Retinal Microvascular Signs Are Associated with Chronic Kidney Disease in Persons with and without Diabetes

G. Liew^a P. Mitchell^a T.Y. Wong^{b,c} J.J. Wang^{a,b}

^aCentre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, NSW, and ^bCentre for Eye Research Australia, University of Melbourne, Melbourne, Vic., Australia;

^cDepartment of Ophthalmology, National University of Singapore, Singapore

Key Words

Retinal microvascular signs • Retinopathy • Venules • Chronic kidney disease • Blue Mountains Eye Study

Abstract

Background/Aims: In persons with diabetes, retinal microvascular abnormalities are associated with chronic kidney disease (CKD). However, it is not clear if the same relationship applies in persons without diabetes. **Methods:** We examined 2,971 participants from a population-based study (240 with, 2,731 without diabetes). Retinal photographs were masked graded for retinal microvascular signs, and CKD was defined as estimated glomerular filtration rate (eGFR_{MDRD}) <60 ml/min/1.73 m². **Results:** Retinal microvascular signs were more frequent in persons with CKD. After adjusting for age, gender, systolic blood pressure and fasting plasma glucose, CKD was associated with both presence of retinopathy (odds ratio, OR, 1.2, 95% confidence interval, CI 1.0–1.5) and venular dilation (OR 1.2, 95% CI 1.0–1.5). These associations were similar in persons with and without diabetes. There was a significant trend for increasing magnitude of associations of retinopathy with increasing severity levels of CKD (p for trend 0.03). **Conclusions:** Retinal microvascular signs, namely retinopathy lesions and venular dilation, are associated

with CKD both in persons with, and without diabetes. This supports the concept that retinal microvascular signs are indicators of generalized microvascular disease even in the absence of diabetes, and reinforces the link between retinal and renal microcirculations.

Copyright © 2012 S. Karger AG, Basel

Introduction

In persons with diabetes, retinal microvascular signs such as retinopathy lesions are often associated with microvascular complications in the kidney [1]. Interestingly, retinal microvascular signs can also be found in between 7–13% of persons without diabetes [2]. The presence of these signs is considered a marker of systemic microvascular disease [3]. Their cause in the absence of diabetes is uncertain, but their presence is associated with systemic cardiovascular disease such as elevated blood pressure, inflammatory markers and an increased risk of cardiovascular disease [3–6].

It remains unclear if these retinal microvascular signs in persons without diabetes are also associated with kidney disease as is the case in persons with diabetes. Some early studies suggest that these retinal microvascular

Fig. 1. Measuring arteriolar and venular calibers.

signs are also associated with chronic kidney disease (CKD) in persons without diabetes [7–9]. However, these early studies mostly utilized only a single fundus photograph of a randomly selected eye of each subject to define presence of retinal microvascular signs, underestimating their prevalence. Further, these studies utilized a relative measure of retinal vessel caliber, the arteriole-to-venule ratio (AVR), which has since been shown to mask specific associations of arteriolar or venular caliber with systemic disease, and its interpretation as an indicator for narrowing arteriolar caliber is based on an erroneous assumption [10]. It is now recommended that arteriolar and venular calibers be measured and analyzed separately [5, 10]. A recent case-control study compared persons with and without CKD, and found narrower arterioles associated with proteinuria. This report did not examine the retina-kidney relationship in persons with and without diabetes separately, was based on a small sample ($n \sim 30$), and also mainly used AVR as a measure of arteriolar narrowing [9]. We thus sought to confirm these findings in a large population-based study of persons with, and without diabetes, using separate measurements of arteriolar and venular caliber.

Methods

We examined baseline participants of the Blue Mountains Eye Study, a population-based study of predominantly Caucasian people aged 49 years or older at the commencement of the study in 1992 [11]. The study was designed to analyze the relationship of systemic disease to ocular conditions [2]. Baseline participants ($n = 3,654$) represented 82.4% of eligible potential participants living in two postcode areas in the Blue Mountains, New South Wales, Australia. This study was conducted according to the recommendations of the Declaration of Helsinki, and was approved by the Western Sydney Area Human Research Ethics Committee and the University of Sydney Human Research Ethics committee. Written, informed consent was obtained from all participants.

Excluding participants without blood test results or suitable retinal photographs left 2,971 for analysis, including 240 with and 2,731 without diabetes, defined from fasting plasma glucose and history [2].

At the baseline examination, stereoscopic retinal photographs (30°) of the macula and other retinal fields of both eyes, using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany), were taken after pupil dilation. Detailed grading methods were described previously [12] and are identical to the methods used in other similar studies [13]. In brief, we used a validated computer-assisted method to measure the internal caliber of retinal arterioles and venules from all gradable digitized retinal images, which were then summarized using formulas by Parr and Hubbard [14, 15], with correction for magnification [7, 16, 17] (fig. 1). The formulas take into account branching patterns and allow all measured vessel calibers in an eye to be summarized as an index representing the mean arteriolar or venular caliber of that eye. As previously reported, intra- and inter-grader grading agreement is high, with quadratic weighted κ values ranging from 0.80 to 0.93 [15]. Arteriolar narrowing was defined as persons with average arteriolar caliber in the smallest quintile and venular dilation as persons with average venular caliber in the largest quintile [9].

Among participants in the largest quintile of venular caliber, mean caliber was $248.7 \mu\text{m}$, range $238.4\text{--}270.8 \mu\text{m}$. Among participants in the other, smaller quintiles, mean caliber was $215.6 \mu\text{m}$, range $174.6\text{--}238 \mu\text{m}$. For arteriolar caliber, among participants in the smallest quintile, mean caliber was $162.6 \mu\text{m}$, range $113.9\text{--}174.0 \mu\text{m}$, whereas among participants in the other, larger quintiles, mean caliber was $197.7 \mu\text{m}$, range $174.0\text{--}258.7 \mu\text{m}$.

Trained, masked graders assessed 6-field retinal photographs of both eyes taken at baseline for retinal microvascular signs: focal arteriolar narrowing, arteriovenous nicking and retinopathy [18]. The modified ETDRS diabetic retinopathy classification [19, 20] was used to grade retinopathy. Retinopathy was diagnosed if any of the following lesions were present: (1) microaneurysms, (2) blot or flame shaped hemorrhages beyond $1/2$ disc diameter from the disc margin, (3) hard exudates or (4) cotton wool spots.

Participants had systolic and diastolic blood pressure (SBP and DBP) measured using a single mercury sphygmomanometer with appropriate adult cuff size, after seating the participants for at least 10 min. Fasting blood samples were collected and processed at the Institute of Clinical Pathology and Medical Research at Westmead Hospital within 4 hours of blood collection [21]. Creatinine was measured with a Hitachi 747 biochemistry analyser.

Fig. 2. Color photographs of normal arterioles (paler) and venules (darker red; **a**), dilated venules (darker red; **b**), retinopathy signs – hemorrhages (**c**), retinopathy signs – microaneurysms (**d**).

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine according to the abbreviated Modification of Diet in Renal Disease (MDRD) formula [9]. CKD was defined as $eGFR_{MDRD} < 60$ ml/min/1.73 m², which corresponds to the National Kidney Foundation definition [22]. Severity of CKD was defined as none/mild ($eGFR_{MDRD} \geq 60$), moderate ($30 \leq eGFR_{MDRD} < 60$) and severe ($eGFR_{MDRD} < 30$). Diabetes was defined as a physician diagnosis of diabetes, or a fasting blood sugar ≥ 7 mmol/l.

Logistic regression models based on maximum likelihoods were constructed to examine the relationship of retinal microvascular signs with the presence of CKD, as well as a test for a trend with increasing severity of CKD, where CKD was the outcome factor. Models were adjusted for age, gender, blood pressure and fasting plasma glucose. Odds ratios (OR) and 95% confidence intervals (CI) were reported.

Results

Baseline characteristics of this population are presented elsewhere [11]. Briefly, 1,360 participants (45.8%) had CKD. The mean age of participants with CKD was 71.2 years, compared to 59.1 years in those without CKD. CKD was more frequent in persons with retinal microvascular signs, including retinopathy. The prevalence of CKD in persons with retinopathy (52.7 vs. 44.9%), arteriovenous nicking (50.0 vs. 45.4%), focal arteriolar narrowing (59.1 vs. 44.7%), and either generalized arteriolar narrowing (51.2 vs. 44.4%) or venular dilation (46.4 vs. 43.3%), was greater in those with than without the lesions, respectively.

After adjusting for age, gender, SBP and fasting plasma glucose, prevalence of retinopathy (OR, 1.2, 95% CI 1.0–1.5) and venular dilation (OR 1.2, 95% CI 1.0–1.5) were associated with CKD in the overall sample, but not other

retinal microvascular signs (table 1; fig. 2). These associations were relatively similar in persons with and without diabetes (table 2). There was a significant trend for stronger associations of retinopathy with increasing severity of CKD (adjusted OR 2.0, 95% CI 0.8–4.8 for severe vs. none/mild levels; OR 1.2, 95% CI 0.9–1.5 for moderate vs. none/mild levels, *p* for trend 0.03; table 3).

Discussion

In this study, we found that certain retinal microvascular signs, namely retinopathy lesions and venular dilation, were associated with CKD both in persons with, and without diabetes. This suggests that retinal microvascular disease correlates with renal microvascular disease, independent of the cause of the systemic microvascular condition. Our findings are consistent with those from the Atherosclerosis Risk in Communities (ARIC) Study [7] and Cardiovascular Health Study [8], in which retinopathy lesions were associated with renal dysfunction. Retinopathy lesions are associated with abnormalities in the coronary circulation [23–26] and may thus be a marker of generalized microvascular disease from vascular endothelial dysfunction [27] in the retina, kidney and other microvascular beds.

Our finding of an association between vessel caliber and CKD is consistent with the ARIC Study [7] and the recent case-control study by Baumann et al. [9]. Both studies reported smaller AVR associated with CKD and attributed smaller AVR to narrower arteriolar caliber, although it could also be due to wider venular caliber [10]. The study by Baumann et al. [9] examined arteriolar caliber separately, and found narrower arteriolar caliber as-

Table 1. Retinal microvascular abnormalities and CKD presented as OR and 95% CI

Retinal microvascular abnormality	CKD			
	No. at risk	% with CKD	Age-gender adjusted OR (95% CI)	Multivariable adjusted OR (95% CI) ¹
Retinopathy				
Present	336	52.7	1.3 (1.0–1.6)	1.2 (1.0–1.5)
Absent	2,635	44.9	1.0	1.0
Arteriovenous nicking				
Present	252	50.0	1.0 (0.7–1.3)	1.0 (0.7–1.2)
Absent	2,719	45.4	1.0	1.0
Focal narrowing				
Present	215	59.1	1.1 (0.8–1.4)	1.0 (0.8–1.4)
Absent	2,756	44.7	1.0	1.0
Arteriolar narrowing				
1st quintile (mean 162.6 μ m, range 113.9–174.0)	598	51.2	0.9 (0.8–1.1)	0.9 (0.8–1.1)
2nd–5th quintile (mean 197.7 μ m, range 174.0–258.7)	2,373	44.4	1.0	1.0
Venular widening				
5th quintile (mean 248.7 μ m, range 238.4–270.8)	598	46.4	1.2 (1.0–1.5)	1.2 (1.0–1.5)
1st–4th quintile (mean 215.6 μ m, range 174.6–238.4)	2,373	43.3	1.0	1.0

¹ Multivariable model adjusting for age, gender, fasting plasma glucose, systolic blood pressure.

Table 2. Retinal microvascular abnormalities and CKD by diabetic status, presented as OR and 95% CI

Retinal microvascular abnormality	With diabetes (n = 240)		Without diabetes (n = 2,731)	
	% with CKD	multivariable adjusted OR (95% CI) ¹	% with CKD	multivariable adjusted OR (95% CI) ¹
Retinopathy				
Present	53.6	1.3 (0.7–2.5)	52.4	1.2 (0.9–1.5)
Absent	49.1	1.0	44.6	1.0
Venular widening				
5th quintile	52.1	1.2 (0.6–2.4)	45.9	1.2 (1.0–1.5)
1st–4th quintile	44.2	1.0	43.2	1.0

¹ Multivariable model adjusting for age, gender, fasting plasma glucose, systolic blood pressure.

sociated with CKD, while ours found an association with wider venules. It may be that both arteriolar narrowing and venular dilation contribute to the smaller AVR found in these studies, and different studies detected different aspects of this relationship. In addition, differences in study findings may be related to our older population (average age 66 years, compared to 62 years in Baumann et

al. [9]) which may have reduced our ability to detect arteriolar narrowing since with increasing age arterioles become stiffer and less able to narrow. In unadjusted analyses, narrower arteriolar caliber was associated with CKD in our study as in Baumann et al. [9]; this association attenuated and became nonsignificant after adjustment for age, blood pressure and other risk factors. Our study is larger than that of Baumann et al. [9], which may have increased our power to detect the association with venular widening. The possibility that venular widening underlies this association is further supported by the fact that venular widening is also associated with retinopathy lesions in persons with diabetes [6], an association that our study also reports.

The observation that venular widening rather than arteriolar narrowing is associated with CKD is significant as these vascular processes are related to different underlying pathologies [5, 6]. Wider retinal venules are reported to be linked to cerebral hypoxia [28], endothelial dysfunction, hyperglycemia [29] and inflammation [6, 30], in contrast to narrower retinal arterioles, which are consistently and strongly related to elevated blood pressure and increasing age. Thus, our findings shed light on the mechanisms underlying microvascular disease in the retina and kidney, and point towards possible important roles for tissue hypoxia, endothelial dysfunction and in-

Table 3. Retinal microvascular abnormalities and severity of CKD, presented as OR and 95% CI

	Severity of CKD						p trend
	none/mild (n = 1,611)		moderate (n = 1,333)		severe (n = 27)		
	% with retinal sign	multivariable adjusted OR ¹	% with retinal sign	multivariable adjusted OR ¹ (95% CI)	% with retinal sign	multivariable adjusted OR ¹ (95% CI)	
Retinopathy	9.9	1.0	12.9	1.2 (0.9–1.5)	18.5	2.0 (0.8–4.8)	0.03
Venular widening	18.5	1.0	19.1	1.2 (1.0–1.5)	21.0	1.3 (0.4–4.0)	0.06

None/mild, eGFR_{MDRD} ≥60; moderate, 30 ≤ eGFR_{MDRD} <60; severe, eGFR_{MDRD} <30. Venular widening is defined as the largest quintile of venular caliber.

¹ Multivariable model adjusting for age, gender, fasting plasma glucose, systolic blood pressure.

flammation [6]. It remains unclear whether these changes in the retina and the kidney occur in parallel, or if one precedes the other. Prospective studies will be needed to understand whether shared mechanisms exist for retinal and renal microvascular diseases.

Of the 27 with severe CKD, 3 (11%) had diabetes. In addition, 17 (63%) had hypertension. We believe that the relatively low prevalence of diabetes in our population with severe CKD is likely due to the fact that we only sampled community-dwelling participants who were relatively free of advanced diabetic complications such as peripheral vascular disease, severe stroke, or severe CKD requiring regular dialysis.

The strengths of our study include a large sample size and accurate assessment of both study and outcome factors, masked and standardized grading of retinal microvascular signs from 6-field fundus photographs, and ascertainment of CKD using criteria defined from the National Kidney Foundation. Limitations include the cross-sectional nature of the study which precludes assessment of causality. The prevalence of CKD in our sample is also somewhat high, possibly due to the older popu-

lation and relatively high prevalence of hypertension in our study population [11]. This is unlikely to bias our findings as our main aim is not to estimate the prevalence of CKD but rather to assess its association with retinal microvascular signs, which should not depend on the prevalence of CKD.

In summary, we report from this population-based study that persons with retinal microvascular signs, namely retinopathy lesions and wider retinal venules, are more likely to have concurrent CKD. This association persisted after adjustment for age, blood pressure and fasting plasma glucose, and was present both in persons with and without diabetes. It supports the concept that retinal microvascular signs are indicators of generalized microvascular disease even in the absence of diabetes, and reinforces the link between retinal and renal micro-circulations.

Disclosure Statement

All authors have no conflicts of interest to declare.

References

- 1 Chavers BM, Mauer SM, Ramsay RC, Steffes MW: Relationship between retinal and glomerular lesions in IDDM patients. *Diabetes* 1994;43:441–446.
- 2 Wong TY, Liew G, Tapp RJ, Schmidt MI, Wang JJ, Mitchell P, Klein R, Klein BE, Zimmet P, Shaw J: Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. *Lancet* 2008;371:736–743.
- 3 Liew G, Wang JJ, Mitchell P, Wong TY: Retinal vascular imaging: a new tool in microvascular disease research. *Circ Cardiovasc Imaging* 2008;1:156–161.
- 4 Wong TY, Mitchell P: Hypertensive retinopathy. *N Engl J Med* 2004;351:2310–2317.
- 5 Wong TY, Mitchell P: The eye in hypertension. *Lancet* 2007;369:425–435.
- 6 Nguyen TT, Wong TY: Retinal vascular manifestations of metabolic disorders. *Trends Endocrinol Metab* 2006;17:262–268.

- 7 Wong TY, Coresh J, Klein R, Muntner P, Couper DJ, Sharrett AR, Klein BE, Heiss G, Hubbard LD, Duncan BB: Retinal microvascular abnormalities and renal dysfunction: the Atherosclerosis Risk in Communities Study. *J Am Soc Nephrol* 2004;15:2469–2476.
- 8 Edwards MS, Wilson DB, Craven TE, Stafford J, Fried LF, Wong TY, Klein R, Burke GL, Hansen KJ: Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the Cardiovascular Health Study. *Am J Kidney Dis* 2005;46:214–224.
- 9 Baumann M, Schwarz S, Kotliar K, von Ey-natten M, Schmidt TA, Burkhardt K, Lutz J, Heemann U, Lanzl I: Non-diabetic chronic kidney disease influences retinal microvas-culature. *Kidney Blood Press Res* 2009;32: 428–433.
- 10 Ikram MK, de Jong FJ, Vingerling JR, Witte-man JC, Hofman A, Breteler MM, de Jong PT: Are retinal arteriolar or venular diame-ters associated with markers for cardiovas-cular disorders? The Rotterdam Study. *Invest Ophthalmol Vis Sci* 2004;45:2129–2134.
- 11 Leeder SR, Mitchell P, Liew G, Rochtchina E, Smith W, Wang JJ: Low hemoglobin, chronic kidney disease, and risk for coronary heart disease-related death: the Blue Mountains Eye Study. *J Am Soc Nephrol* 2006;17:279–284.
- 12 Wang JJ, Mitchell P, Leung H, Rochtchina E, Wong TY, Klein R: Hypertensive retinal ves-sel wall signs in a general older population: the Blue Mountains Eye Study. *Hypertension* 2003;42:534–541.
- 13 Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, Klein BE, Hubbard LD: Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA* 2002;287:1153–1159.
- 14 Leung H, Wang JJ, Rochtchina E, Tan AG, Wong TY, Klein R, Hubbard LD, Mitchell P: Relationships between age, blood pressure and retinal vessel diameters in an older pop-ulation. *Invest Ophthalmol Vis Sci* 2003;44: 2900–2904.
- 15 Sherry LM, Wang JJ, Rochtchina E, Wong T, Klein R, Hubbard L, Mitchell P: Reliability of computer-assisted retinal vessel measure-ment in a population. *Clin Experiment Oph-thalmol* 2002;30:179–182.
- 16 Wagener HP, Clay GE, Gipner JF: Classifica-tion of retinal lesions in the presence of vas-cular hypertension. *Trans Am Ophthalmol Soc* 1947;45:57–73.
- 17 Wong TY, Wang JJ, Rochtchina E, Klein R, Mitchell P: Does refractive error influence the association of blood pressure and retinal vessel diameters? The Blue Mountains Eye Study. *Am J Ophthalmol* 2004;137:1050–1055.
- 18 Wang JJ, Mitchell P, Rochtchina E, Tan AG, Wong TY, Klein R: Retinal vessel wall signs and the 5 year incidence of age related macu-lopathy: the Blue Mountains Eye Study. *Br J Ophthalmol* 2004;88:104–109.
- 19 Early Treatment Diabetic Retinopathy Study Research Group: Early photocoagulation for diabetic retinopathy (report No. 9). *Ophthal-mology* 1991;98:766–785.
- 20 Diabetic Retinopathy Study Research Group. DRS Report Number 7: A modification of the Airlie House classification of diabetic reti-nopathy. *Invest Ophthalmol Vis Sci* 1981;21: 210–226.
- 21 Cumming RG, Mitchell P, Craig JC, Knight JF: Renal impairment and anaemia in a pop-ulation-based study of older people. *Intern Med J* 2004;34:20–23.
- 22 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classifi-cation, and stratification. *Am J Kidney Dis* 2002;39:S1–S266.
- 23 Sundell J, Janatuinen T, Ronnema T, Raita-kari OT, Toikka J, Nuutila P, Knuuti J: Dia-betic background retinopathy is associated with impaired coronary vasoreactivity in people with type 1 diabetes. *Diabetologia* 2004;47:725–731.
- 24 Norgaz T, Hobikoglu G, Aksu H, Guveli A, Aksoy S, Ozer O, Bolca O, Narin A: Retinop-athy is related to the angiographically detect-ed severity and extent of coronary artery dis-ease in patients with type 2 diabetes mellitus. *Int Heart J* 2005;46:639–646.
- 25 Yoon JK, Lee KH, Park JM, Lee SH, Lee MK, Lee WR, Kim BT: Usefulness of diabetic reti-nopathy as a marker of risk for thallium myocardial perfusion defects in non-insu-lin-dependent diabetes mellitus. *Am J Car-diol* 2001;87:456–459, A6.
- 26 Rema M, Mohan V, Deepa R, Ravikumar R: Chennai Urban Rural Epidemiology Study: Association of carotid intima-media thick-ness and arterial stiffness with diabetic reti-nopathy: the Chennai Urban Rural Epidemi-ology Study (CURES-2). *Diabetes Care* 2004; 27:1962–1967.
- 27 Cheung N, Wong TY: Diabetic retinopathy and systemic vascular complications. *Prog Retin Eye Res* 2008;27:161–176.
- 28 De Jong FJ, Vernooij MW, Ikram MK, Ikram MA, Hofman A, Krestin GP, Lugt AV, De Jong PT, Breteler MM: Arteriolar oxygen sat-uration, cerebral blood flow, and retinal ves-sel diameters. The Rotterdam Study. *Oph-thalmology* 2007;115:887–892.
- 29 Ikram MK, Janssen JA, Roos AM, Rietveld I, Witteman JC, Breteler MM, Hofman A, van Duijn CM, de Jong PT: Retinal vessel diame-ters and risk of impaired fasting glucose or diabetes: the Rotterdam Study. *Diabetes* 2006;55:506–510.
- 30 Klein R, Klein BE, Knudtson MD, Wong TY, Tsai MY: Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. *Arch Ophthalmol* 2006;124:87–94.