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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.

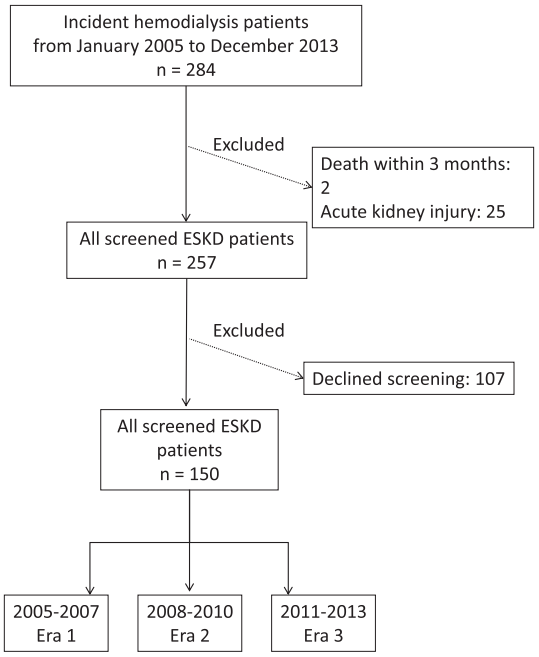

Fig. 1. Schema of the study's design. ESKD, end-stage kidney disease.

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

being examined and their chins angled slightly upwards. First, the segment of the carotid artery that could be observed using short-axis imaging was scanned from the proximal (heart) side towards the distal (head) side to confirm the blood vessel's course and the plaque locations. Then, the long-axis images of the blood vessel were produced in parallel to the probe, as much as possible. Images of the distal common carotid artery bifurcation and the internal carotid artery bifurcation were obtained for all of the patients as recommended by the American Society of Echocardiography Carotid Intima-Media Thickness Task Force [20]. The intima media thicknesses of at least 3 sites, each separated by at least 1 cm from other segments of the common carotid artery, were measured, and the mCA-IMT was obtained. When plaques were present in the individual segments, the mean thicknesses of the plaques were added to the CA-IMT measurement.

A CA-IMT of at least 1.1 mm was defined as a plaque, and the PS was defined as the sum of the thickest CA-IMTs in individual segments of the bilateral carotid arteries. As shown in Fig. 2, Segment 1 was defined as the internal carotid artery (ICA) segment 15 mm distal from the common carotid artery (CCA) bifurcation (Bif). Segment 2 (S2) was defined as the CCA/ICA segment 15 mm proximal from the Bif. Segment 3 (S3) was defined as the CCA segment 30 mm proximal to S2. Segment 4 (S4) was defined as the CCA segment 30 mm proximal to S3. When determining the PS, plaque length was not considered.

2.5. Statistical analyses

Data with normal distributions are expressed as the means ± standard deviations (SD). The data for parameters that did not have normal distributions are presented as the medians and interquartile ranges. The groups were evaluated using the χ^2 test, analysis of variance, and the Kruskal–Wallis test. P values <0.05 were considered significant. Trends over the 9-year period were analyzed using the Jonckheere–Terpstra test. Factors associated with the evaluation items of carotid artery ultrasonography were analyzed using univariate and multivariate linear regression analyses. All statistical analyses were performed using IBM® SPSS® software version 20 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Comparisons between the patients who did and did not undergo carotid artery ultrasonography

Of the 257 patients, 107 (41.6%) did not undergo carotid artery ultrasonography. To understand the trends in carotid artery sclerosis over the years and to confirm that any selection bias was minimal, the patients' characteristics were compared and examined according to the era and in relation to whether the patients had undergone carotid artery ultrasonography. No significant differences were found between the groups in Era 1; however, in Era 2, the ratio of men and the stroke and obstructive arteriosclerosis prevalence rates were higher in the group that had undergone ultrasonography than in the group that had not undergone ultrasonography (Table 1). In Era 3, the group that underwent ultrasonography showed a higher systolic blood pressure and a higher prevalence of diabetes mellitus compared with the group that did not undergo ultrasonography. In the latter half of the 9-year period analyzed, carotid artery ultrasonography was performed on patients with high atherosclerosis risks. Based on these data, we decided to pursue this study to prove our hypothesis; hence, a primary analysis of the 150 patients who had undergone carotid artery ultrasonography was performed.

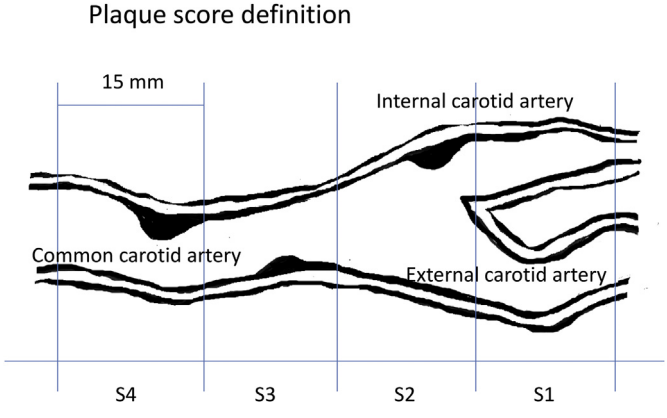

Fig. 2. Schema of plaque score calculation.

3.2. Patients' baseline characteristics

Table 2 presents the baseline characteristics of the 150 patients with ESKD who were evaluated for carotid atherosclerosis. The mean ± SD age of the patients was 68 ± 13 years, and the median age was 70 years (60–78 years). Men accounted for 73% of the patients, and 63% of the patients had diabetes mellitus (DM). The median serum creatinine (Cr) and eGFR values at the initiation of dialysis were 9.3 mg/dL (7.5–11.7 mg/dL) and 4.5 mL/min/1.73 m^2 (3.5–5.9 mL/min/1.73 m^2), respectively. The prevalences of CAD and stroke were 18% and 19%, respectively, and renin-angiotensin system (RAS) inhibitors and statins were administered to 65% and 39% of the patients, respectively.

3.3. Changes in the patients' baseline characteristics and carotid arteriosclerosis over the years

The age of the patients increased significantly over the years ($P < 0.001$); however, with the exception of the lipid profiles, the classical risk factors for atherosclerosis, including diabetes mellitus, smoking, and blood pressure, did not differ over the years (Table 2). A marked decreasing trend was apparent for low-density lipoprotein cholesterol (LDL-C) ($P = 0.005$) and non-high-density lipoprotein cholesterol (non-HDL-C) ($P = 0.006$) levels. C-reactive protein levels, a non-traditional risk factor for atherosclerosis, decreased over the years ($P = 0.04$), hemoglobin levels increased markedly over the years ($P < 0.001$), and serum phosphate levels increased markedly over the years ($P < 0.01$). The use of statins ($P = 0.001$), β-blockers ($P = 0.01$), oral hypoglycemic agents (OHA) ($P < 0.03$), and AST-120 ($P < 0.02$) increased over the 9-year period; however, RAS inhibitor use did not change markedly over the years. No clear trend in the mCA-IMT was observed; however, the PS decreased significantly from 12.8 to 5.4 ($P = 0.01$) (Fig. 3). Hence, the factors that contributed to the PS improvement were examined.

3.4. Factors associated with the PS

Univariate linear regression analysis identified significant positive correlations between the PS and age, CAD, eGFR, and LDL-C (Table 3). Significant negative correlations existed between diastolic blood pressure and BUN and Cr. A positive correlation between the PS and antiplatelet medicine use was observed; however, no correlations were apparent between the PS and other medicines. Based on the changes in the risk factors over the years (Table 2) and the investigation of the factors that contributed to the PS (Table 3), a decrease of LDL-C was considered a key factor involved in the PS improvement over the years. Therefore,

Table 1
Comparison of baseline characteristics between the 257 ESKD patients with and without B-mode ultrasound examination of the carotid artery in 3 separate eras.

	Era 1			Era 2			Era 3		
	US(−)	US(+)	p	US(−)	US(+)	p	US(−)	US(+)	p
Total patients No.	58	34		33	45		16	71	
Male, (%)	41(71)	24(71)	0.5	16(49)	39(87)	***	9(56)	47(66)	0.3
Age, years	64 (54–73)	65 (59–74)	0.3	68 (55–78)	66 (58–75)	0.2	66 (58–82)	75 (63–81)	0.1
BMI, kg/m^2	19.7 (18.4–21.6)	20.7 (18.8–23.0)	0.3	21.2 (20.0–23.6)	22.0 (19.5–23.3)	0.5	20 (18–23)	20.8 (18.6–23.4)	0.7
SBP, mmHg	144 (130–160)	160 (152–183)	0.4	160 (146–170)	150 (140–168)	0.8	136 (130–147)	156 (144–178)	*
DBP, mmHg	70 (66–80)	78 (70–90)	0.1	69 (60–86)	80 (73–91)	0.3	74 (62–84)	76 (68–86)	0.9
Smoking, (%)	17(29)	9(27)	0.4	8(24)	18(40)	0.1	9(56)	37(52)	0.4
DM, (%)	37(64)	21(62)	0.5	17(52)	27(60)	0.3	4(25)	46(65)	**
CAD, (%)	19(33)	6(18)	0.1	4(12)	7(16)	0.4	2(13)	14(20)	0.3
Stroke, (%)	9(16)	7(21)	0.3	1(3)	11(24)	**	0(0)	10(14)	0.1
PAD, (%)	14(25)	13(38)	0.1	2(7)	15(39)	**	2(13)	20(29)	0.1
Statin, (%)	8(14)	8(24)	0.1	8(24)	13(29)	0.4	6(38)	38(54)	0.1
Alb, mg/dL	3.5 (3.0–3.8)	3.4 (3.1–3.7)	0.2	3.3 (2.9–3.4)	3.4 (3.0–3.7)	0.5	3.7 (3.4–4.3)	3.5 (3.1–3.8)	0.8
Cr, mg/dL	8.2 (7.1–10.4)	9.1 (7.3–12.2)	0.1	8.4 (7.0–10.4)	9.4 (8.2–11.9)	0.8	9.3 (7.8–10.1)	9.3 (7.3–11.3)	0.2
eGFR, mL/min/1.73 m^2	5.2 (4.2–5.9)	4.6 (3.4–6.8)	0.1	5.2 (3.9–6.1)	4.5 (3.6–5.6)	0.2	4.7 (3.8–5.4)	4.4 (3.5–5.7)	0.3
TC, mg/dL	163 (142–206)	168 (139–203)	0.6	162 (127–209)	154 (133–176)	0.9	164 (141–193)	152 (128–176)	0.6
HDL-C, mg/dL	45 (39–53)	45 (40–56)	0.1	45 (38–54)	47 (38–55)	0.6	48 (40–63)	46 (38–61)	0.9
LDL-C, mg/dL	95 (83–129)	107 (77–135)	0.6	92 (74–123)	89 (68–112)	0.1	87 (79–115)	83 (67–103)	0.5
NHDL-C, mg/dL	121 (95–168)	119 (94–156)	0.1	111 (92–159)	107 (87–127)	0.6	114 (99–132)	102 (76–127)	0.2
CRP, mg/dL	0.1 (0.0–0.1)	0.1 (0.0–0.1)	0.8	0.04 (0.0–0.2)	0.07 (0.0–0.2)	0.4	0.02 (0.01–0.05)	0.05 (0.02–0.14)	0.4

Data are means ± SD and medians (interquartile range). BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; PAD, Peripheral Artery Disease; Alb, Albumin; Cr, Creatinine; eGFR, estimated Glomerular Filtration Rate; TC, Total Cholesterol; HDL-C, High Density Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; NHDL-C, non-High Density Lipoprotein-Cholesterol; CRP, C-Reactive Protein.
*p < 0.05 **p < 0.01 ***p < 0.001.

multivariate regression analysis models that accounted for LDL-C were constructed, and the contribution of LDL-C to the PS was examined (Table 4).

3.5. Independence of the LDL-C contribution to the PS

Various interrelated factors were adjusted to examine the relationship between LDL-C and the PS. Model 1 was a univariate regression analysis between the PS and LDL-C. Model 2 incorporated renal function, the 3 eras, and the traditional risk factors for atherosclerosis, including age, sex, smoking history, systolic blood pressure, and diabetes mellitus. Model 3 included the non-traditional atherosclerosis risk factors, malnutrition and inflammation, in addition to Model 2. Model 4 incorporated the different values for the lipids in addition to Model 2. Model 5 included factors associated with calcium and phosphorus metabolic disturbances as non-traditional atherosclerosis risk factors. Model 6 incorporated CVD as a complication and the medicines used. Model 7 included factors associated with anemia as a non-traditional atherosclerosis risk factor. Model 8 included factors associated with glycemic control as traditional atherosclerosis risk factors. Model 9 included AST-120. The multivariate linear regression analysis showed a positive correlation between LDL-C and the PS after adjusting the individual models for several variables.

3.6. PS and the lipid profile in statin users and non-users in each era

In Era 3, LDL-C and total cholesterol (TC) were significantly lower in the statin group, but no other noteworthy differences were seen (Table 5). Two points should be taken from this table. First, in all eras, PS tended to be higher in people who used statins than in those who did not. There is a high likelihood that this is a reflection of the results of statin introduction in patients with more carotid atherosclerosis. The second is that PS and LDL-C showed a tendency to decrease together with the era, regardless of whether statins were used. This finding suggests the possibility that improvements in lipids not due to statins may be linked to PS improvements.

4. Discussion

4.1. Main findings of this study

Strict management of blood pressure and dyslipidemia potentially inhibit CKD progression [21–23], and the Japanese guidelines for the treatment of CKD recommend these approaches [24]. Studies in general populations have revealed that the management of blood pressure and dyslipidemia inhibits the progression of atherosclerosis and the onset of cardiovascular events [25], and that it may be effective at slowing atherosclerosis in CKD patients. In the present study, the PS at the initiation of dialysis decreased significantly over 9 years. Furthermore, LDL-C levels decreased and statin use increased in the same timeframe. However, regression analysis showed that there was no correlation between the increase in statin use and improvements in the PS over the 9-year period, but there was a correlation between the LDL-C level and the PS decrease. Other factors thought to contribute to arteriosclerosis

Table 2
Baseline characteristics of the 150 ESKD patients.

	Total	Era 1	Era 2	Era 3	Jonckheere–Terpstra trend test
	150	34	45	71	
Male, (%)	110(73)	24(71)	39(87)	47(66)	0.2
Age, years	70(60–78)	65(59–74)	66(58–75)	75(63–81)	< 0.001
BMI, kg/m^2	21.2(19.2–23.3)	20.7(18.8–23.0)	22.0(19.5–23.3)	20.8(18.6–23.4)	0.1
Smoking, (%)	64(43)	9(27)	18(40)	37(52)	0.1
SBP mmHg	155(144–177)	160(152–183)	150(140–168)	156(144–178)	0.2
DBP mmHg	78(70–89)	78(70–90)	80(73–91)	76(68–86)	0.2
Alb, mg/dL	3.4(3.1–3.7)	3.4(3.1–3.7)	3.4(3.0–3.7)	3.5(3.1–3.8)	0.1
BUN, mg/dL	89(71–103)	96(77–110)	86(71–100)	87(71–99)	0.2
Cr, mg/dL	9.3(7.5–11.7)	9.1(7.3–12.2)	9.4(8.2–11.9)	9.3(7.3–11.3)	0.5
eGFR, mL/min/1.73 m^2	4.5(3.5–5.9)	4.6(3.4–6.8)	4.5(3.6–5.6)	4.4(3.5–5.7)	0.1
UA, mg/dL	8.0(6.5–9.3)	7.9(6.5–8.6)	7.5(6.3–8.9)	8.1(6.5–9.9)	0.9
Ca, mg/dL	8.5(7.8–8.9)	8.3(7.2–8.8)	8.3(7.7–8.8)	8.6(8.0–8.9)	0.2
P, mg/dL	6.1(5.2–7.2)	5.9(4.8–6.8)	5.7(5.4–7.1)	6.4(5.6–7.4)	0.01
TC, mg/dL	156(133–182)	168(139–203)	154(133–176)	152(128–176)	0.08
TG, mg/dL	101(80–138)	112(87–145)	94(73–134)	102(82–140)	0.3
HDL-C, mg/dL	47(38–59)	45(40–56)	47(38–55)	46(38–61)	0.2
LDL-C, mg/dL	88(68–113)	107(77–135)	89(68–112)	83(67–103)	0.005
NHDL-C, mg/dL	108(82–134)	119(94–156)	107(87–127)	102(76–127)	0.006
BS, mg/dL	139(112–169)	149(124–181)	136(111–166)	132(104–167)	0.08
HbA1c (NGSP), %	5.4(5.1–5.9)	5.6(5.3–6.0)	5.4(5.2–5.9)	5.4(5.1–5.7)	0.2
GA, %	18.2(15.7–21.2)	22.0(18.1–24.6)	17.6(15.7–21.6)	18.1(15.6–20.0)	0.4
CRP, mg/dL	0.06(0.00–0.15)	0.1(0.0–0.1)	0.07(0.0–0.2)	0.05(0.02–0.14)	0.04
Hb, g/dL	8.8(7.6–9.9)	7.9(6.9–9.1)	8.6(7.4–9.7)	9.1(8.5–10.1)	< 0.001
iPTH, μg/dL	267(191–369)	229(165–447)	262(171–357)	297(206–360)	0.1
mCA-IMT, mm	0.9(0.7–1.1)	0.8(0.7–1.0)	1.0(0.7–1.3)	0.9(0.7–1.1)	0.1
PS	7.8(3.8–13.2)	12.8(3.3–19.9)	8.1(4.4–11.8)	5.4(3.2–12.6)	0.01
DM, (%)	94(63)	21(62)	27(60)	46(65)	0.6
CAD, (%)	27(18)	6(18)	7(16)	14(20)	< 0.001
Stroke, (%)	28(19)	7(21)	11(24)	10(14)	0.2
RASI total, (%)	98(65)	17(50)	33(73)	8(68)	0.2
CCB, (%)	110(73)	24(71)	33(73)	53(75)	0.6
Beta blocker, (%)	40(27)	5(15)	10(22)	25(35)	0.01
Statin, (%)	59(39)	8(24)	13(29)	38(54)	0.001
Aspirin, (%)	49(33)	12(35)	16(36)	21(30)	0.4
ESA, (%)	114(77)	23(68)	36(80)	55(79)	0.3
Phosphate binders, (%)	13(8)	1(3)	7(16)	5(7)	0.9
Vitamin D analogs, (%)	23(15)	7(20)	8(18)	8(11)	0.2
OHA, (%)	16(11)	2(6)	2(4)	12(17)	0.03
Insulin, (%)	39(26)	12(35)	11(24)	16(23)	0.2
AST-120, (%)	27(18)	10(29)	8(20)	8(11)	0.02

Data are means ± SD and medians (interquartile range). BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; Alb, Albumin; Cr, Creatinine; eGFR, estimated Glomerular Filtration Rate; UA, Uric Acid; Ca, Calcium; P, Phosphate; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High Density Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; NHDL-C, non-High Density Lipoprotein-Cholesterol; BS, Blood Sugar; GA, GlycoAlbumin; CRP, C-Reactive Protein; Hb, Hemoglobin; intactPTH, intact Parathyroid Hormone; mCA-IMT, mean Carotid Artery-Intima Media Thickness; PS, Plaque Score; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; PAD, Peripheral Artery Disease; RASI, Renin Angiotensin System Inhibitor; CCB, Calcium Channel Blocker; ESA, Erythropoiesis Stimulating Agent; OHA, Oral Hypoglycemic Agent.

(Hb, Ca/P metabolic disturbances, blood glucose) were not found to have a clear association with PS. This indicates that changes in CKD treatment and patients' characteristics in recent years have reduced LDL-C levels, which, in turn, have improved carotid atherosclerosis. However, we have to be cautious about discussing direct causal relationships because this was a cross-sectional study that compared individual eras.

4.2. Changes in eras and atherosclerotic disease

Studies examining the effects of changes in treatment over the years, like this study, have been sequentially reported in recent years. A study of patients managed under the Medicare program in the United States reported that the stroke incidence rate has declined over the past 20 years and the use of statins and antihypertensive medicines has increased [26]. Another American study that analyzed the data of 57,000 patients with diabetes mellitus reported substantial changes in the complications associated with type 2 diabetes mellitus from 1990 to 2010, and, in particular, the incidence of acute myocardial infarction decreased by 70% during the 20-year period [27]. We recently reported that, over the past 20 years, the prevalence of CAD at the initiation of dialysis has decreased, risk factors have improved, and drug use has increased [28]. Therefore, it is not surprising that changes in patients' clinical characteristics and treatments over the years have led to a result that suggests that improvements in carotid atherosclerosis may also be seen in patients with CKD.

4.3. LDL-C and carotid atherosclerosis

Many studies have reported on the relationship between LDL-C levels and the severity of carotid atherosclerosis. Salonen et al. studied the relationship between the CA-IMT and abnormal lipid metabolism in 720 healthy men and reported that the CA-IMT increases as the LDL-C level increases [29]. Other studies have reported decreases in LDL-C levels and improvements in carotid atherosclerosis. John et al. reported that the statin-induced decrease in LDL-C levels contributed to improvements in carotid atherosclerosis [30]. In addition, it has been confirmed that carotid atherosclerosis in patients with CKD is more severe even in the early stages of kidney disease than in healthy individuals, and that a positive correlation exists between an increase in the LDL-C level

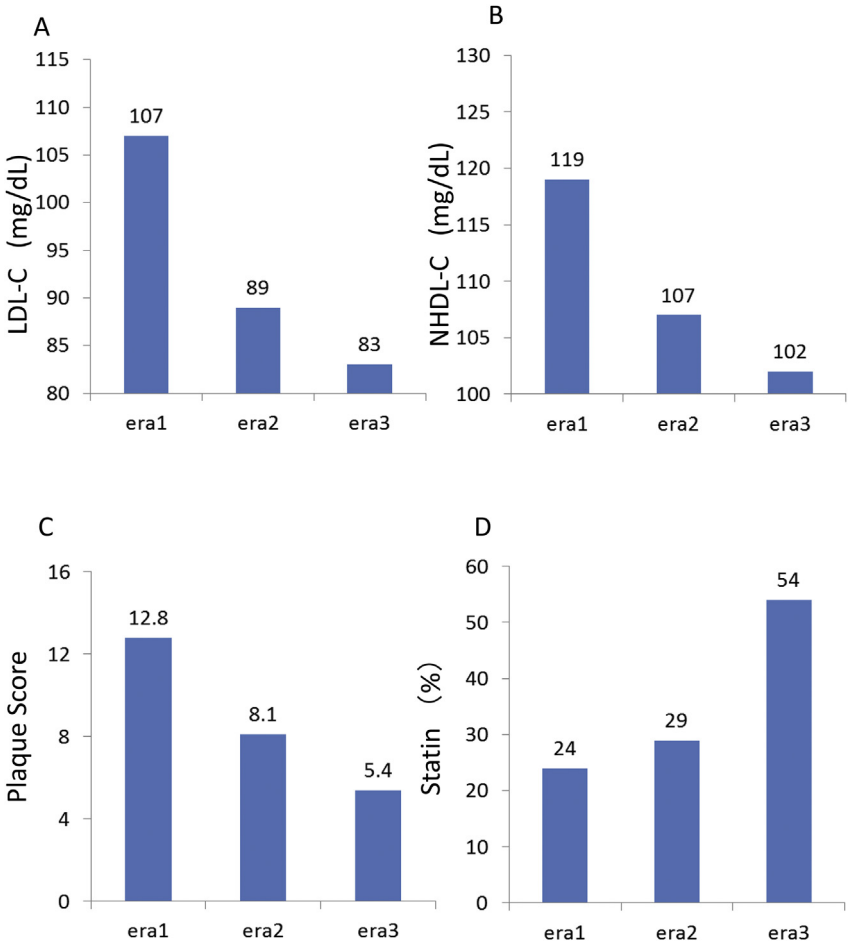

Fig. 3. Trends in the clinical parameters over the 3 eras. [A] Low-density lipoprotein cholesterol (LDL-C) ($P = 0.005$ for trend) and [B] non-high-density lipoprotein cholesterol (HDL-C) ($P = 0.006$ for trend) levels tend to decrease over the years. [C] The rate of statin use increases over the years ($P = 0.001$ for trend). [D] Regarding carotid arteriosclerosis, the plaque score declines markedly from 12.8 to 5.4 ($P = 0.01$ for trend).

and the CA-IMT [31]. In this study, the observed improvements in the carotid artery PS and in LDL-C levels over the years are thought to be in line with the results of those previously published studies [29–31].

4.4. Changes in lipid levels and statin use

In this study, reductions in LDL-C levels and increases in statin use over the years were confirmed. Although it might be natural to deduce that statin use has led to improvements in dyslipidemia, a supplementary analysis did not find a negative correlation between statin use and the LDL-C level. Therefore, the reduction in the LDL-C level over the 9-year period might be associated with lifestyle improvements rather than therapeutic interventions. In fact, as shown in Table 5, PS showed a tendency to improve with the era regardless of whether statins were used. In parallel with this, a tendency for improvements in LDL-C was seen even in people who did not use statins. This suggests that lifestyle improvements contribute to PS improvements more than statin use does. Unfortunately, our database does not contain any parameters associated with lifestyle; hence, this hypothesis could not be proven. A publication that describes a decrease in the incidence of stroke [26] also reports that, over the past 20 years, total cholesterol levels have decreased from 210 mg/dL to 183 mg/dL and from 230 mg/dL to 206 mg/dL in men and women, respectively. However, the article did not describe the relationship between statin use and reductions in cholesterol levels, but this does not necessarily mean that the relationship does not exist. Furthermore, the study's results help to corroborate the findings of the current study.

4.5. Differences between the CA-IMT and the PS

At first, we hypothesized that both the CA-IMT and the PS would decrease equally over the 9-year period. However, while the PS changed, the CA-IMT did not change. Whereas the CA-IMT represents the mean thickness of the intima media, the PS scores the plaques, which are defined as the regions where the CA-IMT is 1.1 mm or thicker. Hence, the CA-IMT is indicative of subclinical early atherosclerosis, and the PS principally signifies advanced atherosclerosis, that is, lesions that are more likely to lead to a cardiovascular event. Some studies that have used carotid artery ultrasonography report that plaque areas and the PS are more closely related to the onset of CVD than the CA-IMT [31–33], which concurs with the description given above. The present study investigated patients with ESKD in whom complications associated with more advanced atherosclerotic lesions would be a concern. Hence, it is understandable that changes were only observed in the PS. As described previously, we have reported that the prevalence CAD at the initiation of dialysis has decreased over the last 20 years [28]. A study undertaken in Japan reported that the severity of CAD correlated only with the PS and not with the CA-IMT [33]. Judging from these results, assessment of PS may be more useful than IMT

Table 3
Univariate linear regression analysis for the factors associated with PS.

	Regression coefficient	95% CI		p
		Lower	Upper	
Age, years	0.333	0.105	0.284	< 0.001
Male, (%)	0.007	−2.714	2.942	0.9
BMI	−0.095	−0.444	0.119	0.2
SBP, mmHg	−0.084	−0.078	0.025	0.3
DBP, mmHg	−0.249	−0.173	−0.037	0.003
Smoking, (%)	0.056	−1.646	3.403	0.4
DM, (%)	0.064	−1.568	3.593	0.4
CAD, (%)	0.254	1.946	8.243	0.002
Stroke, (%)	0.03	−2.61	3.807	0.7
Alb, mg/dL	−0.121	−4.305	0.637	0.1
BUN, mg/dL	−0.190	−0.102	−0.003	0.04
Cr, mg/dL	−0.283	−0.948	−0.275	< 0.001
eGFR, mL/min/1.73 m^2	0.219	0.222	1.519	0.009
UA, mg/dL	0.069	−0.335	0.809	0.4
Ca, mg/dL	−0.065	−1.545	0.668	0.4
P, mg/dL	−0.149	−1.291	0.072	0.07
TC, mg/dL	0.115	−0.007	0.038	0.1
TG, mg/dL	0.053	−0.014	0.026	0.5
HDL-C, mg/dL	−0.007	−0.082	0.075	0.9
LDL-C, mg/dL	0.281	0.021	0.086	0.001
Non-HDL-C, mg/dL	0.132	−0.006	0.045	0.1
BS, mg/dL	0.167	−0.003	0.058	0.07
HbA1c, %	0.154	−0.456	3.534	0.1
GA, %	0.073	−0.151	0.336	0.4
CRP, mg/dL	0.112	−1.104	6.048	0.1
Hb, g/dL	0.024	−0.626	0.848	0.7
iPTH, μg/dL	−0.129	−0.007	0.001	0.1
mCA-IMT, mm	0.559	8.383	13.773	< 0.001
RASI total, (%)	−0.119	−4.537	0.681	0.1
CCB, (%)	−0.067	−3.997	1.647	0.4
Beta blocker, (%)	0.039	−2.156	3.497	0.6
Statin, (%)	0.081	−1.268	3.836	0.3
Aspirin, (%)	0.253	1.569	6.729	0.002
ESA, (%)	0.03	−2.424	3.506	0.7
Phosphate binders, (%)	−0.134	−8.063	0.748	0.1
Vitamin D analogs, (%)	−0.067	−4.899	2.028	0.4
OHA, (%)	−0.125	−7.127	0.913	0.1
Insulin, (%)	0.098	−1.114	4.561	0.2
AST-120, (%)	0.096	−1.246	4.881	0.2

BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; Alb, Albumin; Cr, Creatinine; eGFR, estimate Glomerular Filtration Rate; UA, Uric Acid; Ca, Calcium; P, Phosphate; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High Density Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; NHDL-C, non-High Density Lipoprotein-Cholesterol; BS, Blood Sugar; GA, GlycoAlbumin; CRP, C-Reactive Protein; Hb, Hemoglobin; iPTH, intact Parathyroid Hormone; mCA-IMT, mean Carotid Artery-Intima Media Thickness; RASI, Renin Angiotensin System Inhibitor; CCB, Calcium Channel Blocker; ESA, Erythropoiesis Stimulating Agent; OHA; Oral Hypoglycemic Agent.

in predicting the development of cardiovascular disease in end-stage kidney disease patients.

Alternatively, the results might be a consequence of differences in the methods used to measure the parameters. The PS has greater scope for variation than the CA-IMT, and a large difference in the values could produce a significant difference. However, to produce CA-IMT measurements with a small variation, a larger number of patients may be necessary to confirm the significant difference. Furthermore, changes in the numbers of plaques over the years might have affected the differences in the changes in the CA-IMT and the PS, although this was not evaluated during our study.

4.6. Statin usage in CKD

The 4D study [34] and AURORA study [35], which were randomized, controlled trials involving dialysis patients, showed that the overall risk of cardiovascular disease was not significantly decreased in patients given strong statins in the dialysis treatment period. However, in the Study of Heart and Renal Protection (SHARP) study [36] reported in 2011, a comparison was made between a simvastatin plus ezetimibe group and a placebo group in 9270 patients with CKD stage 3-5D, and the number of arteriosclerotic cardiovascular disease events was reduced significantly, by 17%. In a stratified analysis in the SHARP study, a significant decrease in risk of 20% was obtained in the non-dialysis group, whereas the 10% decrease in the dialysis group was not significant. In a stratified analysis with pretreatment TC level, the decrease in relative risk was significantly greater with higher TC levels, nearly the same as in the stratified analysis with the LDL-C level. Among past large-scale, randomized, controlled trials using statins, subanalyses of subjects equivalent to CKD stage 3 [37–41] showed a similar or larger decrease in relative risk of arteriosclerotic cardiovascular disease as in non-CKD patients.

From the above, although a decreased risk of arteriosclerotic cardiovascular disease with lipid-lowering therapy is also seen in CKD patients, the size of the decrease in risk is not uniform. There is thought to be a greater effect in early-stage CKD patients and patients with high pretreatment TC and LDL-C levels.

4.7. Limitations

The selection bias caused by only including those patients who had undergone carotid artery ultrasonography was the biggest limitation. Since this was a retrospective, observational study, the sample size was small, with a total of 150 patients, and the number of patients analyzed in Era 1 was particularly small. Therefore, before the primary analysis, a preliminary analysis was performed to determine the magnitude of the selection bias by comparing the clinical characteristics of the groups that did and did not undergo carotid artery ultrasonography. No sizeable differences were detected in relation to the clinical characteristics between the groups that did and did not undergo carotid artery ultrasonography within the eras. Therefore, one can conclude that selection bias, if

Table 4
Independent association of LDL-C with PS in multivariate linear regression analysis.

Model	Adjustment	Regression coefficient	95% CI		p	r2
Model 1	Unadjusted	0.281	0.021	0.086	0.001	0.079
Model 2	Age, Male, Smoking, SBP, Era, DM, eGFR	0.252	0.018	0.078	0.002	0.375
Model 3	Model 2 + Alb, CRP	0.246	0.017	0.077	0.003	0.402
Model 4	Model 2 + TC, TG, HDL-C	0.878	0.087	0.248	0.000	0.445
Model 5	Model 2 + Ca, P, iPTH, Vitamin D analogs, Phosphate binders	0.274	0.022	0.083	0.001	0.449
Model 6	Model 2 + CAD, Stroke, RASI, Aspirin, Statin	0.272	0.024	0.080	0.000	0.489
Model 7	Model 2 + Hb, ESA	0.272	0.022	0.082	0.001	0.412
Model 8	Model 2 + HbA1c, OHA, Insulin	0.207	0.001	0.082	0.044	0.531
Model 9	Model 2 + AST-120	0.248	0.017	0.078	0.002	0.375

SBP, Systolic Blood Pressure; DM, Diabetes Mellitus; eGFR, estimate Glomerular Filtration Rate; CRP, C-Reactive Protein; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High Density Lipoprotein Cholesterol; Ca, Calcium; P, Phosphate; iPTH, intact Parathyroid Hormone; CAD, Coronary Artery Disease; RASI, Renin Angiotensin System Inhibitor; ESA, Erythropoiesis Stimulating Agent; OHA, Oral Hypoglycemic Agent.

Table 5
Comparison of baseline characteristics between the 150 ESKD patients with and without statin use for carotid artery atherosclerosis in 3 separate eras.

	Era 1			Era 2			Era 3		
	Statin(−)	Statin(+)	P	Statin(−)	Statin(+)	P	Statin(−)	Statin(+)	P
Total patients No.	26	8		32	13		33	38	
Male, (%)	18(69)	6(75)	0.8	26(81)	13(100)	0.1	23(70)	24(63)	0.6
Age, year	66(55–74)	66(56–74)	0.6	70(59–79)	65(59–70)	0.2	77(64–83)	74(63–80)	0.3
TC, mg/dL	168(148–202)	146(125–208)	0.4	154(133–173)	151(125–206)	0.9	168(138–199)	150(124–169)	0.04
TG, mg/dL	112(87–154)	107(85–135)	0.8	94(72–112)	91(75–134)	0.9	104(85–139)	98(72–140)	0.7
HDL-C, mg/dL	48(40–56)	45(40–56)	0.9	45(36–55)	52(48–56)	0.08	46(38–66)	47(41–59)	0.9
LDL-C, mg/dL	107(87–125)	94(55–135)	0.4	91(68–112)	76(68–130)	0.9	96(76–126)	75(61–91)	0.02
NHDL-C, mg/dL	121(105–158)	101(74–151)	0.3	108(90–125)	95(81–154)	0.8	117(89–153)	96(74–116)	0.05
mCA-IMT, mm	0.7(0.6–0.9)	0.8(0.7–1.2)	0.1	0.9(0.7–1.1)	1.2(0.8–1.4)	0.3	0.9(0.7–1.1)	1.0(0.8–1.2)	0.05
PS	10.1(2.9–20.0)	17.9(10.1–26.0)	0.2	7.8(4.1–10.9)	11.5(6.7–15.1)	0.1	4.7(2.7–11.3)	6.1(4.0–13.3)	0.2

Data are means ± SD and medians (interquartile range). TC, Total Cholesterol; TG, Triglyceride; HDL-C, High Density Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; NHDL-C, non-High Density Lipoprotein-Cholesterol; mCA-IMT, mean Carotid Artery-Intima Media Thickness; PS, Plaque Score.

any, had little impact on the analysis used to prove our hypothesis. In addition, this was a cross-sectional comparative study of separate eras; therefore, proving causal relationships between drug administration or lipid value improvements and carotid atherosclerosis improvements was impossible. In this study, carotid artery ultrasonography had been performed for 9 years, but instruments and technicians changed during the period analyzed in this study. However, we would like to emphasize that the instruments were obtained from the same company, and that the measurements were performed by technicians trained by the same trainer. Since this was a cross-sectional study, it was not possible to determine whether the treatment periods related to the conservative phase of kidney disease or to determine the specifics of the treatment, for example, whether the statins were of conventional or of strong type. In addition to the rate of statin use, the differences in the efficacies of the statins may be strongly associated with the improvement in the PS. Given that this was a single-center, cross-sectional study with a relatively small number of patients, a larger-scale study should be undertaken in the future.

5. Conclusion

Carotid atherosclerosis in patients with ESKD has decreased over the past 9 years. Changes in CKD management and patients' characteristics in recent years have reduced LDL-C levels, which, in turn, may have improved carotid atherosclerosis.

Competing interests

None of the authors has any conflicts of interest of financial disclosures associated with this study.

Authors' contributions

H.H and N.J had full access to all the data in the study and take responsibility for the integrity of the data and the analytic accuracy.
Study concept and design: H.H., N.J., Y.T. and T.H.
Data acquisition: H.H., N.J., Y.T. and T.H.
Data analysis and interpretation: T.A. and N.J.
Drafting of the manuscript: T.A. and N.J.
Statistical analysis: T.A. and N.J.
Administrative, technical and material support: K.H.

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