Retinopathy and Risk of Kidney Disease in Persons With Diabetes

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Rationale & Objective: Retinopathy and chronic kidney disease (CKD) are typically considered microvascular complications of diabetes, and cardiovascular and cerebrovascular diseases are considered macrovascular complications; however, all may share common pathological mechanisms. This study quantified the association of retinopathy with risk of kidney disease and compared with the association with cardiovascular disease in persons with diabetes.

Study Design: Retrospective cohort study.

Setting & Participants: 1,759 participants in the ARIC study who had diabetes at visit 4 and underwent retinal examination at visit 3.

Exposure: Retinopathy.

Outcome: Prevalent CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2), prevalent albuminuria (urinary albumin-creatinine ratio [UACR] > 30 mg/g), incident CKD, incident end-stage kidney disease (ESKD), incident coronary heart disease (CHD), and incident stroke.

Analytical Approach: The cross-sectional association of retinopathy with prevalent CKD and albuminuria was assessed by logistic regression. The associations between retinopathy, incident CKD, incident ESKD, incident CHD, and incident stroke were examined using Cox proportional hazards models. Seemingly unrelated regression was used to compare the strength of association between retinopathy and outcomes.

Results: During the median follow-up period of 14.2 years, 723 participants developed CKD, and there were 109 ESKD events, 399 CHD events, and 196 stroke events. Compared with the participants without retinopathy, participants with retinopathy were more likely to have reduced eGFR (OR, 1.56 [95% CI, 1.09-2.23]) and UACR > 30 mg/g (OR, 1.61 [95% CI, 1.24-2.10]). Retinopathy was associated with risk of incident CKD (HR, 1.22 [95% CI, 1.02-1.46]), ESKD (HR, 1.69 [95% CI, 1.11-2.58]), CHD (HR, 1.46 [95% CI, 1.15-1.84]), and stroke (HR, 1.43 [95% CI, 1.03-1.97]). A stronger relationship was found between retinopathy and CHD when compared with retinopathy and CKD ($P = 0.03$); all other associations were similar.

Limitations: Retinal examination and kidney measurements were taken at different visits.

Conclusions: The presence of retinopathy was associated with higher prevalence of kidney disease and higher risk of incident CKD, ESKD, and CHD. These results may suggest that a similar mechanism underlies the development of retinopathy and other adverse outcomes in diabetes.

Visual Abstract included

Complete author and article information provided before references.

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Diabetes is a great health concern in the United States and worldwide. In 2017, 451 million adults were estimated to have diabetes globally, and this number is predicted to increase to 693 million by 2045.[1] If not well controlled, diabetes can lead to long-term complications such as kidney disease, cardiovascular disease (CVD), vision impairment, and lower extremity amputations.[2] Risk factors for complications in persons with type 2 diabetes include smoking, obesity, physical inactivity, high blood pressure (BP), and hyperlipidemia.[3]

Chronic kidney disease (CKD) is a common complication of diabetes. The prevalence of CKD in US adults with diagnosed diabetes was 36.0% during 2013-2016, compared with a prevalence of 14.8% in the general population. Among 124,675 incident cases of end-stage kidney disease (ESKD) in the United States in 2016, diabetes was reported as the primary cause of 58,183 cases.[4] Studies have indicated that loss of capillary microvasculature in the glomerulus and peritubular area, partly due to imbalanced expression of angiogenic factors in the kidney, is associated with the development of glomerular and tubulointerstitial scarring.[5] Alterations in angiogenic factors are also believed to underlie the pathology of retinopathy in diabetes. Indeed, a classic belief is that diabetes-associated retinopathy is a necessary precedent to diabetes-associated nephropathy. Studies evaluating the association between retinopathy and kidney disease have also observed a positive relationship between retinopathy and CKD progression.[6-8]

In this study, we explored the association between retinopathy and kidney disease in persons with diabetes in the community-based Atherosclerosis Risk in Communities (ARIC) Study. We also examined the association between retinopathy with risk of CVD, and compared the strength of this association to that for retinopathy and kidney disease, hypothesizing that, due to the potentially shared pathology, associations with kidney outcomes would be stronger than those with CVD.[9-12] We then examined the validity of 4-variable kidney failure risk equation (KFRE)—a tool developed to predict the probability of kidney failure by use of age, sex, estimated glomerular filtration rate (eGFR), and urinary albumin-creatinine ratio (UACR)[13-17]—in the

PLAIN-LANGUAGE SUMMARY

As common complications of diabetes, retinopathy and kidney disease may share common underlying pathological mechanisms. This study examined the association of retinopathy and kidney disease among participants with diabetes in the Atherosclerosis Risk in Communities (ARIC) study using Cox proportional hazards models, and compared this association with the association of retinopathy and cardiovascular disease. Significant associations were observed in retinopathy with incident chronic kidney disease (CKD), end-stage kidney disease, coronary heart disease (CHD), and stroke. In addition, a stronger relationship was found between retinopathy and CHD when compared with retinopathy and CKD. These findings support the hypothesis of a relationship between retinopathy and kidney disease in diabetes, and suggest a potential linkage between retinopathy and cardiovascular complications in diabetes.

study population and assessed whether including retinopathy measurements would improve the discrimination of KFRE among persons with diabetes. Similarly, we explored whether including retinopathy measurements in the adapted Pooled Cohort Equations (PCE)—a tool to estimate atherosclerotic cardiovascular disease risk[18]—would improve the prediction of CVD risk among persons with diabetes.

METHODS

Study Population

The ARIC Study is a prospective cohort study that recruited 15,792 participants aged 45-64 years by probability sampling from 4 US communities during 1987 to 1989. Details of the study have been published elsewhere.[19] Follow-up examinations took place every 3 years for visit 2 in 1990-1992, visit 3 in 1993-1995, and visit 4 in 1996-1998, and the cohort was examined again for visit 5 in 2011-2013 and visit 6 in 2016-2017.

Retinal photographs were taken for 12,536 participants at visit 3.[20] Because kidney measurements were not assessed at visit 3, we used visit 4 as our baseline. Of these participants, 11,656 returned for visit 4, among which 1,805 were defined to have prevalent diabetes.[21] Diabetes at visit 4 was classified using the following criteria: fasting blood glucose level ≥ 126 mg/dL, nonfasting glucose level ≥ 200 mg/dL, self-reported history of diagnosis of diabetes by a physician, or use of medications for diabetes or high blood sugar in the past 2 weeks.[22] Because of low numbers, we excluded 8 Black participants (0.4%) in Minnesota and Maryland, 5 participants (0.3%) who reported themselves to be neither White nor Black, 7 participants (0.4%) without kidney measurements, and 26 participants (1.4%) with missing data on other variables, leaving a study population of 1,759 participants. All participants provided written informed consent at each study visit. The institutional review boards at each participating institution approved the study.

Exposure

Details about retinopathy assessment have been published previously.[23,24] In short, one 45° nonstereoscopic color retinal photograph of one eye of each participant was taken at the third visit. The eye to photograph was assigned by an algorithm to systematically achieve balance. The photographs were then assessed by masked graders in the Retinal Reading Center for retinal vascular abnormalities using the Modified Airlie House Classification of Diabetic Retinopathy. A retinopathy severity score was assigned based on the Early Treatment Diabetic Retinopathy Study severity scale. In our study, we defined categories of retinopathy as level 10, none; level 14-20, minimal (minimal nonproliferative retinopathy); level 35, mild (mild nonproliferative retinopathy); level 43+, moderate to severe (moderate to severe nonproliferative retinopathy and proliferative retinopathy).[25]

Outcome

At visits 4, 5, and 6, serum creatinine was measured and used to estimate glomerular filtration rate (eGFR) with the CKD-EPI equation.[26] Furthermore, the participants underwent active surveillance for hospitalizations and death, with *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD-10 codes extracted from all records, and linkage to the US Renal Data System (USRDS) for identification of incident ESKD.

Baseline was considered visit 4. Prevalent CKD was defined as eGFR < 60 mL/min/1.73 m^2 at visit 4 and prevalent UACR as > 30 mg/g at visit 4. Among those with eGFR ≥ 60 mL/min/1.73 m^2 at visit 4, incident CKD was defined as (1) eGFR < 60 mL/min/1.73 m^2 at a subsequent visit and an eGFR decline from visit 4 of at least 25%, (2) a hospitalization or death with a kidney-related diagnostic code excluding acute kidney failure, or (3) ESKD.[27] Among those without ESKD at visit 4, incident ESKD was defined by linkage with USRDS as previously stated.[28] Follow-up time was calculated from the date of visit 4 to the date of an incident event or December 31, 2017, for ESKD or December 31, 2018, for incident CKD.

Cardiovascular events were identified by annual questionnaire, follow-up examinations, and the community-wide surveillance procedures. Incident coronary heart disease (CHD) was defined as fatal coronary heart disease, ascertained from death certificates, or hospitalized acute myocardial infarction, ascertained by hospital records.[19,29] Stroke was identified by full hospital record abstraction. Both incident CHD and stroke events were adjudicated by physicians.

Other Variables

The participants' demographic information, health status, and risk factors for CVD were collected at each visit.[19,22,30] Body mass index (BMI) was calculated using weight and height of the participant. Hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of antihypertensive medication in the past 2 weeks. Total cholesterol was measured using the enzymatic method. Glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase method. Smoking status was categorized into ever smoking versus never smoking. Use of any medication in the past 2 weeks was collected using a questionnaire.

Statistical Analysis

We summarized the distributions of demographic characteristics and risk factors of kidney disease in participants, and compared the distribution between those who did and did not have retinopathy using t tests, χ^2 tests, and nonparametric K-sample test on the equality of medians. Logistic regression was used to assess the association of retinopathy with prevalent eGFR < 60 mL/min/1.73 m^2 and albuminuria at the fourth visit. To account for potential confounders, the models were adjusted for age, sex, race and center, BMI, smoking, hypertension, total cholesterol, use of statin, fasting glucose, use of insulin, and duration of diabetes since visit 1.

To assess the association between retinopathy and incident kidney outcomes, we applied Cox proportional hazards models to estimate the hazard ratios (HR) of incident CKD and ESKD. We also examined the association between retinopathy and cardiovascular outcomes using Cox proportional hazards models and compared the strength of association between retinopathy and kidney outcomes with that of retinopathy and CVD using seemingly unrelated regression.[31] Models were adjusted for age, sex, race and center, BMI, smoking status, hypertension, eGFR at visit 4, UACR at visit 4, total cholesterol, use of statin, fasting glucose, use of insulin, and duration of diabetes since visit 1.

To evaluate the validity of the KFRE and assess the improvement of including retinopathy to the KFRE for predicting risk of kidney failure among individuals with diabetes, we used Cox proportional hazards models to estimate the risk of ESKD in the full study population using variables in the KFRE (age, sex, eGFR, and log UACR) with and without the addition of retinopathy. We then evaluated the discrimination of the models by testing the difference in C statistics. Similarly, the risk of CVD (CHD and stroke) events was estimated using variables in the PCE (age, sex, race, smoking, systolic BP, hypertension treatment medication, total cholesterol, and high-density cholesterol), and discrimination of the models with and without the addition of retinopathy was assessed by testing the difference in C statistics.

RESULTS

Baseline Characteristics

Among the 1,759 participants with diabetes included in the study population, 508 individuals (28.9%) had retinopathy. Compared with the participants without retinopathy, the participants with retinopathy were older, more likely to be Black, and were more likely to use insulin. The participants with retinopathy also had higher BP and higher fasting glucose, as well as lower eGFR and higher UACR (Table 1; Table S1).

Association of Retinopathy With Prevalence of Kidney Disease

At visit 4, there were 176 (10.0%) prevalent cases of eGFR <60 mL/min/1.73 m^2 and 389 (22.1%) cases of UACR > 30 mg/g. In participants with retinopathy, the odds of eGFR <60 mL/min/1.73 m^2 were significantly higher than in participants without retinopathy after adjusting for risk factors (odds ratio [OR], 1.56 [95% CI, 1.09-2.23]) (Table 2). The odds of UACR > 30 mg/g in participants with retinopathy was also higher (OR, 1.61 [95% CI, 1.24-2.10]) than in participants without retinopathy. When evaluated by category, we did not observe a dose response between severity of retinopathy and prevalent kidney disease or albuminuria (Table S2).

Association of Retinopathy With Risk of Kidney Disease

The participants were observed for a median follow-up time of 14.2 years with 723 incident CKD events and 16.2 years with 109 ESKD events (Table 3; Table S3). Figure 1 presents the unadjusted kidney-event-free survival by presence of retinopathy. By crude analysis, we observed higher risks of CKD (HR, 1.51 [95% CI, 1.28-1.77]) (Table 4) in participants with any level of retinopathy compared with the participants with no retinopathy, and the association remained statistically significant after adjusting for risk factors (HR, 1.22 [95% CI, 1.02-1.46]). When comparing among levels of retinopathy, only the mild retinopathy group showed a significantly higher hazard of CKD (HR, 1.57 [95% CI, 1.15-2.15]) (Table S4) compared with the no-retinopathy group after adjustment. Risk of CKD in minimal retinopathy (HR, 1.37 [95% CI, 0.96-1.94]) and moderate-to-severe retinopathy groups (HR, 1.09 [95% CI, 0.88-1.36]) did not show significant differences when compared with the no-retinopathy group.

Similar trends were also observed in the risk of incident ESKD when comparing the participants with retinopathy with the participants without retinopathy, with significantly higher hazards of ESKD in participants with any level of retinopathy (HR, 2.92 [95% CI, 2.00-4.25]) (Table 4) and after adjustment (HR, 1.69 [95% CI, 1.11-2.58]). Analysis by levels of retinopathy showed a significantly higher risk of ESKD in the mild retinopathy group (HR, 2.72 [95% CI, 1.52-4.87]) (Table S4) but not in the

Table 1. Characteristic of Study Population at Baseline (Visit 4), by Presence of Retinopathy

Characteristic	Overall	Retinopathy	No retinopathy	*P*
N	1,759	508	1,251	
Age, y	63.4 ± 5.6	64.2 ± 5.7	63.1 ± 5.5	<0.001
Female	900 (51.2%)	271 (53.3%)	629 (50.3%)	0.24
Race/Center				
Whites, Forsyth Co.	331 (18.8%)	88 (17.3%)	243 (19.4%)	
Whites, Minneapolis	361 (20.5%)	75 (14.8%)	286 (22.9%)	
Whites, Washington Co.	511 (29.1%)	131 (25.8%)	380 (30.4%)	
Blacks, Forsyth Co.	62 (3.5%)	22 (4.3%)	40 (3.2%)	
Blacks, Jackson	494 (28.1%)	192 (37.8%)	302 (24.1%)	
BMI, kg/m^2	31.7 ± 5.9	31.9 ± 6.1	31.6 ± 5.8	0.28
SBP, mm Hg	132.3 ± 19.1	136.1 ± 20.0	130.8 ± 18.5	<0.001
DBP, mm Hg	70.0 ± 10.7	69.8 ± 10.8	70.1 ± 10.7	0.64
Total cholesterol, mg/dL	198.1 ± 41.1	198.4 ± 43.9	198.0 ± 39.9	0.86
Fasting glucose, mg/dL	169.4 ± 64.1	181.8 ± 74.4	164.4 ± 58.7	<0.001
Duration of diabetes, y	8.9 ± 0.3	8.9 ± 0.4	8.9 ± 0.3	0.61
Ever smoker	1,053 (59.9%)	281 (55.3%)	772 (61.7%)	0.01
Hypertension	1,144 (65.0%)	374 (73.6%)	770 (61.6%)	<0.001
Statin use	306 (17.4%)	88 (17.3%)	218 (17.4%)	0.96
Insulin use	388 (22.1%)	224 (44.1%)	164 (13.1%)	<0.001
eGFR, mL/min/1.73 m^2	85.9 ± 19.6	82.1 ± 22.6	87.5 ± 18.0	<0.001
UACR, median (p25, p75), mg/g	5.8 (1.8, 21.4)	8.8 (2.5, 51.1)	5.0 (1.6, 16.0)	<0.001

Values for continuous variables given as mean ± standard deviation; for categorical variables, as count (percentage). *P* value is based on χ^2 test for categorical variables, *t* test for continuous variables, and nonparametric equality-of-medians test for medians, comparing the difference between participants with and without retinopathy.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; p25, 25th percentage; p75, 75th percentage; UACR, urinary albumin-creatinine ratio.

minimal retinopathy (HR, 1.09 [95% CI, 0.33-3.57]) or moderate-to-severe retinopathy (HR, 1.48 [95% CI, 0.91-2.40]) groups.

Association of Retinopathy With Risk of Cardiovascular Disease and Assessing Strength of Association

The participants were observed for a median follow-up time of 14.8 years with 399 incident CHD events and 15.8 years with 196 stroke events. Figure 2 presents the unadjusted CHD- and stroke-free survival by presence of retinopathy.

Table 2. Odds Ratio for Prevalent eGFR <60 mL/min/1.73 m^2 and Albuminuria at Visit 4, Comparing Retinopathy Versus No retinopathy

	Unadjusted		Adjusted	
	OR (95% CI)	*P*	OR (95% CI)	*P*
eGFR <60 mL/min/1.73 m^2	2.31 (1.68-3.17)	<0.001	1.56 (1.09-2.23)	0.01
Albuminuria	2.14 (1.69-2.71)	<0.001	1.61 (1.24-2.10)	<0.001

P value is calculated based on logistic regression. Adjusted models are adjusted for visit 4 variables of age, sex, race-center, body mass index, smoking status, hypertension, eGFR, total cholesterol, use of statin, fasting glucose, use of insulin, and duration of diabetes from visit 1 to visit 4.
Abbreviations: eGFR, estimated glomerular filtration rate; OR, odds ratio.

Compared with the participants without retinopathy, the participants with retinopathy had a higher risk of CHD (HR, 1.46 [95% CI, 1.15-1.84]) (Table 4) and stroke (HR, 1.43 [95% CI, 1.03-1.97]) after fully adjusting for risk factors. When comparing by level of retinopathy, higher risk of CHD was observed in participants with minimal retinopathy (HR, 1.79 [95% CI, 1.16-2.78]) (Table S4) and moderate-to-severe retinopathy (HR, 1.39 [95% CI, 1.06-1.82]), while higher risk of stroke was observed in

Table 3. Number of Participants at Risk and Number of Incident Outcome Events During Follow-up Period

	Overall		No retinopathy		Retinopathy	
	No. at Risk	No. of Events (%)	No. at Risk	No. of Events (%)	No. at Risk	No. of Events (%)
CKD	1,582	723 (45.7)	1,155	514 (44.5)	427	209 (48.9)
ESKD	1,752	109 (6.2)	1,247	55 (4.4)	505	54 (10.7)
CHD	1,469	399 (27.2)	1,068	268 (25.1)	401	131 (32.7)
Stroke	1,693	196 (11.6)	1,216	124 (10.2)	477	72 (15.1)

Participants were observed for a maximum of 21.9 years, with a median follow-up time of 14.2 years for incident CKD, 16.2 years for incident ESKD, 14.8 years for incident CHD, and 15.8 years for incident stroke.
Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; ESKD, end-stage kidney disease.

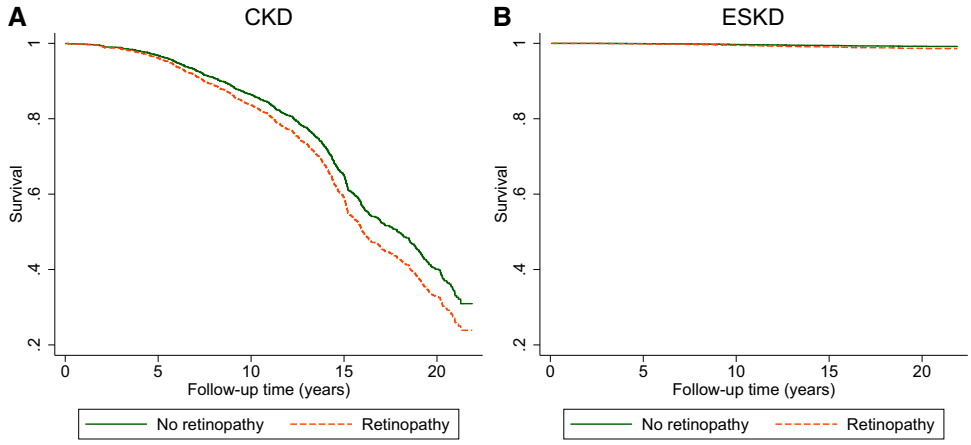

Figure 1. Survival curves of (A) CKD and (B) ESKD in participants, by presence versus absence of retinopathy. Survivor function graphs are based on Cox proportional hazards model. Models are adjusted for visit 4 variables of age, sex, race and center, BMI, smoking status, hypertension, eGFR, UACR, total cholesterol, use of statin, fasting glucose, use of insulin, and duration of diabetes from visit 1 to visit 4. Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; UACR, urinary albumin-creatinine ratio.

participants with minimal retinopathy (HR, 1.85 [95% CI, 1.06-3.26]).

Seemingly unrelated regression indicated a significant difference in the strength of association between retinopathy and CKD versus the association between retinopathy and CHD ($P = 0.03$). The strength of relationship was not significantly different between retinopathy with CKD versus retinopathy with stroke ($P = 0.67$). In addition, no significant difference was observed between the strength of association between retinopathy with ESKD versus that with CHD ($P = 0.66$) or stroke ($P = 0.25$).

Addition of Retinopathy to the KFRE and PCE

The 4-variable KFRE showed good discrimination of ESKD risks (C statistic = 0.863). We did not observe significant improvement after introducing the presence of retinopathy (C statistic = 0.868, P for difference in C statistic = 0.36) into the equation. Similarly, introducing the presence of retinopathy into the PCE did not improve discrimination of the equation (C statistics without retinopathy = 0.655, C statistics with retinopathy = 0.668, $P = 0.29$).

Table 4. Hazards Ratio for Incident CKD, ESKD, CHD, and Stroke, Comparing Retinopathy Versus No Retinopathy

	Unadjusted		Adjusted	
	HR (95% CI)	*P*	HR (95% CI)	*P*
CKD	1.51 (1.28-1.77)	<0.001	1.22 (1.02-1.46)	0.03
ESKD	2.92 (2.00-4.25)	<0.001	1.69 (1.11-2.58)	0.01
CHD	1.54 (1.25-1.90)	<0.001	1.46 (1.15-1.84)	0.002
Stroke	1.78 (1.33-2.38)	<0.001	1.43 (1.03-1.97)	0.03

P value is calculated based on Cox proportional hazards model. Adjusted models are adjusted for visit 4 variables of age, sex, race and center, body mass index, smoking status, hypertension, estimated glomerular filtration rate, urinary albumin-creatinine ratio, total cholesterol, use of statin, fasting glucose, use of insulin and duration of diabetes from visit 1 to visit 4.
Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HR, hazards ratio.

DISCUSSION

In our study of 1,759 persons with diabetes, the presence of retinopathy was a robust risk factor not only for kidney outcomes but also CHD and stroke. The association between CHD and retinopathy was stronger than that between CKD and retinopathy, with no evidence for a dose response between the severity of retinopathy and adverse kidney outcomes. Our study also showed good discrimination of the 4 variables in the KFRE for predicting ESKD risk in this population of patients with diabetes, and including retinopathy did not improve the discrimination.

Our finding of an association between retinopathy and kidney disease is consistent with previous studies in other populations of adults with diabetes.[7,8,32-37] It has been reported that the kidney and eye share a similar structure of the vascular networks, developmental pathways, and pathological progression. Pleiotropic roles of *Pax*, *WT1*, *BMP7*, and *Notch2* genes in kidney and eye development as well as pathologic deterioration have been noted.[38] There are many common pathologic mechanisms for kidney and eye diseases, including atherosclerosis, endothelial dysfunction, oxidative stress, and inflammation.[39]

An interesting aspect of our study was the stronger association between retinopathy and CHD than retinopathy and kidney outcomes. This is seemingly contrary to conventional wisdom, in which the presence of retinopathy has been thought to be a necessary precursor to the development of kidney disease. On the other hand, retinal microvascular impairment has also been reported to predict cardiovascular disease.[9,10,12] Additional studies should evaluate the timing of the onset of retinopathy with the development of CHD. Interestingly, we found that the presence of retinopathy had no additional predictive power over and above eGFR, UACR, age, and sex for the development of ESKD. Similarly, the inclusion of

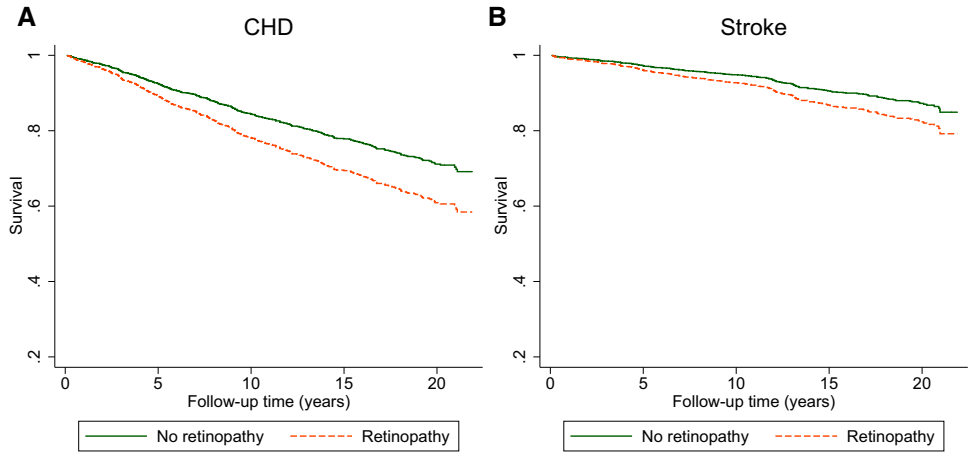

Figure 2. Survival curves of (A) CHD and (B) stroke in participants, by presence versus absence of retinopathy. Survivor function graphs are based on Cox proportional hazards model. Models are adjusted for visit 4 variables of age, sex, race and center, BMI, smoking status, hypertension, eGFR, UACR, total cholesterol, use of statin, fasting glucose, use of insulin and duration of diabetes from visit 1 to visit 4. Abbreviations: BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

retinopathy in CVD risk prediction did not help improve discrimination.

The strengths of our study include the large sample size and long follow-up period, as well as the detailed measurements of risk factors at each examination. One limitation is that the retinal photographs and kidney measurements were taken at different visits. Retinal examinations were only taken in 1 eye of each participant, and a proportion (~16%) of the photographs were ungradable, which may have resulted in misclassification and underestimation of retinopathy cases.[9,11,12,20,21,40,41] Survival bias is also a concern. Among participants who have diabetes at visit 3, those with retinopathy were less likely to attend visit 4 compared with those without retinopathy ($P = 0.002$).

The development of kidney disease was assessed overall, and not kidney disease solely attributable to diabetes. The results may not represent the associations in persons who are not Black or White. Additionally, the small sample size of those with minimal ($N = 90$) or mild retinopathy ($N = 121$) might limit the power of the analysis.

In conclusion, our study indicates that retinopathy is associated with an elevated risk of kidney disease and cardiovascular disease in persons with diabetes. These findings support the hypothesis of microvascular pathology underlying progression of kidney and cardiovascular disease, and might suggest that prevention and early diagnosis of microvascular disease could improve other clinical outcomes in diabetes. Further studies are needed to validate our findings on the strength of relationship between retinopathy, kidney disease, and cardiovascular disease.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Characteristic of study population at baseline (visit 4), by presence of retinopathy categories.

Table S2: Number of participants at risk and number of incident outcome events during follow-up period.

Table S3: Adjusted odds ratio for prevalent eGFR <60 mL/min/1.73 m^2 and albuminuria at visit 4, comparing levels of retinopathy versus no retinopathy.

Table S4: Adjusted hazards ratio for incident kidney disease, ESKD, coronary heart disease and stroke, comparing levels of retinopathy versus no retinopathy.

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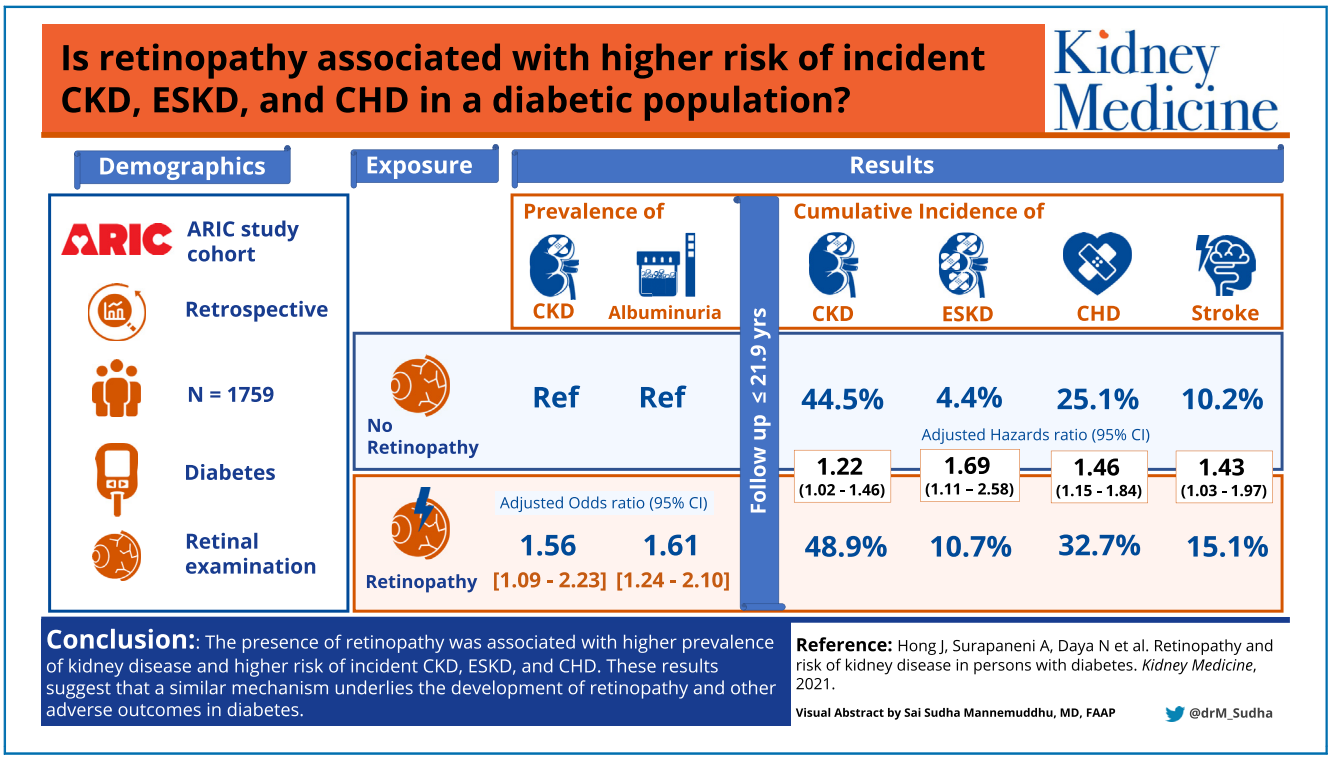
Is retinopathy associated with higher risk of incident CKD, ESKD, and CHD in a diabetic population?
Kidney Medicine
Demographics
Exposure
Results
ARIC study cohort
Retrospective
N = 1759
Diabetes
Retinal examination
Prevalence of
CKD
Albuminuria
Cumulative Incidence of
CKD
ESKD
CHD
Stroke
Follow up ≤ 21.9 yrs
No Retinopathy
Ref
Ref
44.5%
4.4%
25.1%
10.2%
Adjusted Hazards ratio (95% CI)
1.22 (1.02 - 1.46)
1.69 (1.11 – 2.58)
1.46 (1.15 - 1.84)
1.43 (1.03 - 1.97)
Retinopathy
Adjusted Odds ratio (95% CI)
1.56 [1.09 - 2.23]
1.61 [1.24 - 2.10]
48.9%
10.7%
32.7%
15.1%
Conclusion: The presence of retinopathy was associated with higher prevalence of kidney disease and higher risk of incident CKD, ESKD, and CHD. These results suggest that a similar mechanism underlies the development of retinopathy and other adverse outcomes in diabetes.
Reference: Hong J, Surapaneni A, Daya N et al. Retinopathy and risk of kidney disease in persons with diabetes. Kidney Medicine, 2021.
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