Structural Changes in the Retinal Microvasculature and Renal Function

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Purpose. To evaluate the associations between chronic kidney disease (CKD) and microalbuminuria, and a comprehensive range of retinal microvascular abnormalities including traditional and new retinal vascular measures.

Methods. This was a population-based, cross-sectional study on 3280 urban Malay adults. The albumin/creatinine ratio (ACR) was calculated from spot urine samples. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine concentration. Retinal vascular caliber and geometry were quantified from retinal fundus photographs using a semiautomated computer-assisted program. Qualitative changes including focal arteriolar narrowing, arteriovenous nicking, and opacification of the arteriolar wall were assessed by trained graders.

Results. In multivariate analyses adjusting for age, sex, hypertension, diabetes, and smoking, narrower retinal arteriolar caliber ($P = 0.008$), smaller retinal vascular fractal dimensions ($P = 0.014$), and the presence of AV nicking and opacification ($P = 0.005$ and $P < 0.001$, respectively) were significantly associated with lower eGFR. In multivariate adjusted logistic regression analyses, none of the retinal markers was associated with CKD. A smaller fractal dimension ($P < 0.001$) and the presence of focal arteriolar narrowing, AV nicking and opacification were associated with higher ACR ($P < 0.001$, $P = 0.01$, and $P = 0.002$, respectively). Narrower retinal arterioles ($P = 0.041$); smaller fractal dimensions ($P = 0.006$); and focal arteriolar narrowing, AV nicking, and opacification ($P = 0.007$, $P = 0.007$, and $P = 0.012$, respectively) were associated with higher likelihoods of having microalbuminuria.

Conclusions. Quantitative changes of the retinal vascular geometry and qualitative changes in the vessel architecture are associated with markers of renal dysfunction and damage.

Keywords: retinal vasculature, chronic kidney disease, microalbuminuria

Changes in the retinal vasculature have been shown to be biomarkers of microvascular pathology. Retinal microvascular signs including microaneurysms, cotton-wool spots, hemorrhages, arteriovenous nicking, and focal and generalized narrowing are associated with several important cardiovascular outcomes including hypertension, stroke, and heart disease.[1–3] More recently, a range of computer-based programs has been developed to perform quantitative assessment of a new class of geometric parameters of the retinal vasculature, including fractal dimension, tortuosity, and bifurcation.[4–7] These measures are potentially more indicative of the overall developmental health and quality of the retinal vascular network,[8] and may also reflect the state of the systemic circulation.

A defective renal microcirculation, also known as microvascular disease, is a prominent pathological feature in CKD. The associations between both traditional and novel retinal vascular changes, and chronic kidney disease (CKD), have not been clearly established. Diabetic retinopathy and nephropathy are known to be closely associated,[9] but data on renal associations of other retinopathy signs and retinal vascular changes, which could potentially antedate retinopathy changes, are relatively scarce and inconsistent. A summary of the existing literature on retinal signs and CKD is presented in Table 1. The Atherosclerosis Risk in Communities (ARIC) study reported weak associations between AV nicking, retinal hemorrhages, microaneurysms, cotton-wool spots, and the likelihood of renal dysfunction development.[10] The Cardiovascular Health Study (CHS) found strong associations between retinopathy changes and renal function deterioration, but there were no associations with retinal arteriolar abnormalities such as the arteriolar-venular (AV) diameter ratio, AV nicking, or focal arteriolar narrowing.[11] Amongst the quantitative retinal vascular markers, retinal vessel caliber has been inconsistently associated with renal dysfunction,[12–14] while a recent case-control study found that suboptimal fractal dimensions were associated with an increased prevalence of CKD.[15]

The aim of this study was to evaluate the associations between CKD and a comprehensive range of retinal microvascular abnormalities including traditional and new retinal vascular measures, in an adult population.

Table 1. Studies on Retinal Changes and Kidney Disease

Study Reference	Study Design	Retinal Parameters Measured	Renal Outcome	Main Findings
ARIC (n = 10,056)[10]	Cohort study	Qualitative retinal microvascular changes	Incident renal dysfunction	Retinopathy, microaneurysms, retinal hemorrhages, soft exudates, AV nicking associated with development of renal dysfunction
CHS (n = 1,349)[11]	Cohort study	Qualitative retinal microvascular changes	Incident renal dysfunction	Presence of retinopathy associated with development of renal dysfunction
SiMES (n = 3,280)[12]	Cross-sectional study	Retinal vessel caliber	Presence of CKD	Retinal arteriolar narrowing was associated with chronic kidney disease
MESA (n = 675)[13]	Cross-sectional study	Retinal vessel caliber	Presence of albuminuria	A U-shaped pattern was seen with higher prevalence of albuminuria amongst eyes with the widest and narrowest arterioles
MESA (n = 4,594)[14]	Cohort study	Retinal vessel caliber	Incident CKD	Narrower retinal arterioles were associated with a higher risk of developing CKD in white subjects but not other ethnic groups
Sng et al. (n = 261 cases with CKD and 651 controls)[15]	Case-control study	Retinal vessel fractal dimension	Presence of CKD	Cases with CKD had lower mean fractal dimensions than controls without CKD There was a U-shaped relationship with CKD, in which subjects in the highest and lowest quintiles had higher prevalence of CKD

Methods

Study Population

The Singapore Malay Eye Study (SiMES) is a population-based, cross-sectional study of urban Malay adults aged 40 to 80 years residing in Singapore. Study design and population details have been described elsewhere.[16,17] In brief, Malay subjects were selected from a national database using an age-stratified random sampling process. Of those eligible, 3280 (78.7% participation rate) were examined between 2004 and 2006.

All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent was obtained from the subjects, and the study was approved by the Institutional Review Board of the Singapore Eye Research Institute.

Assessment of Renal Function

Spot urine samples were collected and sent for biochemical analyses of albumin, creatinine, and glucose to the National University Hospital Reference Laboratory on the same day. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine concentration by using the Chronic Kidney Disease Epidemiology Collaboration equation[18] (eGFR = 175 × [serum creatinine (milligram per deciliter) −1.154 × age − 0.203 × (0.742 for women)]. CKD was defined by eGFR <60 mL/min/1.73 m^2, representing stage 3 and above of CKD as defined by the US National Kidney Foundation Kidney Disease Outcome Quality Initiative.[19] The albumin/creatinine ratio (ACR) was calculated from assayed albumin and creatinine levels and microalbuminuria was defined as ACR >17.0 for males and ACR >25.0 for females.

Measurement of Retinal Vascular Network Geometry

Digital fundus photography was taken using a 45° digital retinal camera (Canon CR-DGi with a 10D SLR digital camera backing; Canon, Tokyo, Japan) after pupil dilation using tropicamide 1% and phenylephrine hydrochloride 2.5%. Two retinal images of each eye were obtained, one centered at the optic disc and another centered at the fovea. Of the 3280 participants, 3267 subjects (99.6%) had fundus photographs taken for both eyes. We used an optic disc-centered photograph of the right eye of each participant; if the photograph of the right eye was ungradable, the measurement was performed on the left eye.

We used a new semiautomated computer-assisted program (Singapore I Vessel Assessment [SIVA], version 1.0) to quantitatively measure a range of retinal vascular parameters, including retinal vascular caliber, retinal vascular fractal dimension, retinal vascular tortuosity, and retinal branching measures, from digital fundus images.[20,21] Trained graders, masked to participant characteristics, executed the SIVA program to measure the retinal vasculature, according to a standardized protocol. Images of poor quality, including those due to media opacities (e.g., dense lens opacity), small size of the pupil, or images that were out of focus or that had poor contrast were excluded.

The computer-assisted program automatically identifies the optic disc, projects a grid referenced to the optic disc, identifies the vessel types (arterioles and venules), and performs the vessel measurements detailed below. The measured area of retinal vascular tortuosity and branching measures was standardized and defined as the region from 0.5 to 2.0 disc diameters away from the disc margin. Trained graders follow a standardized protocol and perform visual evaluations of the automated measurements with corrections made manually if necessary.[20] Retinal vascular fractal dimension was calculated from the skeletonized line tracing using the box-counting method, a "global" measure summarizing the whole branching pattern of the retinal vascular tree. Retinal vascular tortuosity is defined as the integral of the curvature square along the path of the vessel, normalized by the total path length.[4,20,22] All vessels coursing through the measured zone with a width larger than 40 μm were measured; these measures do not have units. A smaller tortuosity value indicates

Table 2. Demographic Characteristics of Study Population Stratified by CKD and Microalbuminuria Status

	Persons With CKD (n = 1196)		Persons Without CKD (n = 2084)			Persons With Microalbuminuria (n = 268)		Persons Without Microalbuminuria (n = 676)		
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Age, y	66.17	9.11	56.78	10.65	<0.001	60.70	10.55	54.49	9.93	<0.001
Systolic blood pressure, mm Hg	157.06	24.67	144.57	22.85	<0.001	161.10	23.99	142.84	21.56	<0.001
Diastolic blood pressure, mm Hg	80.75	12.04	79.46	10.97	0.008	85.18	12.66	80.47	10.60	<0.001
BMI, kg/m^2	26.70	4.77	26.27	5.19	0.055	26.94	5.11	25.90	4.93	0.004
Creatinine, md/dL	143.05	103.94	80.41	17.46	<0.001	104.36	43.10	94.82	19.62	<0.001
Glucose, mmol/L	7.71	4.34	6.55	3.44	<0.001	8.49	5.08	6.20	2.72	<0.001
Glycosylated hemoglobin, %	6.81	1.67	6.36	1.51	<0.001	7.12	2.00	6.08	1.08	<0.001
Total cholesterol, mmol/L	5.67	1.37	5.62	1.11	0.309	5.72	1.27	5.60	1.06	0.149
LDL cholesterol, mmol/L	3.43	1.11	3.58	0.97	<0.001	3.39	0.97	3.40	0.92	0.635
HDL cholesterol, mmol/L	1.30	0.32	1.37	0.33	<0.001	1.31	0.33	1.34	0.32	0.293
Triglycerides, mmol/L	2.07	1.55	1.48	1.23	<0.001	2.29	1.29	1.91	1.05	<0.001
Female sex, %	10.87		75.58		<0.001		57.84		45.71	0.001
Hypertension, %	73.64		65.55		<0.001		85.45		60.50	<0.001
Diabetes, %	25.96		23.11		0.069		41.51		12.93	<0.001
Hyperlipidemia, %	43.48		39.93		0.048		54.72		38.14	<0.001
Current smoking, %	31.71		13.67		<0.001		17.91		24.70	0.025
History of myocardial infarction, %	11.41		3.71		<0.001		11.61		4.44	<0.001
History of stroke, %	3.52		1.92		0.005		2.99		2.22	0.491

a straighter vessel. The estimates were summarized as retinal arteriolar tortuosity and retinal venular tortuosity, representing the average tortuosity of arterioles and venules of the eye, respectively. Retinal branching angle (BA; ω, which is the sum of $\theta_1 + \theta_2$, $\theta_1 < \theta_2$ that is defined as the angle subtended between two daughter vessels at each vascular bifurcation).[23] All vessels with the first bifurcation within the measured zone were measured.

Qualitative Assessment of Retinal Arteriolar Wall Signs and Retinopathy Lesions

The digital retinal photographs were analyzed for qualitative changes by trained graders based on a standardized protocol and compared against a standard set of images. Retinal arteriolar wall signs included focal arteriolar narrowing, arteriovenous nicking, and opacification of the arteriolar wall. Adjudication was provided by two senior investigators. All qualitative signs were defined as being present if graded as definite.

Assessment and Definitions of Risk Factors

Blood pressure was measured with the patient seated after 5 minutes of rest, using an automated sphygmomanometer (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, WI). Systolic and diastolic blood pressures (SBP and DBP, respectively) were taken.[24] Two readings were taken 5 minutes apart, with a third reading taken if the two differed by >10 mm Hg systolic or >5 mm Hg diastolic. The mean of the two closest readings was then used for the analysis. Hypertension was defined as a systolic pressure of >140 mm Hg, a diastolic pressure >90 mm Hg, or a self-reported history of hypertension.

All participants underwent a standardized interview[17,25,26] that covered socioeconomic measures (e.g., income, education); lifestyle risk factors (e.g., smoking); medication use, and self-reported history of systemic diseases. Diabetes mellitus was identified from plasma glucose ≥200 mg/dL (11.1 mmol/L); self-reported use of diabetic medication, or physician-diagnosed diabetes.

Statistical Analysis and Definitions

Statistical analysis was performed using commercial statistical software (SPSS version 16.0; SPSS, Inc., Chicago, IL). Multivariate logistic and linear regression models were constructed with retinal vascular measurements and signs as the dependent variables to assess the relationships with CKD, eGFR, and microalbuminuria, respectively. Adjustments were made for age and sex initially and secondly for hypertension, diabetes, smoking, history of stroke, body mass index (BMI), lipids, and education. Logarithmic transformation was used for analyses of ACR. Area under receiver operating characteristics (ROC) curves were calculated to compare the ability of two models to predict CKD and microalbuminuria. The first model included the classical risk factors for CKD and microalbuminuria (age, sex, hypertension, diabetes and smoking, history of stroke, body mass index, lipids, and education), while the second added the retinal vascular parameters that were significantly associated with renal function from regression models.

Results

Out of 3280 subjects, 365 subjects (11.1%) had ungradable images and were thus excluded from analysis. The demographic characteristics of the population, stratified by CKD and microalbuminuria status, are summarized in Table 2. Subjects with CKD were more likely to be older, hypertensive, smokers, and have concomitant cardiovascular and cerebrovascular disease. Subjects with microalbuminuria were similarly older and more likely to be hypertensive, diabetic, smokers, and have concomitant cardiovascular disease.

In multivariate analyses with eGFR as the dependent variable and adjusting for age, sex, hypertension, diabetes, and smoking (Table 3), retinal arteriolar caliber and the retinal vascular fractal dimension were significantly associated with eGFR. For every SD reduction in eGFR, the retinal arteriolar caliber was reduced by 0.77 μm (95% confidence interval [CI]

TABLE 3. Associations Between Retinal Vascular Characteristics and eGFR and CKD

	eGFR				CKD			
	Model 1*		Model 2†		Model 1		Model 2†	
Retinal Vascular Characteristics	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Arteriolar caliber, per SD increase	0.91 (0.33, 1.48)	0.002	0.77 (0.20, 1.35)	0.008	0.89 (0.81, 0.99)	0.031	0.90 (0.81, 1.01)	0.074
Venular caliber, per SD increase	0.11 (−0.46, 0.69)	0.696	0.17 (−0.39, 0.74)	0.547	0.96 (0.87, 1.06)	0.417	1.07 (0.86, 1.07)	0.457
Fractal dimension, per SD increase	0.57 (−0.11, 0.25)	0.100	0.83 (0.17, 1.48)	0.014	0.98 (0.86, 1.11)	0.746	0.94 (0.82, 1.08)	0.391
Arteriolar tortuosity, per SD increase	−0.15 (−0.74, 0.44)	0.610	−0.17 (−0.74, 0.40)	0.560	1.01 (0.91, 1.13)	0.801	1.00 (0.89, 1.12)	0.972
Venular tortuosity, per SD increase	−0.07 (−0.65, 0.51)	0.820	−0.20 (−0.77, 0.36)	0.491	1.04 (0.94, 1.16)	0.465	1.04 (0.93, 1.17)	0.474
Arteriolar branching angle, per SD increase	0.18 (−0.41, 0.76)	0.558	0.06 (−0.52, 0.63)	0.849	0.98 (0.88, 1.09)	0.740	1.00 (0.89, 1.12)	0.969
Branching angle venule, per SD increase	0.21 (−0.37, 0.79)	0.482	0.11 (−0.45, 0.68)	0.690	0.98 (0.88, 1.09)	0.710	1.00 (0.90, 1.12)	0.967
Focal arteriolar narrowing	−0.93 (−2.96, 1.10)	0.370	−1.30 (−3.26, 0.66)	0.192	1.21 (0.83, 1.76)	0.330	1.30 (0.87, 1.12)	0.197
AV nicking	−3.05 (−5.26, −0.84)	0.007	−3.09 (−5.25, −0.94)	0.005	1.44 (0.95, 2.17)	0.085	1.52 (0.98, 2.36)	0.062
Opacification	−3.26 (−4.90, −1.63)	<0.001	−3.01 (−4.61, −1.41)	<0.001	1.14 (0.84, 1.55)	0.416	1.11 (0.80, 1.54)	0.538

* Adjusted for age and sex.

† Adjusted for age, sex, hypertension, diabetes, smoking, history of stroke, BMI, lipids, and education.

0.20, 1.35; $P = 0.008$), and the retinal vascular fractal dimension reduced by 0.83 (0.17, 1.48; $P = 0.014$). The presence of AV nicking and opacification were also associated with lower eGFR (mean difference −3.09 [−5.25, −0.94] and −3.01 [−4.61, −1.41], $P = 0.005$ and $P < 0.001$, respectively). In multivariate adjusted logistic regression analyses with CKD as the dependent variable (Table 3), none of the vessel markers were associated with CKD.

In multivariate analyses of the associations with logACR (Table 4), a larger fractal dimension was associated with a lower ACR (mean difference −0.21 [−0.32, −0.10] per SD increase in fractal dimension; $P < 0.001$). The presence of focal arteriolar narrowing, AV nicking, and opacification were also associated with higher ACR (mean difference 0.60 [0.28, 0.92], 0.47 [0.12, 0.83], and 0.40 [0.15, 0.66]; $P < 0.001$, $P = 0.01$ and $P = 0.002$, respectively). In logistic regression analyses with microalbuminuria as the dependent variable (Table 4), larger CRAE and Df were associated with a lower likelihood of microalbuminuria (odds ratio [OR] 0.83 [0.70, 0.99] and 0.75 [0.61, 0.92]; $P = 0.041$ and 0.006, respectively). Focal arteriolar narrowing, AV nicking, and opacification were associated with higher likelihoods of having microalbuminuria (OR 2.06 [1.21, 3.48], 2.18 [1.23, 3.86], and 1.72 [1.13, 2.64]; $P = 0.007$, $P = 0.007$, and $P = 0.012$, respectively).

ROC curves were constructed to determine the discrimination of two risk factor models for CKD and microalbuminuria (Table 5, Figure). The traditional risk factors model included age, sex, hypertension, diabetes, and current smoking, while the additional risk factors model included Df, CRAE, focal arteriolar narrowing, AV nicking, and opacification as well. The additional risk factors model had better discriminative ability for microalbuminuria than the traditional model (area under ROC [SE] 0.80[0.02] vs. 0.77[0.02]; $P = 0.003$).

DISCUSSION

In this population-based study of Asian adults, associations were found between a number of retinal vessel characteristics and markers of renal dysfunction and renal damage. Narrower retinal arterioles were associated with lower eGFR and microalbuminuria, while a smaller retinal vascular fractal dimension was associated with lower eGFR, higher ACR, and higher likelihoods of CKD and microalbuminuria. Some qualitative vascular signs including focal arteriolar narrowing, AV nicking, and opacification were also associated with renal dysfunction.

Data on retinal microvascular changes and renal dysfunction have been limited (Table 1). The CHS,[11] a prospective multicenter cohort study of cardiovascular disease in elderly Americans, evaluated the associations between retinopathy and other retinal arteriolar changes and 4-year changes in serum creatinine levels and decline in GFR as part of an ancillary study. Retinopathy lesions were strongly associated with several measures of renal function decline, but retinal arteriolar abnormalities showed no significant associations with changes in renal function. These results are similar to those found in the ARIC, a population-based cohort study which also examined the associations between retinopathy signs, retinal arteriolar changes, and renal dysfunction defined by the 6-year change in serum creatinine. In multivariate analyses adjusting for diabetes, BP, and other factors, associations between focal arteriolar changes and renal dysfunction were weaker and less consistent than the associations with retinopathy changes.

Retinal microvascular changes associated with systemic vasculopathy may also serve as markers of renal dysfunction.

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TABLE 4. Associations Between Retinal Vessel Measurements and ACR and Microalbuminuria

Characteristics	ACR				Microalbuminuria			
	Model 1*		Model 2†		Model 1*		Model 2†	
	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CRAE, per SD increase	−0.09 (−0.19, 0.01)	0.074	−0.06 (−0.15, 0.04)	0.235	0.87 (0.74, 1.02)	0.077	0.83 (0.70, 0.99)	0.041
CRVE, per SD increase	0.07 (−0.03, 0.16)	0.176	0.05 (−0.04, 0.15)	0.244	1.03 (0.88, 1.20)	0.718	0.98 (0.83, 1.16)	0.804
Fractal (Df), per SD increase	−0.22 (−0.33, −0.11)	<0.001	−0.21 (−0.32, −0.10)	<0.001	0.76 (0.64, 0.92)	0.004	0.75 (0.61, 0.92)	0.006
Simple tortuosity arteriole, per SD increase	−0.03 (−0.14, 0.07)	0.512	−0.02 (−0.12, 0.08)	0.666	0.90 (0.75, 1.07)	0.236	0.90 (0.74, 1.09)	0.267
Simple tortuosity venule, per SD increase	0.02 (−0.07, 0.11)	0.677	−0.02 (−0.11, 0.07)	0.615	1.06 (0.91, 1.23)	0.437	1.01 (0.86, 1.18)	0.918
Branching angle arteriole, per SD increase	0.07 (−0.03, 0.18)	0.152	0.08 (−0.02, 0.18)	0.097	1.14 (0.97, 1.34)	0.119	1.14 (0.95, 1.36)	0.149
Branching angle venule, per SD increase	0.03 (−0.07, 0.13)	0.562	−0.01 (−0.10, 0.08)	0.836	1.09 (0.93, 1.27)	0.290	1.04 (0.88, 1.24)	0.635
Focal arteriolar narrowing	0.60 (0.26, 0.93)	<0.001	0.60 (0.28, 0.92)	<0.001	1.88 (1.15, 3.08)	0.012	2.06 (1.21, 3.48)	0.007
AV nicking	0.52 (0.15, 0.89)	0.006	0.47 (0.12, 0.83)	0.010	2.06 (1.20, 3.54)	0.009	2.18 (1.23, 3.86)	0.007
Opacification	0.48 (0.22, 0.74)	<0.001	0.40 (0.15, 0.66)	0.002	1.88 (1.26, 2.79)	0.002	1.72 (1.13, 2.64)	0.012

* Adjusted for age and sex.

† Adjusted for age, sex, hypertension, diabetes, smoking, history of stroke, BMI, lipids, and education.

TABLE 5. Comparison of Area Under ROC Curves for Predictive Models for CKD and Microalbuminuria

	Adding Eye Variables Model* Area (SE)	Classic Risk Factors Model† Area (SE)	*P* Values
CKD-EPI	0.90 (0.01)	0.90 (0.01)	0.23
Microalbuminuria	0.80 (0.02)	0.77 (0.02)	0.003

* Classic risk factors plus retinal vascular characteristics (retinal arteriolar caliber, retinal vascular fractal dimension, focal arteriolar narrowing, AV nicking, and opacification of arteriolar wall).

† Classic risk factors include age, sex, hypertension, diabetes, smoking, history of stroke, BMI, lipids, and education.

The ARIC study reported weak associations between AV nicking, retinal hemorrhages, microaneurysms, cotton-wool spots, and the likelihood of renal dysfunction development.[10] The CHS found strong associations between retinopathy changes and renal function deterioration, but there were no associations with retinal arteriolar abnormalities such as the arteriolar-venular (AV) diameter ratio, AV nicking, or focal arteriolar narrowing.[11] In both these population-based studies, the associations were independent of diabetes or hypertension, suggesting that retinal microvascular changes may be both relevant to the pathogenesis of renal dysfunction and predictors of subsequent deterioration. In the prospective Multi-Ethnic Study of Atherosclerosis (MESA),[14] narrower retinal arteriolar caliber was associated with a higher risk of incident CKD in whites. In another analysis from the MESA, there was a U-shaped association between albuminuria and retinal arteriolar caliber, with the highest and lowest quintiles of arteriolar caliber showing higher prevalence of albuminuria.[13]

More recently, the use of software to quantitate retinal vessel caliber has confirmed that retinal arteriolar narrowing is associated with CKD[12] due to hypertension. Our study results differ from these data in that retinal vessel caliber was at best marginally associated with CKD, and instead a relationship with GFR was found. Narrower retinal arterioles were associated with lower GFR, consistent with an association with CKD overall. The lack of a definite association between vessel caliber and CKD may be related to the inherent limitation of equations predicting CKD from serum creatinine levels that they perform differently to some extent in different ethnic populations, and particularly in individuals with near

FIGURE. ROC curves for predictive models for CKD and microalbuminuria.

normal GFR levels.[27] Our study population was a racially homogenous Asian population, unlike the Caucasian populations reported in most other studies, and it is also noteworthy that amongst subjects with CKD, the distribution of GFR measurements was skewed toward the near-normal range, with 30.7% within 55 to 60 mL/min/1.73 m^2. Furthermore, the MESA reported that narrower retinal arterioles were associated with a higher risk of developing CKD in white subjects but not other ethnic groups, supporting the notion that ethnic variation may influence the relationship.[14]

The study of vascular network geometry is a field in evolution, and it is still unclear which parameters are the best descriptors. Murray[28,29] first applied the "physiological principle of minimum work" to vascular networks and contended that the vascular tree is optimized to minimize energy losses in oxygen transport. Perturbations in the network may arise from atherosclerosis, aneurysmal changes, as well as vascular occlusions leading to loss of dichotomous branching. To date, increased retinal arteriolar tortuosity has been associated with severe coronary artery disease,[30] diabetes,[31,32] and hypertension,[4,33,34] while deviations in optimality reflected in the fractal dimension have been linked to stroke[35] and coronary heart disease mortality.[36] A recent publication by Sng et al.[15] reported on the results of a case-control study examining the relationship between retinal vessel fractal dimensions and CKD. Compared with controls, cases with CKD had lower mean fractal dimensions than controls without CKD. Stratification of subjects by quintiles of fractal dimensions revealed a U-shaped relationship with CKD, in which subjects in the highest and lowest quintiles had higher prevalence of CKD. However, over the first to fourth quintiles, a declining trend of CKD prevalence with larger fractal dimensions was seen. Our study has found that larger retinal fractal dimensions are continuously associated with increased GFR, a corresponding lower likelihood of CKD, as well as lower ACR levels and correspondingly lower likelihood of microalbuminuria. The consistent associations with both markers of kidney function (eGFR) and dysfunction (microalbuminuria) strengthen the plausibility of the association. The fractal dimension is a measure of the overall complexity of the vascular tree, with a larger fractal dimension representing greater complexity of the vascular tree. Microvascular rarefaction is seen in renovascular disease associated with decreased renal function,[37] and simplification of the glomerular vascular system occurs in chronic renal impairment. These qualitatively similar changes that occur in retinal and renal microvascular disease make the association between a more complex retinal vascular network and better renal function that we have found biologically plausible as well.

The strengths of our study design include in vivo assessments of retinal vascular parameters in a large homogenous population by independent and masked observers, high reproducibility in retinal vessel measurements, and standardized assessment of risk factors and biochemistry at a common facility. Limitations of our study include the cross-sectional nature of the study, and the possibility of residual confounding from hypertension or its control. Errors inherent in retinal photography and measurement,[38] as well as random errors associated with the timing of photography in relation to the cardiac cycle,[39] have been described previously. The measurement of retinal blood vessel caliber from retinal photographs also measures not the true vessel luminal diameter but the width of the column of formed blood particles.[38] These nondifferential random errors, however, would likely bias our results to the null. Selection bias cannot be totally excluded, and our racially homogenous cohort may also limit the generalizability of our findings.

In conclusion, quantitative changes of the retinal vascular geometry and qualitative changes in the vessel architecture are associated with markers of renal dysfunction and damage. These findings support the role of the retinal vasculature as a biomarker for systemic diseases.

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