

Chronic kidney disease and the severity of coronary artery disease and retinal microvasculature changes: a cross-sectional study

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Background: Prior studies have suggested the association between incidence of coronary artery disease (CAD) with chronic kidney disease (CKD) and poor glomerular filtration function. However to the best of our knowledge, few studies have specifically assessed this relationship based on the severity of CAD as quantified using Extent and Gensini scores.

Methods: Between June 2009 and January 2012, data were collected from 1,680 participants as part of the Australian Heart Eye Study (AHES) cohort. Coronary angiograms were scored according to Gensini (severity) and Extent scores. Retinal vessel calibres were measured using validated semi-automated software. Potential confounders were adjusted for using multivariate analysis.

Results: There were no significant associations found between CKD status with Extent and Gensini scores for CAD severity, both unadjusted and when adjusted for confounding factors. In unadjusted analyses, a significant association between CKD and narrower retinal arteriolar diameter was observed ($P=0.0072$). After multivariate adjustment, the association between CKD and retinal arteriolar diameter was attenuated and was no longer significant ($P=0.1466$). No associations were observed between retinal venular calibre and prevalent CKD.

Conclusions: The present study demonstrated no independent associations between CKD and CAD severity. These results warrant validation by future large, prospective longitudinal studies.

Keywords: Chronic kidney disease (CKD); retinal microvasculature; cross-sectional study; Australian Heart Eye Study (AHES); coronary artery disease (CAD)

Submitted May 21, 2016. Accepted for publication Jun 16, 2016.

doi: 10.21037/jtd.2016.07.22

View this article at: <http://dx.doi.org/10.21037/jtd.2016.07.22>

Introduction

Chronic kidney disease (CKD) is a major public health problem worldwide, currently estimated to affect more than 10% of the adult population globally (1). It is an independent risk factor for the development of

coronary artery disease (CAD), which is the leading cause of morbidity and mortality in the CKD population. Underlying causes may include the combination and interaction of multiple mechanisms including inflammation, oxidative stress, endothelial dysfunction, coronary artery calcification and accelerated atherosclerosis. In an analysis

of the Atherosclerosis Risk in Communities Study (ARIC), the incidence of CAD significantly increased with severity of CKD and poor glomerular filtration function (2).

Population-based studies have also shown that retinal microvascular abnormalities, such as retinal arteriolar narrowing and venular widening, are associated with diabetes and hypertension, the two major risk factors for CKD (3-5). Our group has previously reported associations between retinopathy, regular widening and CKD (6). A few prospective studies have also examined the independent association between retinal vessel diameters and CKD, with mixed results (7-9). Assessment of the retinal microvasculature may allow early microcirculatory changes associated with the development of CKD to be examined.

Few published studies have investigated the potential relationship between CAD severity scores versus CKD status. In this present study, we aimed to assess the association between CKD and the severity and extent of CAD; and whether retinal microvascular changes are associated with the presence of renal dysfunction, using data from the Australian Heart Eye Study (AHES) cohort. Between June 2009 and January 2012, data were collected from 1,680 participants who presented to Westmead Hospital, a large tertiary hospital in Sydney, Australia (10-12). Examinations and measurements included a detailed medical history questionnaire, visual acuity testing, biochemical, peripheral blood pressure measurements, invasively measured blood pressure measurements, blood count analysis and retinal photography data. Renal function was assessed according to published National Kidney Foundation guidelines by using the abbreviated Modification of Diet in Renal Disease (MDRD) equation for estimated glomerular filtration rate (eGFR). CKD was defined as eGFR <60 mL/min/1.73 m² (13).

Methods

Assessment of CAD has been described previously (10,14). Coronary angiograms were scored according to Gensini (severity) and Extent scores. For an assessment of retinal vessel calibre, dilated, digital photographs were taken of the optic disc and macula of both eyes using a Canon 60° fundus camera (Model CF-60DSi, Canon Inc., Tokyo, Japan). Retinal vessel calibres were measured using validated semi-automated software. Ethics approval was obtained from Western Sydney Local Health Network Human Research Ethics Committee. Potential confounders were adjusted for using multivariate analysis. SAS statistical software (version 9.2;

SAS Institute, Cary, NC, USA) was used for analyses including *t*-tests, χ^2 tests, linear regression, and logistic regression.

Results

The baseline characteristics of patients without CKD versus those with CKD are summarized in *Table 1*. Those with CKD were older, more likely to be male and to have a higher body mass index (BMI). They were also more likely to be Caucasian, to have hypertension and diabetes mellitus, and higher high-density lipoprotein and cholesterol levels. However, those with CKD were less likely to be smokers.

There were no significant associations between CKD status and the extent and severity of CAD, both unadjusted and when adjusted for confounding factors (age, sex, BMI, ethnicity, hypertension, diabetes mellitus and hypercholesterolemia) (*Table 2*). As well, no significant associations were detected between retinal vessel caliber and prevalent CKD. In unadjusted analyses, a significant association between CKD and narrower retinal arteriolar diameter was observed (P=0.0072). After multivariate adjustment, the association between CKD and retinal arteriolar diameter was attenuated and was no longer significant (P=0.1466). No associations were observed between retinal venular calibre and prevalent CKD (*Table 2*).

Conclusions

Thus, in this population-based study, CKD was not associated with either the severity or extent of CAD, nor with retinal arteriolar or venular calibre, when adjusted for relevant confounding factors. Previous studies have documented an association between decreasing renal function and coronary artery calcification. However, whether this association remains significant after adjusting for traditional cardiovascular risk factors is unclear (15-17). The study by Joosen *et al.* of 2,038 patients, however, showed that after adjustment for traditional cardiovascular risk factors such as smoking, BMI and diabetes mellitus, mild to moderate CKD was not independently associated with coronary plaque burden (16). Similarly, the study by Cho *et al.* of 4,297 asymptomatic subjects found that after adjustment for proteinuria and other traditional risk factors, there was no significant association between a decrease in eGFR and the risk of obstructive CAD or a high coronary calcium score (>100) (17). These latter findings are in line with our results which did not show an independent relationship between CKD and CAD.

Table 1 Baseline characteristics of patients with and without chronic kidney disease (CKD)

Parameter	No CKD (n=1,306, %)	CKD (n=206, %)	P value
Age (years)	60.00±11.30	69.40±11.30	<0.0001
Male	1,010 (77.3)	134 (65.1)	0.0001
BMI	29.50±5.70	30.60±6.30	0.0216
Ethnicity			0.0009
Caucasian	863 (66.1)	161 (78.2)	
Eastern Asian	77 (5.9)	5 (2.4)	
South Asian	122 (9.3)	11 (5.3)	
Middle Eastern	146 (9.7)	10 (4.9)	
Other	98 (7.5)	19 (9.2)	
Systolic blood pressure (mmHg)	126.00±19.00	134.00±23.00	<0.0001
Diastolic blood pressure (mmHg)	73.00±12.00	71.00±13.00	0.0105
Hypertension (%)	866 (66.6)	187 (90.8)	<0.0001
Diabetes mellitus (%)	408 (31.3)	109 (52.9)	<0.0001
Smoker (%)	402 (30.9)	24 (11.7)	<0.0001
HDL (mmol/L)	1.04±0.30	0.98±0.30	0.0358
Triglycerides (mmol/L)	1.76±0.93	1.86±1.06	0.2829
Cholesterol level (mmol/L)	4.66±1.18	4.14±1.17	<0.0001

Table 2 Comparison of non-CKD versus CKD patients in terms of Extent Score, Gensini Score, retinal arteriolar and venular calibres

Parameter	eGFR ≥60	eGFR <60	P value
Extent score* (OR, 95% CI)	1.0 (reference)	1.330 (0.640–2.740)	0.32
Gensini score* (OR, 95% CI)	1.0 (reference)	1.075 (0.670–1.725)	0.27
Retinal arteriolar calibre (µm)	152.910±0.930	148.930±2.740	0.15
Retinal venular calibre (µm)	233.600±1.470	237.170±4.290	0.41

*, participants who had presence of CAD as defined by either having an Extent or Gensini score greater than 0, multivariate adjusted models included the covariates age, sex, body mass index (BMI), ethnicity, hypertension, diabetes mellitus, cholesterol level. OR, odds ratio; CI, confidence interval.

Regarding the association between retinal vessel caliber and CKD, results from prospective studies have been mixed. The ARIC study reported weak associations between arteriovenous (AV) nicking, retinal hemorrhages, microaneurysms, cotton-wool spots, and the likelihood of renal dysfunction development (2,8). The Cardiovascular Health Study (CHS) found strong associations between retinopathy changes and renal function decline, but there were no associations with retinal arteriolar abnormalities such as the arteriolar-venular diameter ratio, AV nicking, or focal arteriolar narrowing (4). We previously reported from the Blue Mountains Eye Study an association of wider venular calibre with CKD (6). There was a suggestion of wider venues in those with CKD in this study but the

association was not significant.

Several study limitations need to be considered while interpreting our results. First, the cross-sectional nature of the study limits making causal inferences. Because retinal arteriolar diameters are closely related to hypertension, statistical adjustment for hypertension in the multivariable model may be viewed as an “overadjustment” strategy. Moreover, the limited number of patients with CKD in the present cohort may not have provided adequate statistical power to demonstrate any significant trends or associations. Baseline characteristics and comorbidities were self-reported using medical questionnaires and hence, will involve a certain proportion of recall misclassification.

In conclusion, the present study demonstrated no

independent associations between CKD and CAD or retinal vessel caliber in the AHES study. These results warrant validation by future large, prospective longitudinal studies.

Acknowledgements

Funding: The study has been supported by National Health and Medical Research Council (NHMRC) Project (Grant 571012).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Western Sydney Local Health Network Human Research Ethics Committee (Westmead) No. HREC2008/5/4.1 6(2796) AU RED 08/WM EAD/I 22 and written informed consent was obtained from all patients.

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Cite this article as: Phan K, Au C, Mitchell P, Liew G, Plant AJ, Wang SB, Chiha J, Thiagalingam A, Burlutsky G, Gopinath B. Chronic kidney disease and the severity of coronary artery disease and retinal microvasculature changes: a cross-sectional study. *J Thorac Dis* 2016;8(8):2111-2114. doi: 10.21037/jtd.2016.07.22