

Factors Associated with the Change in Carotid Maximum Intima-Media Thickness in Patients with Moderate-to-Advanced Stage Chronic Kidney Disease

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Purpose: The objective of this study was to determine factors associated with the change in carotid maximum intima-media thickness (IMT), an established surrogate marker of atherosclerosis, in moderate-to-advanced stage chronic kidney disease (CKD) patients.

Methods: In total, 130 moderate-to-advanced stage CKD patients (mean age: 67.6 ± 11.0 years old; 91 men and 39 women) were included in this retrospective, single-center, observational study. Relationships between the change in carotid maximum IMT and clinical and laboratory data were analyzed by using multivariate linear regression analyses.

Results: Mean observation period was 2.9 ± 1.6 years. Mean carotid maximum IMT at baseline was 2.2 ± 1.0 mm, and the annual change in carotid maximum IMT was 0.06 ± 0.22 mm/year. Low-density lipoprotein (LDL)-cholesterol ($\beta = 0.173$, $p < 0.05$) and annual change in triglyceride ($\beta = 0.175$, $p < 0.05$) independently correlated with the annual change in carotid maximum IMT.

Conclusion: Increases in LDL-cholesterol and triglyceride were associated with the rate of progression of carotid maximum IMT in moderate-to-advanced stage CKD patients.

Keywords: atherosclerosis, carotid maximum intima-media thickness, chronic kidney disease

Introduction

Atherosclerosis is a frequently observed complication in patients with chronic kidney disease (CKD).¹ Various factors including uremic toxins, oxidative stress, diabetes mellitus, hypertension, and dyslipidemia have been considered to be responsible for progression of atherosclerosis in CKD patients.² Atherosclerosis contributes to the development of cardiovascular diseases including coronary artery disease and stroke, which are common causes of death in CKD patients.³ Therefore, assessment of subclinical atherosclerosis is important for preventing the development and progression of cardiovascular disease.⁴

Carotid intima-media thickness (IMT) is an indicator of generalized atherosclerosis.⁵ Measurement of carotid IMT with ultrasonography is noninvasive, repeatable, and easy to perform. Compared with mean IMT, maximum IMT has been reported to more strongly predict coronary artery disease.⁶ Additionally, several studies have shown that the progression of carotid maximum IMT was associated with the risk of developing atherosclerotic disease, including coronary

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artery disease and stroke.^{7,8} Therefore, carotid maximum IMT has been widely used as a surrogate marker for atherosclerosis and cardiovascular disease. In moderate-to-advanced stage CKD patients, blood pressure and renal function have been shown to be associated with changes in mean IMT.^{9,10} However, few studies have examined the factors associated with progression of carotid maximum IMT in moderate-to-advanced stage CKD patients. Therefore, in the present study, we investigated the factors associated with changes in carotid maximum IMT in moderate-to-advanced stage CKD patients.

Methods

Ethical Statement

This study protocol was approved by the institutional review board of Saitama Medical Center, Jichi Medical University (RIN S20-024) and was conducted in accordance with the ethical principles contained the Declaration of Helsinki and its subsequent amendments. Written informed consent was not obtained because of the retrospective study design. The patient data were treated carefully to keep confidentiality. We presented the study information on the notice boards in our institution and informed all the patients of their opt out rights, therefore only those who chose to opt out were excluded.

Patients

We collected and analyzed the data from patients who had regularly visited Saitama Medical Center, Jichi Medical University between 2010 and 2018. Inclusion criteria were: 1) age >20 years; 2) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (CKD stage G3 to G5); and 3) carotid artery ultrasonography performed twice with an interval of 1 year or more. The exclusion criteria were: 1) renal replacement therapy; 2) patients who wished to opt out from the study. Based on previous reports,^{9,10} patients with early stage CKD (G1 and G2) were excluded from the study.

Study Design

This study was a retrospective, single-center, observational study involving 130 patients. Figure 1 shows a diagram of the study design. Demographic and clinical data were obtained from patient medical charts. Factors that were independently associated with the change in carotid maximum IMT during the study period were analyzed by using multivariate linear regression analysis.

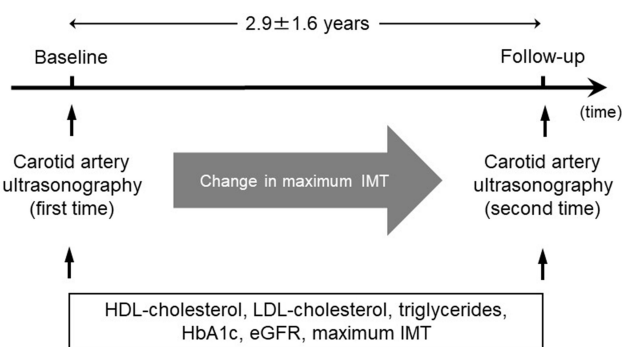


Figure 1 Study design.

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, serum hemoglobin A1c; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein.

Laboratory methods

Blood and urinary data were measured at the Department of Clinical Laboratory, Saitama Medical Center. Serum hemoglobin A1c (HbA1c) levels are shown as National Glycohemoglobin Standardization Program format values. eGFR was calculated by a modified equation of the Modification of Diet in Renal Disease study for Japanese patients with chronic kidney disease as follows: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times (0.739 \text{ if female})$.¹¹ Hypertension was defined by an average systolic blood pressure ≥ 140 mmHg or/and diastolic blood pressure ≥ 90 mmHg, or current use of blood pressure-lowering drugs. Diabetes mellitus was defined by HbA1c level $\geq 6.5\%$ or current use of blood glucose lowering drugs or/and insulin treatment.

Ultrasonographic Measurement of Carotid Maximum IMT

Carotid maximum IMT was determined using a B-mode ultrasound imaging with a 7.5-MHz linear transducer (Aplio 500; Toshiba Medical Systems, Tokyo, Japan). Carotid IMT was determined as the distance between two echogenic lines corresponding to the lumen-intima interface and the media-adventitia interface on the far wall of the artery (Figure 2A).¹² Carotid maximum IMT was defined as the greatest measurable carotid IMT on the left and right sides of the common carotid artery, bifurcation, and internal carotid artery (Figure 2B). All scans were carried out by experienced ultrasonographers.

Statistical Analysis

Statistical analyses were carried out using JMP 11 software (SAS Institute Inc., North Carolina, USA). Data are

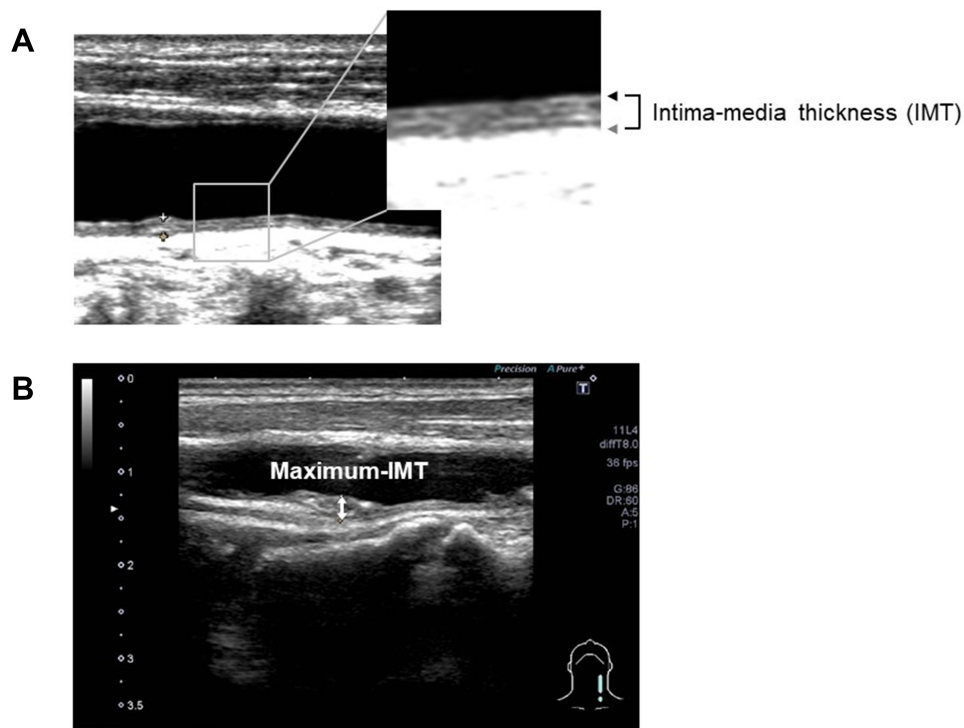


Figure 2 Longitudinal B-mode ultrasonographic images of the common carotid artery. **(A)** IMT was determined as the distance between the lumen-intima interface (black arrow) and the media-adventitia interface (gray arrow). **(B)** Maximum IMT was recorded as the largest IMT value measured on both sides of the common carotid artery, bifurcation, and internal carotid artery (two-headed arrow).
Abbreviation: IMT, intima-media thickness.

presented as means \pm standard deviations for continuous variables, and as numbers and percentages for categorical variables. Annual changes in carotid maximum IMT and lipid parameters were calculated by subtracting baseline data from follow-up data, and dividing the differences by the observation period. Correlations between two variables were examined by linear regression analyses. Multivariate linear regression analysis was performed using the step-wise forward selection method with entry criterion of $p < 0.05$ and removal criterion of $p < 0.05$. P-values < 0.05 were considered to indicate statistical significant.

Results

Baseline Parameters and Medication Use

Baseline parameters and medication use of patients are shown in Table 1. In total, 130 patients (mean age: 67.6 ± 11.0 years old; 91 men and 39 women) were analyzed. Mean observation period was 2.9 ± 1.6 years. Mean eGFR at baseline was 31.3 ± 12.6 mL/min/1.73 m², and CKD stages were: stage G3a, 23 (18%); stage G3b, 42 (32%); stage G4, 52 (40%); and stage G5, 13 (10%). Mean carotid maximum IMT at baseline was 2.2 ± 1.0 mm and the annual change in carotid maximum IMT was $0.06 \pm$

0.22 mm/year. The distribution of patients according to annual changes in maximum IMT of the carotid artery is shown in Figure 3. The proportions of patients with diabetes mellitus, dyslipidemia, and hypertension were 38%, 84%, and 95%, respectively. The proportions of patients with a history of coronary artery disease, ischemic stroke, and peripheral artery disease were 13%, 14%, and 11%, respectively. Medication use among patients was as follows: antiplatelet agent, 35%; statin, 65%; eicosapentaenoic acid, 52%; antihypertensive drug, 89%; renin-angiotensin system blocker, 74%; aldosterone receptor antagonist, 7%; β -blocker, 27%; calcium channel blocker, 69%; diuretic, 28%; antihyperuricemic drug, 74%; dipeptidyl peptidase 4 inhibitor, 18%; glucagon-like peptide-1 receptor agonist, 10%; insulin, 12%; vitamin D analogue, 18%; phosphate binder, 1%; and corticosteroid, 6%.

Factors Associated with Change in Carotid Maximum IMT

Simple linear regression analysis showed that the annual change in carotid maximum IMT significantly correlated with change in high-density lipoprotein (HDL)-cholesterol (standard coefficient (β) = -0.209 , $p < 0.05$), change in

Table 1 Baseline Parameters and Medication Use

	All Patients (n = 130)
Age (years)	67.6 ± 11.0
Male sex (number, %)	91 (70%)
Body mass index (kg/m ²)	24.2 ± 3.9
Systolic blood pressure (mmHg)	137.6 ± 18.5
Diastolic blood pressure (mmHg)	78.8 ± 12.1
HDL-cholesterol (mg/dL)	48.7 ± 14.9
LDL-cholesterol (mg/dL)	96.2 ± 29.8
Triglycerides (mg/dL)	159.6 ± 101.3
Change in HDL-cholesterol (mg/dL/year)	-0.4 ± 5.6
Change in LDL-cholesterol (mg/dL/year)	-6.4 ± 15.7
Change in triglyceride (mg/dL/year)	3.1 ± 51.6
Uric acid (mg/dL)	6.6 ± 1.4
HbA1c (%)	6.4 ± 1.1
Total calcium (mg/dL)	9.1 ± 0.5
Phosphate (mg/dL)	3.5 ± 0.6
C-reactive protein (mg/dL)	0.13 ± 0.17
CKD stage (number, %)	
G3a	23 (18%)
G3b	42 (32%)
G4	52 (40%)
G5	13 (10%)
eGFR (mL/min/1.73 m ²)	31.3 ± 12.6
Change in eGFR (mL/min/1.73 m ² /year)	-2.1 ± 3.1
Urinary protein excretion (g/gCr)	1.4 ± 2.0
Maximum IMT of the carotid artery (mm)	2.2 ± 1.0
Change in maximum IMT of the carotid artery (mm/year)	0.06 ± 0.22
Observation period (years)	2.9 ± 1.6
Underlying causes of CKD (number, %)	
Hypertensive nephrosclerosis	49 (37.7%)
Diabetic kidney disease	44 (33.8%)
Chronic glomerulonephritis	25 (19.2%)
Chronic interstitial nephritis	3 (2.3%)
Polycystic kidney disease	4 (3.1%)
Obstructive nephropathy	2 (1.5%)
Vasculitis	3 (2.3%)
Hypertension (number, %)	123 (95%)
Hyperuricemia (number, %)	116 (89%)
Dyslipidemia (number, %)	109 (84%)
Diabetes mellitus (number, %)	49 (38%)
Coronary artery disease (number, %)	17 (13%)
Ischemic stroke (number, %)	18 (14%)
Peripheral artery disease (number, %)	14 (11%)
Past or current smoking (number, %)	75 (58%)
Antiplatelet agent (number, %)	45 (35%)
Statin (number, %)	84 (65%)
Eicosapentaenoic acid (number, %)	67 (52%)
Antihypertensive drug (number, %)	116 (89%)
Renin-angiotensin system blocker (number, %)	96 (74%)

(Continued)

Table 1 (Continued).

	All Patients (n = 130)
Aldosterone receptor antagonist (number, %)	9 (7%)
β-blocker (number, %)	35 (27%)
Calcium channel blocker (number, %)	90 (69%)
Diuretic (number, %)	37 (28%)
Antihyperuricemic drug (number, %)	96 (74%)
Dipeptidyl peptidase 4 inhibitor (number, %)	24 (18%)
Glucagon-like peptide-1 receptor agonist (number, %)	13 (10%)
Insulin (number, %)	15 (12%)
Vitamin D analogue (number, %)	23 (18%)
Phosphate binder (number, %)	1 (1%)
Corticosteroid (number, %)	8 (6%)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, serum hemoglobin A1c; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein.

triglyceride ($\beta = 0.173, p < 0.05$), eGFR ($\beta = 0.182, p < 0.05$), and maximum IMT of the carotid artery ($\beta = -0.201, p < 0.05$) (Table 2). Multivariate stepwise linear regression analysis revealed that low-density lipoprotein (LDL)-cholesterol ($\beta = 0.173, p < 0.05$) and annual change in triglyceride ($\beta = 0.175, p < 0.05$) independently correlated with the annual change in carotid maximum IMT.

Discussion

In the present study, we investigated the factors associated with changes in carotid maximum IMT in moderate-to-advanced stage CKD patients. We found that baseline LDL-cholesterol concentration and annual change in triglyceride concentration were associated with the annual

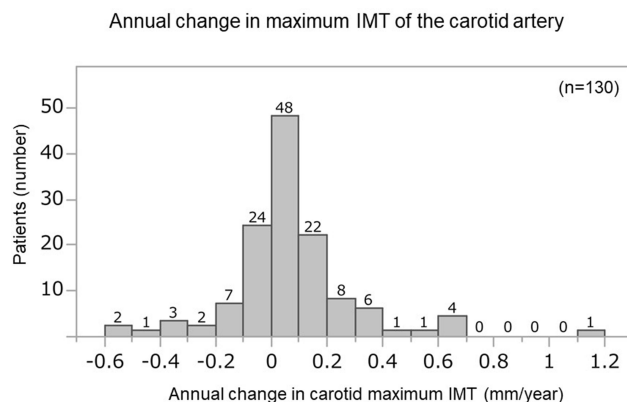


Figure 3 Distribution of patients according to annual change in maximum IMT of the carotid artery.

Abbreviation: IMT, intima-media thickness.

Table 2 Simple and Multivariate Linear Regression Analyses of Variables Associated with the Annual Change in Carotid Maximum IMT During the Observation Period

Variable	Simple Linear Regression Analysis		Multivariate Linear Regression Analysis	
	Standard Coefficient	P-value	Standard Coefficient	P-value
Age (years)	0.007	0.93		
Male sex (yes vs no)	-0.044	0.62		
Body mass index (kg/m ²)	-0.039	0.66		
Systolic blood pressure (mmHg)	0.027	0.76		
HDL-cholesterol (mg/dL)	0.016	0.86		
LDL-cholesterol (mg/dL)	0.172	0.05	0.173	<0.05
Triglycerides (mg/dL)	0.106	0.23		
Change in HDL-cholesterol (mg/dL/year)	-0.209	<0.05		
Change in LDL-cholesterol (mg/dL/year)	-0.123	0.16		
Change in triglyceride (mg/dL/year)	0.173	<0.05	0.175	<0.05
HbA1c (%)	-0.149	0.22		
Total calcium (mg/dL)	0.129	0.15		
Phosphate (mg/dL)	-0.042	0.64		
C-reactive protein (mg/dL)	-0.077	0.38		
eGFR (mL/min/1.73 m ²)	0.182	<0.05		
Change in eGFR (mL/min/1.73 m ² /year)	0.001	0.99		
Maximum IMT of the carotid artery (mm)	-0.201	<0.05		
Hypertension (yes vs no)	0.018	0.83		
Diabetes mellitus (yes vs no)	0.112	0.20		
Past or current smoking (yes vs no)	-0.070	0.43		
Statin (yes vs no)	-0.070	0.43		
Eicosapentaenoic acid (yes vs no)	0.042	0.63		
Antihypertensive drug (yes vs no)	-0.087	0.32		
Incretin agent (yes vs no)	0.105	0.23		

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, serum hemoglobin A1c; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein.

change in carotid maximum IMT in moderate-to-advanced stage CKD patients.

Carotid IMT is a well-established surrogate marker for atherosclerosis⁵ and is associated with various atherosclerotic risk factors such as diabetes mellitus, hypertension, and dyslipidemia.¹³ Several recent studies investigated factors associated with the change in carotid maximum IMT in patients without renal impairment.^{14,15} These studies showed that age, smoking, systolic blood pressure, and LDL-cholesterol were associated with the annual change in carotid maximum IMT.^{14,15} In the present study, baseline LDL-cholesterol concentration and the annual change in triglyceride concentration correlated with the annual rate of change of carotid maximum IMT.

Atherosclerosis is a chronic vascular inflammatory disease characterized by deposition of lipids and accumulation of inflammatory cells within the inner walls of arteries.¹⁶ Injury to the vascular endothelium through multivariate mechanisms including high blood pressure,

hyperglycemia, and dyslipidemia leads to infiltration and retention of monocytes in the subendothelial space.¹⁶ Several studies reported that LDL-cholesterol was positively correlated with the annual change in carotid maximum IMT in patients without renal impairment.^{14,15} In the present study, LDL-cholesterol was positively correlated with the annual change in carotid maximum IMT in moderate-to-advanced stage CKD patients. These results suggest that LDL-cholesterol may be associated with progression of carotid atherosclerosis in both patients with and without renal impairment.

Hypertriglyceridemia is a frequently observed lipid abnormality in patients with CKD.¹⁷ In patients with CKD, insulin sensitivity decreases as GFR declines.¹⁸ Insulin resistance promotes hepatic production of triglyceride-rich lipoproteins such as very low-density lipoprotein, leading to development of hypertriglyceridemia.¹⁹ Additionally, the downregulation of very low-density lipoprotein receptor expression in skeletal muscle has been

reported in an animal model of CKD.²⁰ In the present study, triglyceride was positively correlated with the annual change in carotid maximum IMT in moderate-to-advanced stage CKD patients. However, previous studies reported that triglyceride was not correlated with the annual change in carotid maximum IMT in patients without renal impairment.^{14,15} These results suggest that triglyceride might be associated with progression of carotid atherosclerosis in patients with renal impairment but not in patients without renal impairment.

Previous studies reported that age, smoking, and systolic blood pressure were associated with the annual change in carotid maximum IMT.^{14,15} In the present study, there was no association between age, smoking, blood pressure, and the annual rate of change of carotid maximum IMT. The mean age of participants was higher in this study (67.6 years) than in previous ones (56.3 years and 36.6 years),^{14,15} which may have affected our results. In the present study, almost all patients (95%) had a history of hypertension. It has been reported that the higher range of systolic blood pressure was associated with a greater progression of carotid IMT in patients with renal impairment.⁹ In the present study, nearly 90% of all patients were taking antihypertensive drugs including renin-angiotensin system blocker, calcium channel blocker, and diuretic. Systolic blood pressure was controlled below 140 mmHg, which was better than that in previous study.¹⁴ These findings might explain the discrepancy between our result and those of previously published reports. A prospective cohort study of moderate-to-advanced stage CKD patients reported that neither smoking nor blood pressure was associated with progression of carotid plaque.²¹ Smoking and blood pressure may not be associated with progression of carotid atherosclerosis in moderate-to-advanced stage CKD patients. Further studies are necessary to clarify the factors associated with progression of carotid atherosclerosis in moderate-to-advanced stage CKD patients.

To our knowledge, this is the first study to demonstrate factors associated with changes in carotid maximum IMT in moderate-to-advanced stage CKD patients. Our results may promote further studies investigating factors associated with carotid atherosclerosis in moderate-to-advanced stage CKD patients.

This study had several limitations. First, this was a retrospective study that may have included reporting and patient's selection biases. Second, the sample size was relatively small and the study was conducted at a single center, which restricts to generalize our study

findings. Third, observation periods differed among patients, which may have affected the results. Fourth, the ratio of male patients was higher than that of female patients in this study, which might have influenced the results of the study. Therefore, further large-scale, prospective, multicenter studies are required to clarify the factors associated with changes in carotid maximum IMT in moderate-to-advanced stage CKD patients.

In conclusion, increases in LDL-cholesterol and triglyceride were associated with the rate of progression of carotid maximum IMT in moderate-to-advanced stage CKD patients.

Acknowledgments

We thank Richard Robins, PhD, from Edanz Group (<https://en-author-services.edanzgroup.com/>) for editing a draft of this manuscript.

Disclosure

The authors declare that they have no conflicts of interest related to this manuscript.

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