.17	
Simple Tortuosity	1.06 (0.92,1.22)	0.43		1.04 (0.87,1.23)	0.70		1.17 (1.03,1.34)	0.02		1.03 (0.90,1.18)	0.67	
Curvature Tortuosity	1.05 (0.90,1.24)	0.53		1.00 (0.84,1.19)	0.99		1.30 (1.13,1.49)	<0.001		1.15 (1.01,1.30)	0.04	
Branching Angle	0.96 (0.82,1.14)	0.68		0.99 (0.83,1.18)	0.93		0.93 (0.79,1.10)	0.39		1.00 (0.83,1.20)	0.98	
Angle Asymmetry	0.94 (0.80,1.11)	0.47		0.88 (0.73,1.06)	0.18		0.98 (0.83,1.17)	0.83		0.91 (0.75,1.11)	0.37	
Branching Coefficient	0.98 (0.81,1.19)	0.85		0.97 (0.79,1.18)	0.75		0.93 (0.76,1.13)	0.47		1.08 (0.91,1.28)	0.36	
Asymmetry Factor	1.07 (0.91,1.25)	0.39		1.09 (0.91,1.29)	0.35		0.82 (0.69,0.96)	0.02		0.94 (0.78,1.12)	0.47	
Junctional Exponent	1.07 (0.90,1.27)	0.46		1.08 (0.90,1.29)	0.40		1.22 (1.03,1.44)	0.02		1.04 (0.86,1.25)	0.69	
Length-to-Diameter Ratio	0.87 (0.73,1.04)	0.12		0.84 (0.70,1.01)	0.06		0.94 (0.79,1.12)	0.48		1.03 (0.86,1.23)	0.76	

D: Relationships of Retinal Vessel Geometric Characteristics to Incidence of Clinically Significant Macular Edema for Arterioles and Venules

RVGC	Arterioles						Venules					
	Base Model			Full Model			Base Model			Full Model		
	OR (95% CI)	p-val		OR (95% CI)	p-val		OR (95% CI)	p-val		OR (95% CI)	p-val	
Fractal Dimension	0.95 (0.71,1.28)	0.75		1.09 (0.79,1.50)	0.60		0.93 (0.72,1.19)	0.55		0.98 (0.77,1.26)	0.88	
Simple Tortuosity	1.08 (0.90,1.30)	0.41		1.06 (0.88,1.29)	0.55		1.09 (0.89,1.35)	0.40		1.09 (0.84,1.42)	0.52	
Curvature Tortuosity	1.17 (0.94,1.44)	0.16		1.16 (0.94,1.44)	0.18		1.21 (1.01,1.45)	0.04		1.23 (0.98,1.54)	0.08	
Branching Angle	1.20 (0.93,1.55)	0.16		1.20 (0.91,1.58)	0.20		1.37 (1.07,1.74)	0.01		1.41 (1.10,1.82)	0.007	
Angle Asymmetry	1.01 (0.80,1.28)	0.95		1.03 (0.81,1.31)	0.80		0.80 (0.64,0.99)	0.04		0.81 (0.65,1.01)	0.06	
Branching Coefficient	1.10 (0.89,1.36)	0.38		1.03 (0.82,1.31)	0.79		1.15 (0.98,1.33)	0.08		1.12 (0.94,1.34)	0.20	
Asymmetry Factor	1.18 (0.92,1.51)	0.19		1.11 (0.84,1.46)	0.47		1.14 (0.92,1.41)	0.23		1.16 (0.93,1.46)	0.19	
Junctional Exponent	0.92 (0.72,1.17)	0.49		0.95 (0.75,1.22)	0.71		1.07 (0.86,1.35)	0.53		1.15 (0.90,1.46)	0.26	
Length-to-Diameter Ratio	1.10 (0.84,1.44)	0.48		1.05 (0.81,1.36)	0.73		0.91 (0.69,1.20)	0.49		0.97 (0.73,1.27)	0.80	

Base Multivariate model adjusted for diabetes type, sex, duration of diabetes, age at diagnosis of diabetes, glycosylated hemoglobin A1c, and further adjusted in a Full Model for central retinal arteriolar equivalent in arteriole model and central retinal venular equivalent, proteinuria, and baseline DR severity level

TABLE 3

Change in area under the curve (AUC) from the addition of all RVGC measures (first 10 principal components) to the model with duration, age at diagnosis, diabetes type, HbA1c, MAPB, proteinuria, baseline retinopathy level, CRAE and CRVE

outorder	Without RVGC	WITH RVGC	Difference	C-Test	P-value
Incident DR	0.726	0.737	0.011	2.40	0.12
Progress DR	0.718	0.721	0.002	0.46	0.50
Incident PDR	0.859	0.862	0.002	0.98	0.32
Incident CSME	0.800	0.815	0.015	2.53	0.11