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ORIGINAL ARTICLE

Impact of kidney function and urinary protein excretion on intima–media thickness in Japanese patients with type 2 diabetes

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Abstract

Background Carotid echo indexes [intima–media thickness (IMT)] are commonly used surrogate markers for cardiovascular disease; however, the impacts of chronic kidney disease (CKD) on changes in IMT are unclear. We examined associations between CKD and IMT in participants with and without type 2 diabetes through longitudinal analysis.

Methods In total, 424 subjects were enrolled in this study. IMT was measured as per carotid echo indexes. Relationships between IMT and risk factors were analyzed using multiple linear regression analysis, in which we defined IMT as the dependent variable and atherosclerosis-related factors (age, sex, systolic pressure, total cholesterol, body mass index, estimated glomerular filtration rate (eGFR), uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein levels, past cardiovascular event, glycated hemoglobin, and diabetes duration) as independent variables.

Results The study population was composed of 70.3 % male subjects. Participants with diabetes accounted for 64.4 % of the total population. The mean follow-up duration was 2.2 ± 1.5 years. Alterations in IMT tended to be associated with systolic blood pressure (+10 mmHg) ($\beta = -0.0084$, $p = 0.09$) and eGFR (+10 mL/min/1.73 m^2) ($\beta = -0.0049$, $p = 0.06$) in all participants. In participants without diabetes, alterations in IMT were associated with eGFR (+10 mL/min/1.73 m^2) ($\beta = -0.0104$, $p = 0.03$) and tended to be associated with systolic blood pressure (+10 mmHg) ($\beta = 0.0094$, $p = 0.06$). No significant relationships were found in participants with diabetes.

Conclusion Low eGFR was associated with progression of carotid thickness independent of common cardiovascular risk factors in non-diabetic participants.

Keywords Carotid ultrasonography · Chronic kidney disease · Intima–media thickness · Type 2 diabetes

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Introduction

Carotid artery is an easily accessible site for evaluating the severity of systemic atherosclerosis. Intima–media thickness (IMT) of the carotid artery is routinely measured by carotid ultrasonography and is useful for quantitative evaluation of atherosclerosis. Various studies have indicated associations between IMT and coronary artery [1–6] and cerebrovascular disease [7–10] Therefore, IMT is considered a suitable surrogate marker for cardiovascular disease (CVD).

Chronic kidney disease (CKD), mainly evaluated by estimated glomerular filtration rate (eGFR) and proteinuria [11–14], is a risk factor not only for end-stage kidney disease, but also for CVD [15, 16]. The CKD classification by KDIGO (Kidney Disease: Improving Global Outcomes) in 2012 clearly reflects its role as a CVD risk factor [17]. Thus, we reported previously that low eGFR might be related to pulmonary function, such as carbon monoxide diffusing capacity [18]. Conversely, some studies reported the associations between decreased eGFR and increased IMT [19–21]. However, most of them are cross-sectional studies, and the precise impact of CKD on alterations in IMT through longitudinal studies remain uncertain.

In addition to CKD, diabetes is also a well-known risk factor for atherosclerotic disease [22–24] Patients with diabetes have more advanced carotid arteriosclerosis than those without diabetes [25–30]. To assess the impact of risk factors on the progression of IMT, evaluation of the changes in the carotid artery might be a more appropriate method for causal association. To the best of our knowledge, no previous longitudinal studies have assessed the associations between CKD and the severity of carotid atherosclerosis in patients with diabetes. Therefore, we conducted a prospective study to investigate the relationships between CKD and IMT in participants with and without type 2 diabetes.

Methods

Subjects

The carotid ultrasonography and clinical data were selected from our laboratory database from October 30, 2005 to October 30, 2013. Participants with records of two or more carotid ultrasonography examinations and clinical information [eGFR, urinary protein, total cholesterol, urinary acid, body mass index (BMI), systolic blood pressure, diastolic blood pressure, smoking habit, history of antihypertensive drugs, history of statin use, history of cerebrovascular disease, and history of cardiovascular disease] during this period were enrolled in the current study (Fig. 1). The follow-up period was defined as the time between the first and last examination of ultrasonography. Cardiovascular disease included ischemic heart disease, congestive heart failure, or stroke, which needed hospital admission. Diabetes was defined as a clinical history of diabetes treatment or a glycated hemoglobin (HbA1c) $\geq$6.1 % [National Glycohemoglobin Standardization Program (NGSP)]. This study was approved by the Ethics Committee of the Kanazawa University Hospital (Approval No. 907) and was conducted in accordance with the Declaration of Helsinki. Information of this study was announced to potential candidates on the website of the Kanazawa University Hospital instead of obtaining informed consent of each patient. All analyses were performed on the condition of anonymity and participants had their right to withdraw from the study at any given time.

Carotid ultrasonography measurements

Parameters of carotid ultrasonography were measured using an Aplio carotid ultrasonography machine (Toshiba Medical Systems, Tokyo, Japan) with a 7.5-MHz transducer. The carotid IMT was recorded during the ultrasound examination. Ultrasonographers performed the examinations following a standard protocol [31]. The common carotid arteries, bifurcation, and internal carotid arteries were measured in all participants. IMT from the right and left sides was measured from the far wall, the location of which was identified as the vertical distance from the leading edge of the first to the second echogenic line. Three IMT determinations were measured in the walls at the site of the greatest thickness of each common carotid artery, and these measurements of both arteries were averaged and expressed as the mean IMT.

Laboratory data

All laboratory tests were performed at Kanazawa University Hospital. If laboratory test results from the day of the first ultrasonography examination were unavailable, the most recent test results from each day were used for the analysis. The Japan Diabetes Society (JDS) value of HbA1c was converted to the NGSP according to the formula in the JDS guidelines [32].

$$\text{NGSP}\ (\%) = 1.02 \times \text{JDS}\ (\%) + 0.25\%$$

Kidney function measurements

Kidney function was evaluated on the basis of eGFR and urinary protein levels. eGFR (mL/min/1.73 m^2) was calculated using the prediction formula $194 \times \text{Cr}^{-1.094} \times \text{age (year)}^{-0.287}$ (multiplied by 0.739 in females) developed by the Japanese Society of Nephrology [33].

Data analysis

A total of 424 subjects were included in this analysis. Clinical and biochemical characteristics of subjects at baseline and baseline data by yearly changes of IMT are summarized in Table 1. Subjects were divided into tertiles according to yearly changes of IMT. Differences across tertiles were analyzed by ANOVA for continuous variables

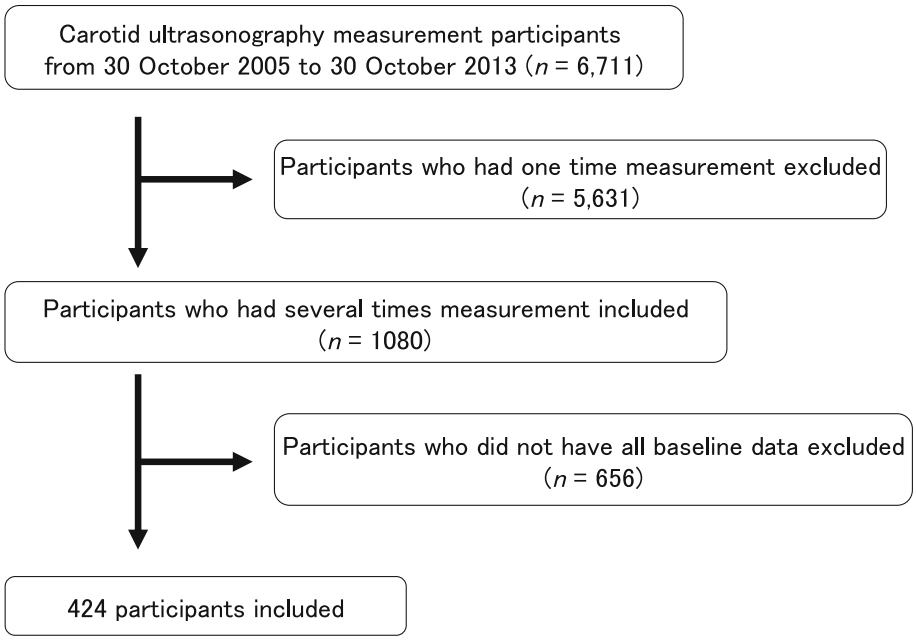

Fig. 1 Inclusion and exclusion criteria

or Pearson Chi-square test for categorical variables. Considering differences in baseline risk of cardiovascular disease [34], we stratified participants according to the status of diabetes. Associations between IMT and potential risk factors, including systolic blood pressure and eGFR, were examined using simple and multiple linear regression analysis. We performed multiple linear regression analysis using baseline IMT or annual changes in IMT throughout the follow-up period as an outcome variable and baseline eGFR as explanatory variable. The ordinary least-square method was used to estimate the annual changes in IMT. In Model 1, coefficients were adjusted for age, sex, diastolic pressure, total cholesterol, BMI, uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein levels, and past cardiovascular events as explanatory variables. In Model 2 for participants with diabetes, HbA1c and the duration of diabetes as explanatory variables were additionally adjusted to Model 1. For participants without diabetes, variables were adjusted in the same manner as that in Model 1.

Stata 12.1 (Stata Corp., College Station, TX, USA) was used for all statistical analyses. In all analyses, a p value of <0.05 was considered to be statistically significant.

Results

Characteristics of participants

A total of 424 subjects were included in this analysis. Clinical and biochemical characteristics of subjects at baseline and baseline data by yearly changes of IMT are summarized in Table 1. The study population was composed of 70.3 % male subjects. Participants with diabetes accounted for 64.4 % of the total population. The mean follow-up duration was 2.2 ± 1.5 years. Mean frequency of examination during the study period was 2.6 times. The majority (63.9 %) of participants were undergoing treatment with one or more antihypertensive drugs.

Baseline IMT

The relationships between baseline IMT and potential risk factors are illustrated in Fig. 2. Baseline systolic blood pressure was positively correlated between baseline IMT, and baseline eGFR was negatively correlated with baseline IMT. Both risk factors had relatively steeper correlations among participants without diabetes. Systolic blood pressure was significantly associated with baseline IMT even after adjusting for confounding factors (Table 2). The magnitude of standard regression coefficient was higher in participants without diabetes (Model 2: $\beta = -0.0093$, $p < 0.01$) than in those with diabetes (Model 2: $\beta = -0.0159$, $p = 0.01$). Baseline IMT was not significantly associated with eGFR.

Changes in IMT

The relationships between annual changes in IMT and potential risk factors are shown in Fig. 3. There was a negative correlation between eGFR and changes in IMT for participants without diabetes (Fig. 3a). Regarding systolic blood pressure, positive correlations were not observed (Fig. 3b). After adjusting for multiple risk factors, there

Table 1 Baseline data by yearly changes of IMT

	All	Changes of IMT (mm/year)			
		≤−0.031	−0.030 to 0.017	≥0.018	*p* value
n	424	142	141	141	
Carotid factors					
IMT [mm/year (SD)]	0.00 (0.21)	−0.15 (0.21)	0.00 (0.01)	0.14 (0.21)	<0.01
IMT [mm, mean (SD)]	0.8 (0.2)	0.9 (0.2)	0.7 (0.2)	0.8 (0.2)	<0.01
Follow-up period [years, mean (SD)]	2.2 (1.5)	1.6 (1.2)	3.0 (1.5)	2.0 (1.4)	
Age [years, mean (SD)]	64.2 (12.6)	64.4 (11.7)	62.5 (12.6)	65.6 (13.4)	0.12
Sex [*n* (%) of males]	298 (70.3)	101 (71.1)	99 (70.2)	98 (69.5)	0.96
Kidney factors					
eGFR [mL/min/1.73 m2, mean (SD)]	69.1 (25.9)	66.5 (26.3)	72.3 (25.9)	68.5 (25.3)	0.16
Urinary protein					0.46
−/Trace [*n* (%)]	333 (78.5)	105 (73.9)	117 (83.0)	111 (78.7)	
1 + [*n* (%)]	38 (9.0)	16 (11.3)	9 (6.4)	13 (9.2)	
>2 + [*n* (%)]	53 (12.5)	21 (14.8)	15 (10.6)	17 (12.1)	
Diabetes factors					
Diabetes [*n* (%)]	273 (64.4)	95 (66.9)	94 (66.7)	84 (59.6)	0.34
HbA1c [%, mean (SD)]	6.9 (1.9)	6.9 (1.9)	7.0 (1.8)	6.7 (2.0)	0.38
Duration of diabetes [years, mean (SD)]	13.6 (10.9)	9.2 (10.3)	8.0 (10.2)	8.3 (11.9)	0.63
Blood pressure (mmHg)					
Systolic blood pressure [mean (SD)]	129.3 (21.8)	131.2 (24.5)	129.1 (21.1)	127.5 (19.4)	0.36
Diastolic blood pressure [mean (SD)]	75 (14.0)	76.3 (15.5)	75.4 (12.4)	73.3 (13.7)	0.19
Pulse pressure [mean (SD)]	54.2 (18.1)	54.9 (21.1)	53.7 (16.9)	54.1 (16.1)	0.86
Smoking habit					0.45
Never smoker [*n* (%)]	187 (44.1)	61 (43.0)	67 (47.5)	59 (41.8)	
Ex-smoker [*n* (%)]	161 (38.0)	59 (41.6)	45 (32.0)	57 (40.4)	
Current smoker [*n* (%)]	76 (17.9)	22 (15.5)	29 (20.6)	25 (17.7)	
Smoking index [median (IQR)]	300 (0–900)	310 (0–1050)	100 (0–800)	300 (0–900)	0.25
Previous cardiovascular event [*n* (%)]	142 (33.5)	53 (37.3)	40 (28.4)	49 (34.8)	0.26
Other major risk factors					
Body mass index (kg/m^2) [mean (SD)]	31.2 (14.3)	24.2 (3.9)	24.3 (4.7)	24.2 (3.8)	0.98
Total cholesterol [mg/dL, mean (SD)]	185.6 (44.3)	190.3 (47.0)	181.8 (38.9)	184.6 (46.4)	0.26
Uric acid [mg/dL, mean (SD)]	6.9 (3.2)	7.1 (3.1)	6.8 (3.4)	6.6 (3.2)	0.46
Number of antihypertensive drugs					0.88
0 [*n* (%)]	153 (36.1)	48 (33.8)	53 (37.6)	52 (36.9)	
1 [*n* (%)]	83 (19.6)	27 (19.0)	30 (21.3)	26 (18.4)	
2 [*n* (%)]	65 (15.3)	22 (15.5)	21 (14.9)	22 (15.6)	
3 [*n* (%)]	77 (18.2)	25 (17.6)	22 (15.6)	30 (21.3)	
4 [*n* (%)]	32 (7.6)	13 (9.2)	10 (7.1)	9 (6.4)	
5 [*n* (%)]	13 (3.1)	6 (4.2)	5 (3.6)	2 (1.4)	
6 [*n* (%)]	1 (0.2)	1 (0.7)	0 (0.0)	0 (0.0)	
Use of statins [*n* (%)]	119 (28.1)	41 (28.9)	34 (24.1)	44 (31.2)	0.40

Percentages may not add to 100 % because of rounding

SD standard deviation, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *IQR* interquartile range, *IMT* intima–media thickness

was a tendency for increased IMT with lower eGFR (Model 1: $\beta = -0.0091$, $p = 0.06$) in all participants (Table 3). In participants without diabetes, eGFR was significantly associated with increased IMT even after adjusting for confounding factors (Model 2: $\beta = -0.0235$, $p = 0.03$). In contrast, no trend was observed in

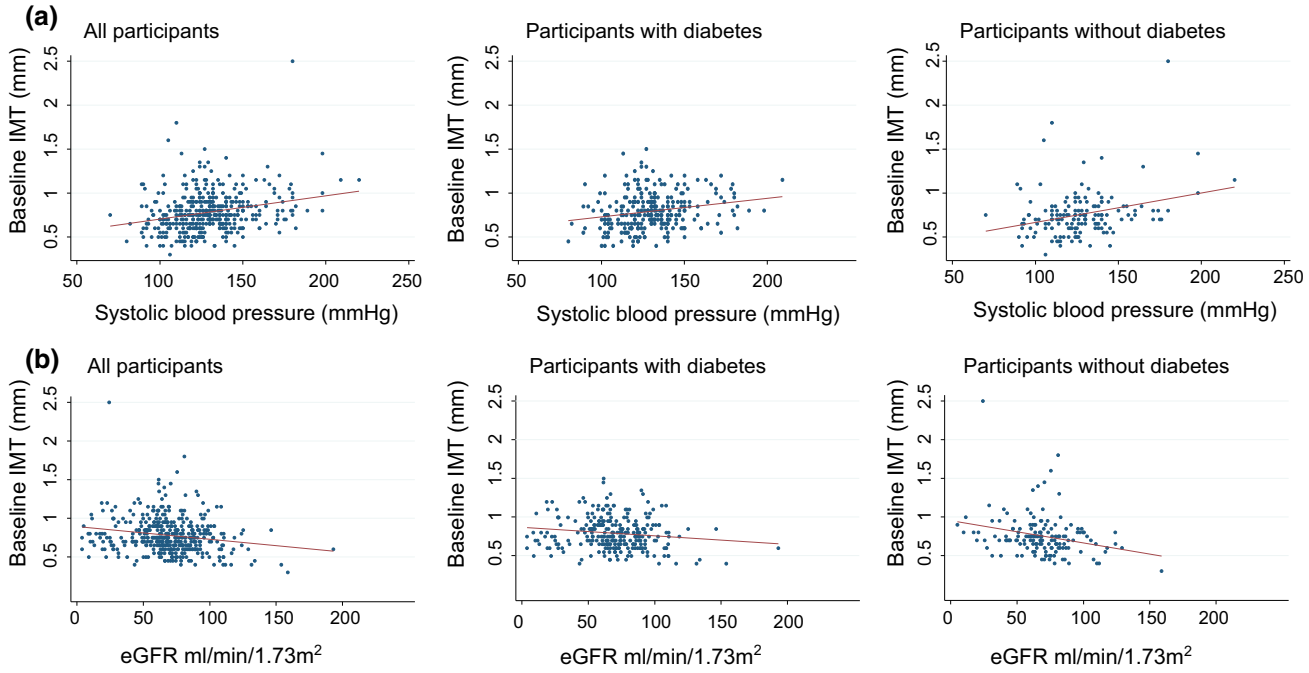

Fig. 2 Scatter plots of baseline intima–media thickness (IMT) and systolic blood pressure (**a**) and estimated glomerular filtration rate (eGFR) (**b**). *Solid lines* represent regression lines

Table 2 Adjusted and unadjusted correlations between baseline IMT (mm) and risk factors

	Unadjusted			Model 1			Model 2					
	All participants $n = 424$			All participants $n = 418$			Participants with diabetes $n = 245$			Participants without diabetes $n = 150$		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Systolic blood pressure (+10 mmHg)	0.0265	0.0050	<0.01	0.0226	0.0049	<0.01	0.0159	0.0057	0.01	0.0312	0.0093	<0.01
eGFR (−10 mL/min/1.73 m^2)	0.0165	0.0042	<0.01	0.0040	0.0048	0.41	−0.0023	0.0056	0.69	0.0182	0.0103	0.08

Model 1: Regression analysis adjusted for age, sex, systolic pressure, total cholesterol, body mass index, eGFR, uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein levels, and past cardiovascular event

Model 2: Regression analysis adjusted for glycated hemoglobin and duration of diabetes added to Model 2 in participants with diabetes; the parameters were adjusted in the same manner as that as in Model 1 for participants without diabetes

IMT intima–media thickness, β standard regression coefficient, *SE* standard error of β; p p value, *eGFR* estimated glomerular filtration rate

participants with diabetes. In this analysis, blood glucose, quantitative urinary protein, uses of statins, or number of antihypertensive drugs was not significantly related in participants with and without diabetes (data not shown). To verify the independence of eGFR, we extended the analysis by adding an interaction term between eGFR and urinary protein (– or trace/+ 1 or more) to Model 2 in participants without diabetes; however, the interaction term was not significant ($p = 0.792$) in this model. In participants both with and without diabetes, systolic blood pressure was not significantly associated with changes in IMT.

Discussion

This longitudinal study was conducted to determine the impacts of eGFR on atherosclerosis among participants with and without diabetes. In participants without diabetes,

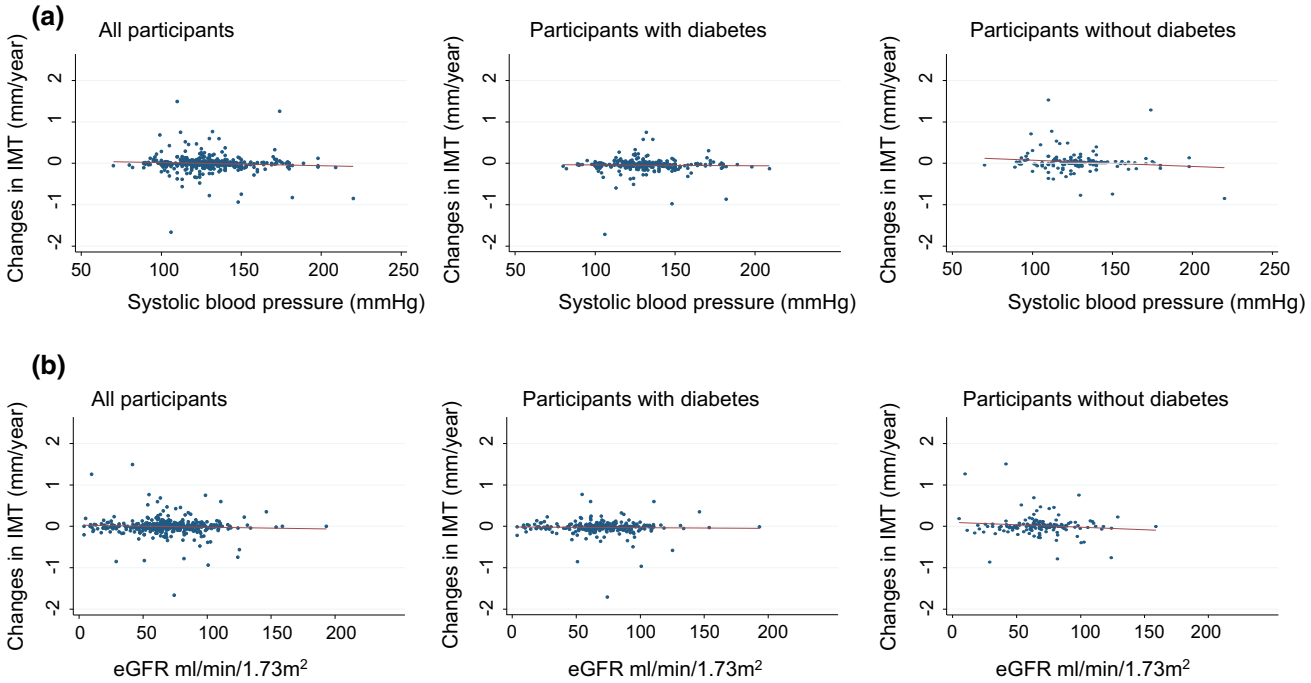

Fig. 3 Scatter plots of changes in intima–media thickness (IMT) and systolic blood pressure (**a**) and estimated glomerular filtration rate (eGFR) (**b**). *Solid lines* represent regression lines

Table 3 Adjusted and unadjusted correlations between changes in IMT (mm/year) and risk factors

	Unadjusted			Model 1			Model 2					
	All participants $n = 424$			All participants $n = 418$			Participants with diabetes $n = 245$			Participants without diabetes $n = 150$		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Systolic blood pressure (+10 mmHg)	−0.0080	0.0046	0.10	−0.0084	0.0049	0.09	−0.0014	0.0059	0.81	−0.0179	0.0094	0.06
eGFR (−10 mL/min/1.73 m^2)	0.0050	0.0039	0.22	0.0091	0.0049	0.06	0.0003	0.0059	0.96	0.0235	0.0104	0.03

Model 1: Regression analysis adjusted for age, sex, systolic pressure, total cholesterol, body mass index, eGFR, uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein levels, and past cardiovascular event

Model 2: Regression analysis adjusted for glycated hemoglobin and duration of diabetes added to Model 2 in participants with diabetes; the parameters were adjusted in the same manner as that in Model 1 for participants without diabetes

IMT intima–media thickness, β standard regression coefficient, *SE* standard error of β, p p value, *eGFR* estimated glomerular filtration rate

eGFR was independently associated with alterations in carotid IMT; however, such relationships were not observed in participants with diabetes. These findings suggested that impaired kidney function is a high risk factor for the progression of atherosclerosis in participants without diabetes.

Regarding the baseline characteristics, systolic blood pressure was associated with IMT in participants with and without diabetes. These findings are consistent with those of previous studies, including the European Lacidipine Study on Atherosclerosis [35], which indicated that some clinical variables such as systolic blood pressure were associated with IMT. Hypertension is a potential cause of the development and progression of CKD [36, 37]. Further, hypertension might exacerbate the effect of IMT progression on eGFR, which was observed in the longitudinal analysis in this study.

Our data indicated that low eGFR was correlated with the progression of IMT; however, these relationships were not observed at baseline. This outcome can be explained

partially by the baseline characteristics of participants of this study, wherein there was a higher proportion of participants with normal kidney function (mean eGFR 69.1 mL/min/1.73 m^2, mean IMT 0.8 mm) compared with other studies. For example, Kawamoto et al. [19] reported a negative correlation between eGFR and IMT in a cross-sectional study that included a high proportion of subjects with CKD stage 3 or more. Other cross-sectional studies included mainly elderly patients or patients with progression of IMT, both factors deeply related to overall atherosclerosis. In these studies, associations between impaired eGFR and atherosclerosis were reported [15, 19, 20]. Conversely, other cross-sectional studies on participants with normal or mild atherosclerosis did not indicate relationships between impaired eGFR and the severity of IMT [38, 39]. Thus, low GFR might be associated with an increase in IMT at the beginning of atherosclerosis.

In this study, relationships between eGFR and the progression of IMT were not observed in participants with diabetes either at baseline or follow-up analyses. These results are not consistent with those of a previous study on subjects with diabetes [40], which reported associations between eGFR and the severity of IMT. This variability in reporting might be partially caused by glycemic control. A recent large-scale study revealed that intensive blood glucose control is effective for the reduction of the risk of macrovascular events [41]; the mean baseline HbA1c in our cohort was 6.9 %, which is more than 1 % lower than reported in a previous study by Taniwaki et al. [40]. We evaluated the effect of diabetes by stratified analysis and precisely assessed the effect of eGFR by longitudinal analysis. These results suggested that associations between eGFR and the progression of IMT might exist in individuals without diabetes. Patients with diabetes are at higher risk for cardiovascular events compared to patients without diabetes [34] and in daily medical practice are often treated with statin and antihypertensive agents to prevent these complications. It has been reported that CKD [43] and poor blood glucose control cause cardiovascular event [44–46], which might be related to arteriosclerosis. Participants with these risk factors might have a trend toward receiving more intensive treatment than others, which may be the reason that impact of eGFR and HbA1c was not found in diabetic patients. Different from previous report [47] which reported relationships between microalbuminuria and thickness of IMT, we used qualitative urinary protein as a confounding factor. It may be a possible cause for not detecting the relevance of proteinuria for IMT in early stage.

There are some limitations to this study. First, there may have been a selection bias. Participants in this study were limited to those who visited a university hospital and were checked more than once for atherosclerosis by their doctor. Moreover, because university hospitals are advanced medical institutions, there may have been a bias in selecting participants with multiple complications. These patients underwent treatment that may have affected the progression of atherosclerosis. Therefore, the results of this study might not be applicable to patients visiting municipal hospitals or clinics. Second, there might be a possibility of observer bias. Information about participants was provided to the ultrasonographer prior to examinations, so that they could detect the IMT of high-risk participants with higher sensitivity. Third, we could not obtain information of the medication started after the first examination of IMT. It is a well known fact that carotid IMT can be influenced by treatment with antihypertensive agents, statins [1, 41, 42]. Subjects with increased IMT could be treated with these drugs, which may result in attenuation of progression of carotid arteriosclerosis. However, we adjusted for confounding factors as much as possible and suggested adequate evidence for the progression of atherosclerosis.

In conclusion, our study indicated that carotid thickness is progressive in participants with impaired eGFR, but without diabetes. Therefore, we recommend that IMT should be evaluated in patients without diabetes who have impaired eGFR, because they might progress to atherosclerosis rapidly. This is of clinical importance, because atherosclerosis is a surrogate marker of cardiovascular disease. In the future, a longer follow-up study and basic research are warranted for clarifying the exact relationships and mechanisms.

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Conflict of interests All authors declare that they have no conflicts of interest in the publication of the present manuscript.

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