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Changes over the last decade in carotid atherosclerosis in patients with end-stage kidney disease

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ABSTRACT

Objective: Therapies for chronic kidney disease have changed greatly over the last decade. The aim of this study was to examine the changes in the clinical characteristics and carotid atherosclerosis of patients with end-stage kidney disease (ESKD) over the last 9 years.

Methods: A cross-sectional study of 150 consecutive patients with ESKD who had initiated maintenance dialysis between January 2005 and December 2013 was conducted. The patients' mean age was 68 ± 13 years. The group comprised 73% men, and 63% of the patients had diabetic nephropathy. The carotid artery-intima media thicknesses and the plaque scores (PS) were measured using carotid artery ultrasonography within 3 months of dialysis initiation. Changes in the patients' carotid atherosclerosis and clinical characteristics over the years were examined by categorizing the patients into 3 groups representing 3-year intervals based on when dialysis was initiated.

Results: The PS declined from 12.8 to 5.4 ($P = 0.001$). Low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol levels declined over the 9-year period ($P = 0.005$ and $P = 0.006$, respectively), and the ratio of statin users increased markedly from 24% to 54% ($P = 0.001$). Univariate regression analysis identified a positive correlation between the PS and LDL-C ($r = 0.281$; $P = 0.01$), and a strong positive correlation was found between the PS and LDL-C after adjusting for various risk factors for atherosclerosis.

Conclusion: Carotid atherosclerosis in patients with ESKD has decreased over the past 9 years, which may be a consequence of improvements in dyslipidemia management.

1. Introduction

It has been suggested that atherosclerosis progression accelerates during the conservative phase of chronic kidney disease (CKD). Shoji et al. demonstrated that the carotid artery-intima media thickness (CA-IMT), an early lesion of atherosclerosis measured by carotid artery ultrasonography, showed a significantly higher value in patients in the conservative phase of CKD compared with the general population. Importantly, there was little difference in the CA-IMT between patients receiving dialysis and those in the conservative phase of CKD, which demonstrates that atherosclerosis has already developed before dialysis begins [1]. A strong relationship has been reported between the severity of CA-IMT and atherosclerotic cardiovascular disease (CVD) development in patients in the conservative phase of CKD [2]. CVD onset increases as renal dysfunction deteriorates [3,4]. Therefore, to improve the prognosis of patients with CKD, atherosclerosis progression must be prevented from an early stage of the disease.

The involvement of non-traditional risk factors for atherosclerosis that are specific to CKD, including chronic inflammation, malnutrition, and metabolic disturbances associated with calcium and phosphorus, tends to be regarded as the involvement of factors underlying atherosclerosis development and progression of atherosclerosis in patients with CKD. However, the classical risk factors for atherosclerosis, including hypertension and dyslipidemia, are also strongly involved in atherosclerosis progression in patients with CKD [5–7]. Statins and renin-angiotensin-aldosterone system (RAS) inhibitors prevent atherosclerosis progression in the general population [6], and RAS inhibitors also have renoprotective effects. Recently, it has been reported that using statins to manage dyslipidemia reduces proteinuria and retards the

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progression of renal impairment [7]. Therefore, strict blood pressure control, mainly using RAS inhibitors, lifestyle modifications, and using statins for lipid management will slow the progression of renal dysfunction and prevent the progression of atherosclerosis. Consequently, some international guidelines strongly recommend the use of these therapies [8–10]. However, we do not know the extent of the effect, how patients' clinical characteristics have been altered by these changes, and what the favorable effects have been on atherosclerosis.

A strong relationship exists between the findings of carotid artery ultrasonography and CVD. In the general population, the CA-IMT, determined by carotid artery ultrasonography, and the severity of the plaque score (PS) are related to complications associated with stroke or coronary artery disease (CAD) [11–15]. Similarly, some studies of patients with CKD have also reported that findings from carotid artery ultrasonography are useful for predicting CVD [16–18]. Carotid artery ultrasonography, which can be performed non-invasively, is useful for evaluating atherosclerotic lesions and predicting CVD complications in patients with CKD.

We hypothesized that recent changes in CKD management have improved atherosclerosis. Thus, a study to examine the changes in carotid atherosclerosis at the initiation of dialysis in parallel with the changes in patients' clinical characteristics, the changes in atherosclerosis risk factors, and the changes in pharmacotherapy over the past decade was conducted.

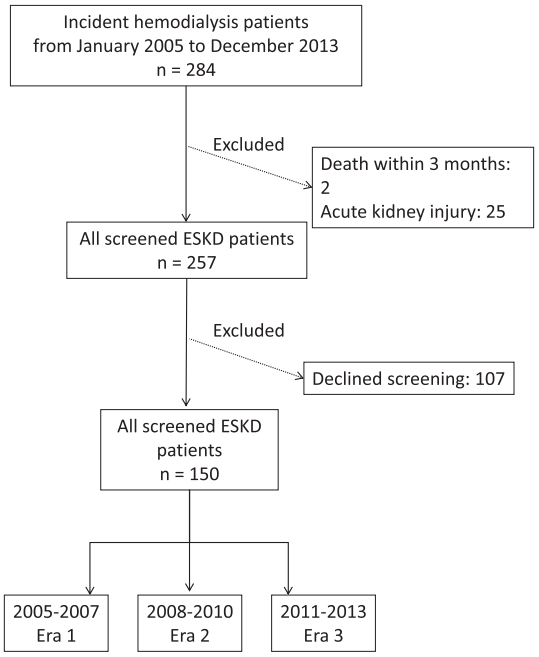

Fig. 1. Schema of the study's design. ESKD, end-stage kidney disease.

2. Methods

2.1. Study design and patients

A retrospective cross-sectional comparative study by era that involved 284 consecutive patients who started maintenance dialysis for end-stage kidney disease (ESKD) at the Toho University Ohashi Medical Center between January 2005 and December 2013 was conducted. Two of the exclusion criteria (1, death within 3 months of starting dialysis and 2, ESKD due to acute renal impairment) led to 2 patients and 25 patients, respectively, being excluded from the study, and the remaining 257 patients were included in the study. Of these patients, 107 had not undergone carotid artery ultrasonography. Consequently, 150 patients were divided into 3 groups that represented 3-year intervals, which were based on the day of dialysis initiation, and their carotid artery ultrasonography findings were compared (Fig. 1). There was some concern that a selection bias may have been introduced that related to the characteristics of the patients who did and did not undergo carotid artery ultrasonography. Therefore, to investigate the validity of the study, the 257 patients were divided into 2 groups according to whether they had undergone carotid artery ultrasonography, and their characteristics were compared before starting the main analysis. The sample size for the retrospective data collection was not pre-specified.

The ethics committee at the Toho University Ohashi Medical Center approved the study protocol [Approval number, 13–52, 13–61]. Since this was a retrospective, observational study, the need for consent for individual patients was waived; however, a notice about the start of this study and that the patients could express their objections to the use of their data was posted.

2.2. Collection of data

Clinical information was collected from each patient to determine age, sex, smoking history, diseases underlying their kidney disease, treatments taken during the conservative phase of the kidney disease, and disease history. Blood pressure was measured immediately before the first dialysis session in the supine position, and a blood sample taken immediately before the first dialysis session was analyzed. Serum calcium (Ca) was corrected using the following equation: corrected Ca = measured Ca (mg/dL) + (4 − measured albumin [g/dL]). The estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR (mL/min/1.73 m^2) = 194 × Cr − 1.094 × age − 0.287 (women × 0.739) [19]. Body mass indices were calculated as weight (kg)/(height [m])^2. HbA1c was recorded as the National Glycohemoglobin Standardization Program (NGSP) value.

2.3. Definitions of complications

CAD was defined as a history of myocardial infarction, angina pectoris, or coronary revascularization therapy. Patients were also defined as having complications associated with CAD if they had significant stenotic lesions that were observed on coronary arteriography, or if fixed defects or irreversible defects were observed using stress myocardial scintigraphy at the initiation of dialysis. Patients who had been diagnosed with peripheral artery disease (PAD) and had undergone catheterization or bypass graft surgery, or those who had a history of amputation for ischemic lower extremities were defined as patients with PAD. Patients diagnosed with cerebral hemorrhage or cerebral embolism and who had prior treatment for these conditions were defined as patients with stroke.

2.4. Carotid artery ultrasonography

Carotid artery ultrasonography was performed at the time of dry weight after dialysis or on a day that the patients did not undergo dialysis. Carotid atherosclerosis was evaluated using the mean CA-IMT (mCA-IMT) of the common carotid artery and the PS. An experienced clinical laboratory technician evaluated the carotid artery with a 7.5-MHz linear probe and an Aplio XV, Aplio XG, or a Xario ultrasonography system (Toshiba Medical Systems Corporation, Tokyo, Japan), using the B mode and a pulsed Doppler system. The patients were examined in the supine position without a pillow, with their necks tilted slightly away from the carotid artery