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Clinical impact of coexisting retinopathy and vascular calcification on chronic kidney disease progression and cardiovascular events

H.S. Hwang [a,b], S.Y. Kim [a,b], Y.A. Hong [a,b], W.K. Cho [c], Y.K. Chang [a,b], S.J. Shin [a,d], C.W. Yang [a], S.Y. Kim [a,b], H.E. Yoon [a,d,*]

[a] *Division of Nephrology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Republic of Korea*
[b] *Department of Internal Medicine, Daejeon St. Mary's Hospital, Republic of Korea*
[c] *Department of Ophthalmology and Visual Science, College of Medicine, The Catholic University of Korea, Republic of Korea*
[d] *Department of Internal Medicine, Incheon St. Mary's Hospital, Republic of Korea*

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Abstract *Background and aims:* Retinopathy and vascular calcification (VC) are representative markers of microvascular and macrovascular dysfunction in patients with chronic kidney disease (CKD). However, their relationship and combined effects on clinical outcomes remain undetermined.

Methods and results: We included 523 patients with nondialysis-dependent CKD stage 3–5 who had been examined with fundus photography for diabetic or hypertensive retinopathy. Simple radiographs were analyzed for the presence of VC. The clinical significance of VC of the abdominal aorta and iliofemoral artery (apVC) and retinopathy was evaluated in terms of the rate of renal function decline and composite of any cardiovascular event or death. CKD patients with retinopathy showed higher prevalence of apVC than those without retinopathy (25.6% vs. 12.5%, $P < 0.001$).The presence of retinopathy was independently associated with apVC (OR 2.13, 95% CI 1.31, 3.49). In multivariate analysis, compared with subjects with neither apVC nor retinopathy, the coexistence of both apVC and retinopathy were independently associated with rapid renal function decline ($\beta = -1.51$; 95% CI −2.40, −0.61), whereas apVC or retinopathy alone were not. Compared with subjects with neither apVC nor retinopathy, the HRs for composite end points were 1.05 (95% CI 0.48, 2.27), 1.79 (95% CI 1.14, 2.80), and 2.07 (95% CI 1.17, 3.67) for patients with apVC only, those with retinopathy only, and those with both apVC and retinopathy, respectively.

Conclusion: The coexistence of VC and retinopathy was independently associated with CKD progression and cardiovascular events or deaths, and its combined effect was stronger than any separate condition.

* Corresponding author. Division of Nephrology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu,137-701, Republic of Korea. Tel.: +82 32 280 5886; fax: +82 32 280 5987.
E-mail address: berrynana@catholic.ac.kr (H.E. Yoon).

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Introduction

Patients with chronic kidney disease (CKD) have increased risks of cardiovascular (CV) morbidity and mortality [1–3]. Vascular calcification (VC) becomes more prevalent as CKD progresses, and is a well-known risk factor for CV morbidity and mortality in these patients [4]. VC is associated with arterial stiffness, left ventricular hypertrophy, decreased coronary perfusion, and renal and brain microcirculation [5]. Therefore VC is considered as a representative marker of macrovascular dysfunction in patients with CKD [6].

Microvascular dysfunction in the kidney is one of the early histopathological changes in CKD and is thought to play an important role in the development of renal insufficiency [7]. The retina can be examined in a noninvasive manner at the arteriolar level, and accumulating evidence has demonstrated that the retinal artery shares a common anatomical structure, risk factors, and pathogenetic mechanisms for organ dysfunction with arteries in the kidney [8]. Ocular fundus pathology is prevalent in CKD patients [9], and retinal microvascular abnormalities are associated with incident CKD and CKD progression [10,11]. Retinopathy is a strong predictor of mortality in the CKD population [12].

We sought to examine the combined effects of retinopathy and VC on CKD progression, CV events, and all-cause mortality. We hypothesized that patients with both VC and retinopathy will have the highest risk for CKD progression and CV events compared with those with either VC or retinopathy alone. We also endeavored to investigate whether retinopathy was independently associated with VC in CKD patients.

Methods

Study population

We included patients with nondialysis-dependent CKD stage 3–5 who were treated at Daejeon St. Mary's Hospital from December 2004 to April 2013. CKD was defined as evidence of kidney damage that had been present for more than 3 months and was classified into CKD stages 3, 4, and 5, based on an estimated glomerular filtration rate (eGFR, mL/min per 1.73 m^2) of 30–59, 15–29, and <15, respectively [13]. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease formula [14]. The CKD patients were considered as being at risk of microvascular dysfunction if they had diabetes or hypertension. We identified patients who had been examined with 50-degree wide fundus photography (Retinal Camera 508 wide, TRC-50IX, Topcon, Tokyo, Japan) for diabetic or hypertensive retinopathy and with plain X-ray images of the abdomen and pelvis for VC. A total of 523 patients with CKD stages 3–5 were enrolled in this study. Participants were categorized as those having any type of retinopathy and those having no retinopathy. The participants were then subdivided into groups according to the presence or absence of VC.

Data collection and definitions

The baseline demographics, risk factors for CV disease, and laboratory data were collected at the time of retinopathy and VC examination. Body mass index (BMI) was calculated as the ratio of weight in kilograms divided by the square of height in meters. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third of pulse pressure. Proteinuria was estimated by measuring protein concentration in a 24-h urine sample or the protein–creatinine ratio of spot urine. Because the proteinuria distribution was skewed, log-transformed values were used. A single board certified ophthalmologist performed the retinopathy grading to reduce inter-observer bias, who was blinded to the condition of the patients. The Keith–Wagener–Barker classification system was used to determine the grade of hypertensive retinopathy, and the grade of diabetic retinopathy was determined according to the Early Treatment of Diabetic Retinopathy Study classification [15–18]. Fundus fluorescein angiography was clinically indicated in patients with moderate to severe retinopathy, and angiographic photography was also used for grading. Ungraded retinopathy was defined as the presence of definite retinopathy, but where discrimination of scale was not discernible. Any grade of hypertensive or diabetic retinopathy was considered as positive.

VC was examined at abdominal aorta, iliofemoral axis, and aortic arch using plain radiographs. The arterial calcification in the abdominal aorta and iliofemoral axis was assessed using abdominal and pelvic X-ray images [19]. Any vascular calcification lining the arterial walls of abdominal aorta and iliofemoral artery was considered as positive for abdominal and pelvic VC (apVC). Aortic arch calcification was observed using plain chest radiography, and total length of calcification was measured by adding the length of separate linear calcific densities along the aortic arch [20]. More than 1 cm length of calcification along the aortic arch was defined as positive for aortic arch calcification (aaVC).

Outcome measures

The primary end point for the study was the rate of decline of renal function. The individual eGFR values were obtained at 3-month intervals within 1 year of the index examination and then at 6-month intervals after 1 year. The rate of renal function decline in each patient was assessed by the eGFR slope, which was defined as the regression coefficient between eGFR and time in units of mL/min/1.73 m^2/y. The secondary end point was a composite of CV events or patient death. The CV events were defined as coronary artery disease (coronary artery bypass surgery, percutaneous intervention, or myocardial infarction), heart failure, ventricular arrhythmia, cerebrovascular accident (cerebral infarction, transient ischemic attack, or cerebral hemorrhage), or peripheral arterial disease (peripheral vascular revascularization or amputation).