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

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Abstract

Objective To investigate the association between retinopathy and chronic kidney disease.

Methods In this observational, cross-sectional study, 2605 patients of the Chronic Renal Insufficiency Cohort (CRIC) study, a multicenter study of chronic kidney disease, were offered participation. Nonmydriatic fundus photographs of the disc and macula in both eyes were obtained in 1936 of these subjects. The 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 nontraditional 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 after adjustment for traditional and nontraditional risk factors. The presence of vascular abnormalities usually associated with hypertension was also associated with lower estimated glomerular filtration rate. We found no strong direct relationship between estimated glomerular filtration rate 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 nontraditional risk factors for chronic kidney disease, suggesting that retinovascular pathology reflects renal disease.

may provide a noninvasive method for assessing the vascular condition of the kidneys. Indeed, several studies have shown associations between retinopathy and nephropathy among subjects with diabetes mellitus[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.[9-11] Retinopathy in CRIC (RCRIC) is an ancillary study of the association between retinopathy and CKD.

We previously reported that nearly 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.

Methods

The design of the parent CRIC study has been reported previously.[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 nonophthalmic 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) was used to obtain 45° digital, color fundus photographs. Participants were seated in a darkened room for 5 minutes to induce physiologic papillary dilatation. No dilatory pharmacologic compounds were used. Two images, 1 centered on the macula and 1 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 at the 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 participants. 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 Study (ETDRS) and the Atherosclerosis Risk in Communities (ARIC) fundus photographic grading protocols[13,14] were used to assess retinopathy. The Multi-Ethnic Study of Atherosclerosis protocol was used for the evaluation of macular edema from nonstereo color photographs.[15] These grading protocols have been previously used in diabetic and nondiabetic 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 panretinal photocoagulation or focal photocoagulation. Other ocular conditions were graded: central vein occlusion, branch retinal vein occlusion

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 nonproliferative retinopathy (14-20), nonproliferative retinopathy (35-53), and proliferative retinopathy (≥60). The score of the eye with the more advanced retinopathy was used as the participant's score; when the 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 intragrader and intergrader reliability for retinopathy grading was assessed in 200 eyes of 100 participants. Weighted κ for the participants' ETDRS scores were 0.77 (95% CI, 0.67-0.88) for intragrader agreement and 0.80 (95% CI, 0.69-0.91) for intergrader agreement. These values are consistent with the reproducibility reported by ETDRS.[14]

Assessment of arteriovenous 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 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 arteriole-venular ratio[13] was calculated.

The intragrader and intergrader reliability for retinal vessel caliber assessment was assessed in 98 eyes of 50 subjects. The intraclass correlation coefficient for intragrader 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 intraclass correlation coefficient for the intergrader agreement was 0.89 (95% CI, 0.80-0.94) for arterioles and 0.97 (95% CI, 0.95-0.98) for venules.

Data analyses

We compared baseline characteristics for participants with ungradable and gradable photographs. We used *t* tests to compare continuous variables and Fisher 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 estimated glomerular filtration rate (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/ethnicity, systolic blood pressure, diabetes mellitus status, and 24-hour urine protein). A second set of models included traditional factors plus the following nontraditional risk factors: anemia status (yes or no), use of

level (continuous measure), and smoking status (never, former, or current). Only those nontraditional risk factors meeting the .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 as well as by regression analysis with adjustment by traditional risk factors only and by traditional plus nontraditional risk factors. Hypertension was defined as either systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of antihypertensive medications. Diabetes mellitus was defined as either a fasting glucose level of 126 mg/dL or greater (to convert to micromoles per liter, multiply by 0.0555), random glucose level of 200 mg/dL or greater, or use of insulin or antidiabetic medication.[11] Estimated glomerular filtration rate was calculated using the Modification of 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 mellitus 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 eligible participants (74%) were photographed. Their characteristics have been described in a previous report.[12] Mean systolic blood pressure, prevalence of diabetes mellitus, proportion of women, and body mass index were significantly lower, while average eGFR was significantly higher in participants who had photographs, indicating that participants photographed were healthier than those not photographed.[12]

Among the 1936 participants with baseline photographs, 1820 (94%) had photographs that were of sufficient quality to allow ETDRS severity retinopathy scoring in 1 or both eyes, and 1599 participants (82.6%) had photographs on which measurement of retinal vessel caliber could be carried out in 1 or both eyes.

In comparison to the 1820 participants who had gradable photographs, the 116 participants who 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 rates of diabetes mellitus, hypertension, and cardiovascular disease (Table 1).

Table 1. Comparisons of Demographic and Clinical Characteristics in Participants With and Without Gradable Fundus Photographs

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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 ($P < .001$; **Table 2**). There were 182 participants with neither diabetes mellitus or hypertension and 4 (2%) had mild retinopathy

Table 2. Crude and Adjusted Mean eGFR for Each ETDRS Retinopathy Category Overall and by Diabetes Status

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Among all participants, the presence of retinopathy was associated with lower eGFR ($P < .001$; 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 nontraditional risk factors ($P = .005$). Similar relationships were observed for diabetic participants ($P < .007$; **Table 2**). For persons without diabetes mellitus, this association was significant for the univariate analysis ($P < .001$) and after adjustment for traditional factors ($P < .001$) but not after adjustment of both traditional and nontraditional risk factors ($P = .35$; **Table 2**). There was no significant interaction of diabetes mellitus on the association of retinopathy and eGFR ($P = .75$). There was also no interaction with low (<500 mg) and high (≥500 mg) 24-hour urine protein ($P = .98$), 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 nontraditional 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**).

Table 3. Crude and Adjusted Mean eGFR for Individual ETDRS Retinopathy Features in All 1936 Subjects

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Table 4. Multivariate Analysis of ETDRS Retinopathy Features With eGFR for All Participants


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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 mL/min/1.73 m^2 vs a mean of 42.1 mL/min/1.73 m^2 in participants without sheathing. Participants with arteriovenous abnormalities had a mean eGFR of 37.3 mL/min/1.73 m^2 vs a mean of 42.2 mL/min/1.73 m^2 in participants without these abnormalities ($P < .001$); however, the difference in means decreased and did not remain significant after adjustment for traditional and nontraditional risk factors ($P = .33$; **Table 5**).

Table 5. Crude and Adjusted Mean eGFR for Retinopathy Features Not Contributing to the ETDRS Score

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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 ($P = .25$) after adjustment by both traditional and nontraditional risk factors.

Among all participants, mean caliber of retinal veins and arteriole-venular ratio were significantly associated with eGFR (P values for overall difference = .01 and .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 nontraditional risk factors (**Table 6**). The average caliber of retinal arterioles was not associated with eGFR.

Table 6. Crude and Adjusted Mean eGFR for Each Quartile of IVAN Caliber Measurements for 1599 Participants

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Comment

To our knowledge, this is the first comprehensive study of retinal pathology in a cohort of patients with CKD 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 nontraditional CKD risk factors, suggesting that severity of retinopathy provides additional information on severity of CKD. The association is stronger among participants previously diagnosed as having diabetes mellitus. Nondiabetic 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.[2,6,7]

Most of the retinopathy features contributing to the ETDRS score were associated with reduced 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 arteriovenous abnormalities, which are 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[17,18] and endothelial dysfunction,[17] leading to circulatory abnormalities and reduced vascular reactivity.[19,20] Both retinopathy and nephropathy involve thickening of basement membrane[6] and muscular layers and increased leakage.[21] 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 mellitus, and other processes.[17,22,23] Furthermore, a recent study has suggested common inherited susceptibilities to retinopathy and CKD in diabetic patients.[24]

The results of our study show only a marginal association between retinal venular caliber and kidney function that could be owing 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,[25] poor glycemic control,[26] obesity, inflammation, and endothelial dysfunction.[17] Possibly, the effects of reduced kidney function may counteract the effects of diabetes mellitus on vascular diameter; therefore, no strong association between eGFR and venular calibers was observed.

Several studies have shown arteriolar narrowing related to current and past blood pressure.[27-29] Similar changes have been observed in myocardial arterioles[30,31] and kidney arterioles.[32] 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 receiving medications, may have blunted an association. Sabanayagam et al[33] 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.[32]

The fact that some of the participants of our study had ungradable photographs is a limitation of our study. However, ungradable photographs were associated with decreased renal function. Decreased media clarity by

ungradable photographs have more eye pathology,[13] suggesting that there was important information in the fact that photographs were 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 to evaluate whether the presence of retinopathy in patients with CKD offers information of prognostic value regarding accelerated loss of kidney function.

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