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Retinopathy and Chronic Kidney Disease in the Chronic Renal Insufficiency Cohort Study (CRIC)

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Abstract

Objectives—Retinal vascular and anatomic abnormalities caused by diabetes, hypertension, and other conditions can be observed directly in the ocular fundus and may reflect severity of chronic renal insufficiency. The purpose of this study was to investigate the association between retinopathy and chronic kidney disease (CKD).

Methods—In this observational, cross-sectional study, 2605 participants of the Chronic Renal Insufficiency Cohort (CRIC) study, a multi-center study of CKD, were offered participation. Non-mydriatic fundus photographs of the disc and macula in both eyes were obtained in 1936 of these subjects.

Photographs were reviewed in a masked fashion at a central photograph reading center using standard protocols. Presence and severity of retinopathy (diabetic, hypertensive or other) and vessel diameter caliber were assessed by trained graders and a retinal specialist using protocols developed for large epidemiologic studies. Kidney function measurements and information on traditional and non-traditional risk factors for decreased kidney function were obtained from the CRIC study.

Results—Greater severity of retinopathy was associated with lower estimated glomerular filtration rate (eGFR) after adjustment for traditional and non-traditional risk factors. Presence of vascular abnormalities usually associated with hypertension was also associated with lower eGFR. We found no strong direct relationship between eGFR and average arteriolar or venular calibers.

Conclusions—Our findings show a strong association between severity of retinopathy and its features and level of kidney function after adjustment for traditional and non-traditional risk factors for CKD, suggesting that retinovascular pathology reflects renal disease.

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Keywords

Retinopathy; Retinal Vascular Diameter; Chronic Kidney Disease

Introduction

Photography of the ocular fundus allows direct visualization of the retinal vasculature. Because retinal vascular abnormalities may reflect similar vascular changes in the kidneys, heart and other tissues, ocular photography may provide a non-invasive method for assessing the vascular condition of the kidneys. Indeed, several studies have shown associations between retinopathy and nephropathy among subjects with diabetes [1–6] and systemic hypertension.[7,8]

The Chronic Renal Insufficiency Cohort (CRIC) study is a multicenter, longitudinal cohort study of adults with chronic kidney disease (CKD), a condition affecting more than 27 million Americans.[9, 10,11] Retinopathy in CRIC (RCRIC) is an ancillary study of the association between retinopathy and CKD. We previously reported that nearly one-half of study participants had fundus pathology that was associated with CKD risk factors.[12] We now report on a variety of retinopathy features, including measurements of retinal vascular calibers, and their association with CKD. We evaluate whether retinopathy status provides information on kidney function that is independent of the information provided by known risk factors.

Materials and Methods

The design of the parent CRIC study has been reported.[10,11] Participants for RCRIC were recruited during a CRIC visit at 6 of the 7 CRIC clinical centers. All 2605 CRIC participants from these 6 sites were offered participation. From June 2006 to May 2008, 1936 participants were photographed. The study was approved by the Institutional Review Boards of the participating institutions, and written consent was obtained. Photographs were obtained by non-ophthalmic personnel trained by the Fundus Photograph Reading Center. Most photography sessions coincided with CRIC visits. A Canon CR-DGI, Non-Mydriatic Retinal Camera (Canon Inc, Tokyo Japan) was used to obtain 45 degree digital, color fundus photographs. Participants were seated in a darkened room for five minutes to induce physiologic papillary dilatation. No dilatory pharmacologic compounds were used. Two images, one centered on the macula and one on the optic disc, were obtained from each eye.

Retinopathy and retinal vessel caliber assessment protocols

Digital photographs were mailed to the RCRIC Fundus Photograph Reading Center, University of Pennsylvania, where they were assessed by trained graders and a retinal specialist. Standard protocols with standardized photographic field definitions were used to evaluate fundus pathology including retinopathy (diabetic, hypertensive, or other) and measurement of the diameter of the major retinal arterioles and venules. Images were viewed on color calibrated monitors by a single grader. Graders were masked to all other information about the participant. Because the graders were unaware of the diabetic or hypertensive status of the participants, retinopathy was evaluated without assumption of cause.

The Early Treatment of Diabetic Retinopathy (ETDRS) and the Atherosclerosis Risk in Communities (ARIC) fundus photographic grading protocols[13,14] were used to assess retinopathy. The Multi-Ethnic Study of Artherosclerosis (MESA) protocol was used for the evaluation of macular edema from non-stereo color photographs.[15] These grading protocols

have been previously used in diabetic and non-diabetic populations. The following retinal abnormalities were graded by referring to standard photographs: microaneurysms, retinal hemorrhages, hemorrhages and/or microaneurysms, retinal hemorrhage type (flame or blot), drusen, hard exudates, cotton-wool patches or soft exudates, intraretinal microvascular abnormalities, new vessels on or within 1 disc diameter of the disc, new vessels elsewhere, fibrous proliferation, and scars from previous pan retinal photocoagulation or focal photocoagulation. Other ocular conditions were graded: central vein occlusion, branch retinal vein occlusion, central artery occlusion, branch artery occlusion, disciform macular degeneration, and chorioretinal scar other than photocoagulation scar.

An ETDRS severity score for retinopathy was assigned for each eye.[14] The score is on an ordinal scale and is not a continuous variable. Scores were classified as normal (< 14), very mild non-proliferative retinopathy (14 to 20); non-proliferative retinopathy (35 to 53); and proliferative retinopathy (≥60). The score of the eye with the more advanced retinopathy was used as the participant's score; when grading of only 1 eye was available, the score of that eye was used. A total of 116 participants had photographs that could not be graded for both eyes. In this group, 38 participants had photographs in which no features could be detected in both eyes. The other 78 participants had photographs that were blurry or dark, and although some mild retinopathy features were present, an accurate grading could not be assigned because more advanced retinopathy features were not discernible.

The intra-grader and inter-grader reliability for retinopathy grading was assessed in 200 eyes of 100 participants. Weighted Kappa for the participant's ETDRS score was 0.77 (95% CI: 0.67–0.88) for intra-grader agreement, and 0.80 (95% CI: 0.69–0.91) for inter-grader agreement. These values are consistent with the reproducibility reported by the ETDRS study.[14]

Assessment of arterio-venous nicking and arteriolar sheathing, features associated with systemic hypertension, were graded according to the ARIC protocol. [13] For the assessment of macular edema, graders searched for signs of edema and leakage such as rings of organized hard exudate, localized areas of color change, and a deviation of the normal pathway of the retinal blood vessels.[15]

Image processor measurements of arteriolar and venular diameters were performed according to the ARIC protocol, using IVAN (interactive vessel analysis) software developed at the University of Wisconsin.[13] Graders overlaid a grid centered on the disc to establish the distance from the optic nerve. Vessels were measured within an annulus spanning 0.5 to 1 disc diameter from the edge of the disc. Graders identified the major arterioles and venules and chose segments for measurement according to the vessel's sharpness and straightness. The diameters of up to 6 arterioles and 6 venules were averaged, and an overall A/V ratio[13] was calculated.

The intra-grader and inter-grader reliability for retinal vessel caliber assessment was assessed in 98 eyes of 50 subjects. The intraclass correlation coefficient (ICC) for intra-grader agreement was 0.96 (95% CI: 0.93 – 0.98) for arteriolar diameters, and 0.99 (95% CI: 0.98 – 0.99) for venular diameters. The ICC for the inter-grader agreement was 0.89 (95% CI: 0.80 – 0.94) for arterioles, and 0.97 (95% CI: 0.95 – 0.98) for venules.

Data Analysis

We compared baseline characteristics for participants with ungradable and gradable photographs. We used t-tests to compare continuous variables and Fisher's exact tests to compare the distributions of categorical variables. Participants with ungradable photographs

were included in a separate retinopathy category. Analyses involving retinopathy categories did not assume ordering among the categories.

The relationship between fundus features and eGFR was assessed by analysis of variance techniques and multiple linear regression, using stepwise model selection to identify independent risk factors. Data values from the CRIC annual visit that was closest to the date of photography were used in the analyses of risk factors. One set of multivariate models included traditional risk factors for CKD (age, race, systolic blood pressure, diabetes, and 24 hour urine protein). A second set of models included traditional factors plus the following non-traditional risk factors: anemia status (yes/no), use of angiotensin receptor blockers (yes/no), any self reported cardiovascular disease (yes/no), body mass index (BMI), cyclase-activating parathyroid hormone level (continuous measure), and smoking status (never/former/current). Only those non-traditional risk factors meeting the 0.05 selection criterion were retained in the model.

For the analysis of the association between vascular diameter and eGFR, the averages of the vascular diameters from both eyes were calculated for each subject; when measurements were available for only 1 eye, the measurements of that eye were used. Comparisons of eGFR among 4 quartiles of vessel diameters were assessed by analysis of variance and by regression analysis with adjustment by traditional risk factors only, and by traditional plus non-traditional risk factors. Hypertension was defined as either systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medications. Diabetes was defined as either fasting glucose ≥126 mg/dl, random glucose ≥200 mg/dl, or use of insulin or anti-diabetic medication.[11] Estimated glomerular filtration rate (eGFR) was calculated using the Modification in Diet in Renal Disease equation.[10,11,16] A log transformation was applied to the values for 24 hour urine protein because the distribution was highly skewed. The test of interaction of retinopathy with diabetes was assessed separately by including retinopathy, diabetes, and the interaction terms between diabetes and retinopathy in the statistical model. A similar test of interaction between retinopathy with urine protein was also performed.

Results

A total of 1936 of 2605 (74%) eligible participants were photographed. Their characteristics have been described in a previous report.[12] Mean systolic blood pressure, prevalence of diabetes, proportion of women and body mass index were significantly lower, and average eGFR was significantly higher in participants that had photographs, indicating that participants photographed were healthier than those not photographed.[12]

Among the 1936 participants with baseline photographs, 1820 (94.0%) had photos that were of sufficient quality to allow ETDRS severity retinopathy scoring in one or both eyes, and 1599 (82.6%) participants had photographs on which measurement of retinal vessel caliber could be carried out in one or both eyes.

In comparison to the 1820 participants that had gradable photographs, the 116 participants that had ungradable photographs were older and had significantly lower average eGFR, higher systolic blood pressure and lower diastolic blood pressure. They were also more likely to be African American, and have higher prevalence of diabetes, hypertension, and cardiovascular disease (Table 1).

ETDRS Retinopathy Score and eGFR

Among 925 participants with diabetes mellitus, 456 (49%) had retinopathy, and among 1011 participants without diabetes mellitus, 115 (11%) had retinopathy (Table 2; $p<0.001$). There were 182 participants with neither diabetes mellitus nor hypertension and 4 (2%) had mild

retinopathy Among all participants, the presence of retinopathy was associated with lower eGFR ($p<0.0001$, univariate analysis, Table 2) with the highest eGFR observed in patients without retinopathy, and the lowest eGFR in the patients with proliferative retinopathy; this association remained after adjustment by traditional and non-traditional risk factors ($p=0.005$). Similar relationships were observed for diabetic participants ($p<0.007$, Table 2). For persons without diabetes this association was significant for the univariate analysis ($p<0.0001$) and after adjustment for traditional factors ($p<0.0008$), but not after adjustment of both traditional and non-traditional risk factors ($p=0.35$, Table 2). There was no significant interaction of diabetes on the association of between retinopathy and eGFR ($p=0.75$). There was also no interaction with low (<500 mg) and high (≥ 500 mg) 24 hour urine protein ($p=0.98$), implying that the association of retinopathy and eGFR was not modified by proteinuria level.

When retinopathy features contributing to the ETDRS score were considered individually, each was significantly associated with lower eGFR (Table 3). These associations remained significant for most features after adjustment for traditional and non-traditional risk factors, These associations remained significant for most features after adjustment for traditional and non-traditional risk factors, although there was a decrease in the range of mean eGFR within the categories of each individual retinopathy feature (Table 3). The number of retinal hemorrhages, and intraretinal microvascular abnormalities were identified through stepwise multiple regression as independently associated with eGFR (Table 4).

Other Retinal Features and eGFR

Among features typically associated with hypertension, arteriolar sheathing was the only feature significantly associated with decreased eGFR after adjustment for risk factors (Table 5). Participants with sheathing had a mean eGFR of 28.5 versus a mean of 42.1 mL/min/ $1.73m^2$ in participants without sheathing. Participants with arterio-venous abnormalities had a mean eGFR 37.3 versus a mean of 42.2 mL/min/$1.73m^2$ in participants without these abnormalities ($p=0.0003$); however, the difference in means decreased and did not remain significant after adjustment for traditional and non-traditional risk factors ($p=0.33$, Table 5).

Participants with macular edema had lower mean eGFR in the univariate analysis but not after adjustment by traditional risk factors (Table 5). Participants with focal laser photocoagulation scars had lower eGFR in both univariate analysis and after adjustment by traditional risk factors (Table 5), although the association was no longer statistically significant ($p=0.25$) after adjustment by both traditional and non-traditional risk factors.

Among all participants, mean caliber of retinal veins and arteriole-vein ratio were significantly associated with eGFR (p-value for overall difference =0.01, 0.02, respectively, univariate analysis, Table 6) although the relationships were not monotonic. These relationships remained statistically significant after adjustment for traditional risk factors (Table 6) but not after adjustment for both traditional and non-traditional risk factors (Table 6). The average caliber of retinal arterioles was not associated with eGFR.

Discussion

This is the first comprehensive study of retinal pathology in a cohort of CKD patients with a wide range of kidney dysfunction. Our findings show a significant association between worse ETDRS retinopathy scores and lower eGFR. This association remains significant after adjustment for both traditional and non-traditional CKD risk factors, suggesting that severity of retinopathy provides additional information on severity of CKD. The association is stronger among participants previously diagnosed with diabetes. Non-diabetic participants with retinopathy have lower eGFR, but not to a statistically significant degree. Other studies

have shown associations between retinal and kidney disease, but without adjustment for the high number of risk factors included in this analysis. [2,7, 17]

Most of the retinopathy features contributing to the ETDRS score were associated with lower kidney function when considered without regard to other retinopathy features (Table 3). Multivariate analyses demonstrated that retinal hemorrhage count and intraretinal microvascular abnormalities were independently associated with lower eGFR (Table 4). Arteriolar sheathing, caused by hypertension, was associated with lower eGFR, whereas there was no association with arterio-venous abnormalities, also thought to be caused by hypertension.

Our findings support the hypothesis that common mechanisms may cause both retinal and renal vascular changes[8]. Retinal pathologic features are associated with inflammatory processes,[18,19,] and endothelial dysfunction,[18] leading to circulatory abnormalities and reduced vascular reactivity.[20,21] Both retinopathy and nephropathy involve thickening of basement membrane[17] and muscular layers and increased leakage.[22] These pathologic and hemodynamic abnormalities may occur throughout the body and their effects on the retinal vasculature may be useful indicators of cumulative microvascular damage from hypertension, inflammation, diabetes and other processes.[18,23,24] Furthermore, a recent study has suggested common inherited susceptibilities to retinopathy and CKD in diabetic patients.[25]

The results of our study show only a marginal association between retinal venular caliber and kidney function that could be due to limited power. Although the relationship was not monotonic, in general smaller venular caliber was weakly associated with lower eGFR, and adjustment for traditional and novel factors weakened the associations. No such relationships were seen when participants with diabetes mellitus were assessed separately (data not shown). Retinal venular dilatation has been associated with progression of diabetic retinopathy[26, poor glycemic control27], obesity, inflammation and endothelial dysfunction.[18] Possibly, the effects of reduced kidney function may counteract the effects of diabetes mellitus on vascular diameter, and therefore, no strong association between eGFR and venular calibers was observed.

Several studies have shown arteriolar narrowing related to current and past blood pressure. [28–30] Similar changes have been observed in myocardial arterioles[31,32] and kidney arterioles.[33] We detected no significant association in our study between retinal arteriolar caliber and eGFR (Table 6). The fact that nearly 90% of our study group was hypertensive with most on medications may have blunted an association. Sabanayagam[34] found a cross-sectional association between arteriolar narrowing and lower eGFR in one study but did not detect an association with risk for progression of CKD.[33]

The fact that some of the participants of our study had ungradable photographs is a limitation of our study. Ungradable photographs, however, were associated with decreased renal function. Decreased media clarity by cataracts, vitreous hemorrhage, retinal detachment, and small pupils contribute to poor photographic quality. In addition, ill patients are less likely to sit quietly and maintain fixation. Another study has reported that eyes with ungradable photographs have more eye pathology[13], suggesting that there is important information in the fact that photos are ungradable.

One must be cautious in the interpretation of our results. We cannot exclude the possibility that the relationship between retinopathy and eGFR is driven by a direct damage of hypertension on the retinal vasculature. Although we have used current systolic blood pressure as a covariate for our adjustments, it is possible that this relationship is confounded by the history of hypertension, which is not fully addressed in this study. In addition, we do

not have a good characterization of the cause of kidney disease to be able to assess the impact of this factor on the relationship between retinopathy and eGFR.

In summary our study demonstrates a strong association between retinopathy and decreased kidney function, highlighting the need for eye evaluations in patients with CKD. Our data are consistent with the hypothesis that retinovascular pathology may reflect renal vascular pathology, although they do not prove this relationship because of the cross sectional nature of our study. Further investigations are needed in order to evaluate whether presence of retinopathy in patients with CKD offers information of prognostic value regarding accelerated loss of kidney function.

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Table 1

Comparisons of demographic and clinical characteristics in participants with and without gradable fundus photographs

	Gradable photograph (N=1820)	Not gradable photograph (N=116)	P-value*
	n(%)	n(%)	
Sex			0.56
Male	995 (54.7)	60 (51.7)	
Female	825 (45.3)	56 (48.3)	
Race			0.0002
White	928 (51.0)	37 (31.9)	
Black	788 (43.3)	70 (60.3)	
Other	104 (5.71)	9 (7.76)	
Ethnicity			0.67
Hispanic	96 (5.27)	7 (6.03)	
Non-Hispanic	1724 (94.7)	109 (94.0)	
Hypertension			0.01
Absent	216 (11.9)	5 (4.31)	
Present	1603 (88.1)	111 (95.7)	
Diabetes Mellitus			<0.0001
Absent	975 (53.6)	36 (31.0)	
Present	845 (46.4)	80 (69.0)	
Any CVD			<0.0001
Absent	1195 (65.7)	50 (43.1)	
Present	625 (34.3)	66 (56.9)	
Age, Mean (SD)	60.0 (10.9)	64.3 (9.2)	<0.0001
Systolic BP (mmHg)	127 (21.5)	134 (23.6)	0.0001
Diastolic BP (mmHg)	69.9 (12.8)	67.3 (12.6)	0.04
eGFR (mL/min/1.73m^2)	41.7 (16.0)	36.0 (15.1)	0.0002
BMI (Kg/m^2)	31.5 (7.55)	32.2 (7.86)	0.35

*P-value for comparisons calculated by Fisher exact test for categorical variables and two sample t-test for continuous variables.

Table 2

Crude and adjusted mean eGFR (ml/min/1.73m^2) for each ETDRS retinopathy category overall and by diabetes status (N=1,936)

		Univariate Analysis	**Multivariate Analysis adjusted by traditional risk factors***	**Multivariate Analysis adjusted by traditional and non-traditional risk factors****
ETDRS retinopathy score	n	Mean eGFR (SE)	Mean eGFR (SE)	Mean eGFR (SE)
All participants (N=1936)		**P<0.0001**†	**P<0.0001**†	**P=0.005**†
Normal	1249	44.3 (0.44)	43.8 (0.58)	40.7 (0.61)
Very mild non-proliferative	142	39.6 (1.29)	40.2 (1.22)	38.7 (1.15)
Non-proliferative	243	36.4 (0.99)	39.5 (1.03)	38.5 (0.99)
Proliferative	186	32.3 (1.14)	36.7 (1.17)	36.7 (1.13)
Ungradable	116	36.0 (1.44)	38.9 (1.37)	39.1 (1.27)
Diabetic participants (N=925)		**P<0.0001**†	**P<0.0001**†	**P=0.007**†
Normal	389	42.8 (0.76)	41.5 (0.93)	39.2 (0.92)
Very mild non-proliferative	67	39.3 (1.83)	38.5 (1.77)	37.8 (1.69)
Non-proliferative	214	36.6 (1.03)	37.5 (1.10)	36.8 (1.07)
Proliferative	175	32.2 (1.14)	34.2 (1.22)	34.4 (1.21)
Ungradable	80	36.0 (1.69)	37.2 (1.65)	37.6 (1.56)
Non-diabetic participants (N=1011)		**P<0.0001**†	**P=0.0008**†	P=0.35†
Normal	860	45.1 (0.54)	45.8 (0.72)	42.2 (0.84)
Very mild non-proliferative	75	40.0 (1.82)	42.1 (1.66)	40.1 (1.57)
Non-proliferative or worse	40	35.1 (2.49)	39.3 (2.32)	39.7 (2.23)
Ungradable	36	36.2 (2.62)	39.6 (2.43)	40.2 (2.21)

*Adjusted by age, race, systolic BP, diabetes (yes/no), and 24 hours urine protein. Diabetes was not included in the model for diabetic participants only or non-diabetic participants only.

**Adjusted by age, race, systolic BP, diabetes (yes/no), 24 hours urine protein, anemia status (yes/no), use of angiotensin receptor blockers (yes/no), any cardio-vascular disease (yes/no), body mass index, cyclase-activating parathyroid hormone level, and smoking status (never/former/current).

†For test assessing whether there is any statistically significant difference in eGFR among categories of ETDRS retinopathy score.

Table 3

Crude and adjusted mean eGFR (ml/min/1.73m^2) for individual ETDRS retinopathy features in all subjects (n=1936)

		Univariate Analysis	**Multivariate Analysis adjusted by traditional risk factors***	**Multivariate Analysis adjusted by traditional and non-traditional risk factors****
ETDRS retinopathy features	n§	Mean eGFR (SE)	Mean eGFR (SE)	Mean eGFR (SE)
Panretinal photocoagulation		**P<0.0001**†	**P=0.0004**†	P=0.10†
No	1687	42.5 (0.39)	42.5 (0.52)	39.9 (0.56)
Yes	162	32.7 (1.25)	38.1 (1.24)	38.0 (1.19)
Microaneurysm count (Ma)		**P<0.0001**†	**P=0.005**†	P=0.09†
None/Questionable	1354	43.7 (0.43)	43.5 (0.58)	40.7 (0.61)
1–2	109	38.0 (1.50)	39.5 (1.42)	38.3 (1.33)
3–4	34	36.7 (2.69)	40.8 (2.47)	42.2 (2.36)
5	252	36.0 (0.99)	40.6 (1.06)	38.9 (1.02)
Retinal hemorrhage count (RH)		**P<0.0001**†	**P<0.0001**†	**P=0.0008**†
None/Questionable	1347	44.0 (0.43)	43.7 (0.58)	40.8 (0.60)
1	90	37.5 (1.64)	38.8 (1.53)	38.0 (1.45)
≥2	353	34.9 (0.83)	39.0 (0.93)	37.6 (0.91)
RH-type		**P<0.0001**†	**P<0.0001**†	**P=0.0006**†
None/Questionable	1344	44.0 (0.43)	43.7 (0.58)	40.8 (0.61)
Flame/ Blot	364	35.9 (0.82)	39.2 (0.89)	38.3 (0.87)
Both	84	33.8 (1.71)	38.8 (1.66)	35.8 (1.55)
RH/Ma		**P<0.0001**†	**P<0.0001**†	**P=0.001**†
None/Questionable	1296	44.1 (0.43)	43.9 (0.59)	41.0 (0.62)
<Standard 1	334	37.6 (0.86)	40.2 (0.89)	39.1 (0.87)
>1, <Standard 2A	116	33.6 (1.45)	38.5 (1.42)	36.8 (1.34)
≥Standard 2A	23	30.3 (3.32)	36.2 (3.05)	33.2 (2.75)
Hard exudates		**P<0.0001**†	**P=0.003**†	**P=0.09**†
None/Questionable	1634	42.6 (0.39)	42.7 (0.54)	40.1 (0.57)
< Standard 3	36	29.7 (2.64)	34.7 (2.45)	35.2 (2.30)
≥ Standard 3	125	35.9 (1.42)	40.8 (1.37)	39.2 (1.31)
Soft exudate		**P<0.0001**†	P=0.06†	**P=0.01**†
None/Questionable	1620	42.5 (0.40)	42.8 (0.54)	40.2 (0.58)
Definite	49	32.7 (2.27)	38.7 (2.14)	35.3 (1.99)
Intraretinal microvascular abnormality		**P<0.0001**†	**P<0.0001**†	**P<0.0001**†
None/Questionable	1731	42.2 (0.38)	42.6 (0.53)	40.2 (0.57)
Yes	33	28.7 (2.81)	32.7 (2.55)	31.0 (2.36)

		Univariate Analysis	**Multivariate Analysis adjusted by traditional risk factors***	**Multivariate Analysis adjusted by traditional and non-traditional risk factors****
Neovascularization-disc		**P<0.0001**†	**P=0.01**†	**P=0.003**†
None/Questionable	1861	41.8 (0.37)	42.2 (0.50)	39.9 (0.54)
Yes	28	29.2 (3.00)	35.5 (2.71)	32.8 (2.42)
Neovascularization elsewhere		**P=0.0007**†	P=0.10†	P=0.07†
None/Questionable	1741	42.1 (0.38)	42.5 (0.53)	40.1 (0.57)
Yes	28	31.8 (3.01)	38.0 (2.73)	35.7 (2.49)
Fibrous proliferation		**P<0.0001**†	**P=0.0005**†	**P=0.0006**†
None/Questionable	1791	42.0 (0.38)	42.4 (0.52)	39.9 (0.55)
Definite	35	27.8 (2.72)	33.6 (2.52)	32.0 (2.31)

§Patients with both eyes ungradable/undeterminable to a specific feature were excluded from analysis of this specific feature.

*Adjusted by age, race, systolic BP, diabetes (yes/no), and 24 hours urine protein.

**Adjusted by age, race, systolic BP, diabetes (yes/no), 24 hours urine protein, anemia status (yes/no), use of angiotensin receptor blockers (yes/no), any cardio-vascular disease (yes/no), body mass index, cyclase-activating parathyroid hormone level, and smoking status (never/former/current).

†For test assessing whether there is any statistically significant difference in eGFR among categories of retinopathy features.

Table 4

Multivariate analysis of ETDRS retinopathy features with eGFR (ml/min/1.73m^2) for all participants

	Retinal features only without adjustment by other risk factors (n=1746)[§]	**Adjustment by traditional risk factors[*] (n=1733)[§]**	**Adjustment by traditional and non-traditional risk factors[**] (n=1649)[§]**
ETDRS retinopathy features	Mean eGFR (SE)	Mean eGFR (SE)	Mean eGFR (SE)
Panretinal photocoagulation	**P=0.002**[†]	**P=0.006**[†]	P=0.09[†]
No	32.5 (1.73)	35.5 (1.64)	34.5 (1.56)
Yes	27.1 (2.28)	31.2 (2.15)	32.0 (2.03)
Retinal hemorrhage	**P<0.0001**[†]	**P=0.002**[†]	**P=0.03**[†]
None/Questionable	33.8 (2.00)	35.8 (1.88)	34.8 (1.77)
1	28.6 (2.42)	31.8 (2.25)	32.7 (2.13)
≥2	27.0 (1.73)	32.3 (1.70)	32.1 (1.61)
Hard exudates	**P=0.01**[†]	P=0.06[†]	P=0.27[†]
None/Questionable	32.6 (1.65)	34.8 (1.56)	33.9 (1.47)
<Standard 3	24.3 (3.15)	29.2 (2.95)	30.7 (2.78)
≥ Standard 3	32.5 (2.13)	35.9 (2.00)	35.1 (1.90)
Intraretinal microvascular abnormality	**P=0.0005**[†]	**P=0.0006**[†]	**P=0.0003**[†]
None/Questionable	34.7 (1.32)	37.7 (1.29)	37.5 (1.25)
Yes	25.0 (2.98)	29.0 (2.76)	29.0 (2.58)

[*] Adjusted by age, race, systolic BP, diabetes (yes/no), and 24 hours urine protein.

[**] Adjusted by age, race, systolic BP, diabetes (yes/no), 24 hours urine protein, anemia status (yes/no), use of angiotensin receptor blockers (yes/no), any cardio-vascular disease (yes/no), body mass index, cyclase-activating parathyroid hormone level, and smoking status (never/former/current).

[§] Number of subjects included in the analysis after excluding the subjects with missing data in one or more predictors.

[†] For test assessing whether there is any statistically significant difference in eGFR among categories of retinopathy features.

Table 5

Crude and adjusted mean eGFR (ml/min/1.73m^2) for retinopathy features not contributing to the ETDRS score

		Univariate Analysis	**Multivariate Analysis adjusted by traditional risk factors***	**Multivariate Analysis adjusted by traditional and non-traditional risk factors****
Feature	n§	Mean eGFR (SE)	Mean eGFR (SE)	Mean eGFR (SE)
Arterio-venous abnormalities		**P=0.0003**†	P=0.18†	P=0.33†
None/Questionable	1694	42.2 (0.39)	42.4 (0.52)	40.1 (0.55)
Yes	159	37.3 (1.27)	40.8 (1.21)	39.0 (1.15)
Sheathing of arterioles		**P<0.0001**†	**P<0.0001**†	**P=0.005**†
No	1799	42.1 (0.37)	42.5 (0.51)	40.1 (0.55)
Yes	59	28.5 (2.08)	33.8 (1.93)	35.0 (1.81)
Macula edema		**P=0.002**†	P=0.44†	P=0.80†
None/Questionable	1728	42.1 (0.39)	42.5 (0.53)	40.0 (0.57)
Yes	61	35.7 (2.05)	41.0 (1.89)	39.5 (1.76)
Focal laser		**P<0.0001**†	**P=0.01**†	P=0.25†
No	1695	42.3 (0.39)	42.4 (0.52)	39.8 (0.56)
Yes	154	34.3 (1.28)	39.3 (1.25)	38.5 (1.20)

§Participants with both eyes ungradable/undeterminable to a specific feature were excluded from analysis of this specific feature.

*Adjusted by age, race, systolic BP, diabetes (yes/no), and 24 hours urine protein.

**Adjusted by age, race, systolic BP, diabetes (yes/no), 24 hours urine protein, anemia status (yes/no), use of angiotensin receptor blockers (yes/no), any cardio-vascular disease (yes/no), body mass index, cyclase-activating parathyroid hormone level, and smoking status (never/former/current).

†For test assessing whether there is any statistically significant difference in eGFR among categories of retinopathy features.

Table 6

Crude and adjusted mean eGFR (ml/min/1.73m^2) for each quartile of IVAN caliber measurements (N=1,599)

		Univariate Analysis	**Multivariate Analysis adjusted by traditional risk factors***	**Multivariate Analysis adjusted by traditional and non-traditional risk factors****
Vessel caliber measure (based on the average of two eyes)	n	Mean eGFR (SE)	Mean eGFR (SE)	Mean eGFR (SE)
Arteriole diameter		P=0.41†	P=0.57†	P=0.30†
1st quartile (99 – 140)	399	41.8 (0.80)	43.2 (0.86)	40.7 (0.86)
2nd quartile (>140 – 149)	401	43.2 (0.80)	44.3 (0.83)	41.8 (0.83)
3rd quartile (>149 – 159)	401	42.5 (0.80)	43.0 (0.84)	40.1 (0.82)
4th quartile (>159 – 199)	398	43.5 (0.80)	43.4 (0.84)	40.9 (0.81)
Venular diameter		**P=0.01†**	**P=0.01†**	P=0.16†
1st quartile (141 – 203)	400	40.9 (0.79)	41.5 (0.86)	39.8 (0.88)
2nd quartile (>203 – 219)	399	44.4 (0.80)	44.4 (0.85)	41.9 (0.85)
3rd quartile (>219 – 236)	401	42.5 (0.79)	43.0 (0.84)	40.9 (0.84)
4th quartile (>236 – 317)	399	43.2 (0.80)	44.7 (0.84)	40.8 (0.82)
Arteriole-venular ratio		**P=0.02†**	**P=0.007†**	P=0.15†
1st quartile (0.38 – 0.64)	445	41.9 (0.76)	44.5 (0.80)	41.4 (0.79)
2nd quartile (>0.64 –0.68)	400	43.0 (0.79)	42.8 (0.85)	40.3 (0.83)
3rd quartile (>0.68 – 0.73)	388	44.8 (0.81)	44.5 (0.84)	41.8 (0.83)
4th quartile (>0.73 – 0.97)	366	41.4 (0.83)	41.5 (0.87)	39.9 (0.86)

*Adjusted by age, race, systolic BP, diabetes (yes/no), and 24 hours urine protein.

**Adjusted by age, race, systolic BP, diabetes (yes/no), 24 hours urine protein, anemia status (yes/no), use of angiotensin receptor blockers (yes/no), any cardio-vascular disease (yes/no), body mass index, cyclase-activating parathyroid hormone level and smoking status (never/former/current).

†For test assessing whether there is any statistically significant difference in eGFR among quartiles of IVAN vascular caliber measure.