



# Relationship between serum lipid concentrations and impaired renal function in patients with chronic kidney disease: the Fukuoka Kidney Disease Registry Study

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## Abstract

**Background** Patients with chronic kidney disease (CKD) have a higher risk of atherosclerotic cardiovascular disease (ASCVD). Dyslipidemia has been established as a risk factor for ASCVD. In the present study, we aimed to determine the prevalence of dyslipidemia at each stage of CKD.

**Methods** We conducted a cross-sectional study among 4476 patients registered in the Fukuoka Kidney Disease Registry Study, a Japanese prospective cohort study in patients with non-dialysis-dependent CKD. Outcomes were the prevalence of hyper-low-density lipoprotein (LDL) cholesterolemia, hyper-non-high-density lipoprotein (non-HDL) cholesterolemia, hypertriglyceridemia, and hypo-high-density lipoprotein (hypo-HDL) cholesterolemia at each stage of CKD. We analyzed the relationships between CKD stage and the prevalence of dyslipidemia using logistic regression models.

**Results** Patients in the advanced stages of CKD were more likely to have hypertriglyceridemia [OR 2.16 (95% CI 1.03–4.56), OR 2.24 (95% CI 1.04–4.84), OR 2.62 (95% CI 1.19–5.78), and OR 2.47 (95% CI 1.04–5.88) for CKD stages G3a, G3b, G4, and G5, respectively] and hypo-HDL-cholesterolemia [OR 2.66 (95% CI 1.21–5.82), OR 3.10 (95% CI 1.38–6.95), OR 2.86 (95% CI 1.25–6.53), and OR 3.30 (95% CI 1.35–8.10) for CKD stages G3a, G3b, G4, and G5, respectively] as compared with patients in CKD stage G1. The prevalence of hyper-LDL-cholesterolemia and hyper-non-HDL-cholesterolemia was not related to CKD stage.

**Conclusion** Patients with advanced CKD stages are more likely to have hypertriglyceridemia and hypo-HDL-cholesterolemia than those in early stages. This type of lipid profile may represent a risk factor for ASCVD in patients with CKD.

**Keywords** Dyslipidemia · Chronic kidney disease · Triglyceride · High-density lipoprotein-cholesterol

## Introduction

Patients with chronic kidney disease (CKD) are predisposed to cardiovascular diseases, including coronary artery disease, stroke, peripheral artery disease, and congestive

heart failure [1, 2]. Dyslipidemia plays an important role in the development of atherosclerotic cardiovascular disease (ASCVD), and previous studies have shown that patients with CKD often also have dyslipidemia [3–5]. Impaired lipoprotein metabolism, especially higher levels of triglyceride and lower levels of high-density lipoprotein (HDL) cholesterol have been observed in predialysis patients with CKD and dialysis patients [6–9]. Moreover, patients with CKD often have associated malnutrition and inflammation [10]; however, there was no study have evaluated the characteristics of dyslipidemia in CKD after adjusting for potentially confounding factors, such as age, nutritional status, and inflammation.

The population-based Atherosclerosis Risk in Communities (ARIC) Study revealed that high serum concentrations of cholesterol and triglyceride in patients with CKD are associated with a high risk of coronary heart disease

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[11]. Several randomized controlled trials of statins have been performed in patients with CKD to determine their efficacy for the prevention of ASCVD. Sub-analyses of randomized trials conducted in predialysis patients with CKD have revealed that statin treatment significantly reduces the incidence of ASCVD [12, 13]. Recently, the Chronic Renal Insufficiency Cohort (CRIC) study showed that very low-density lipoprotein-cholesterol (VLDL-C) and apolipoprotein B (Apo-B) levels, but not low-density lipoprotein-cholesterol (LDL-C), are positively associated with the risk of ASCVD [14]. This result differed from findings of the ARIC study. The reason could be that the use of statins has become the standard means of preventing cardiovascular disease (CVD); therefore, the lipid profiles of patients with CKD may have changed in recent years. Consideration of the lipid profile in patients with CKD under current therapy may be useful to refine strategies for the prevention of CVD.

In the present study, we aimed to investigate the relationship between CKD stage and dyslipidemia, including hyper-LDL-cholesterolemia, hyper-non-high-density lipoprotein (HDL)-cholesterolemia, hypertriglyceridemia, and hypo-HDL-cholesterolemia after adjustment for potentially confounding factors in patients with CKD undergoing current therapy.

## Methods

### Study design and population

The Fukuoka Kidney Disease Registry (FKR) Study was a prospective, multicenter cohort study of non-dialysis-dependent outpatients with CKD [15]. The inclusion criteria were age  $\geq 16$  years and conformance with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for CKD [16]. The study sample consisted of 4,476 outpatients who were being managed by nephrologists in 12 hospitals in Fukuoka Prefecture of Japan [15]. Patient enrollment took place between January 2013 and March 2017, and all patients were scheduled to be followed up for at least 5 years. Of the 4,476 patients, 111 were excluded because of a lack of baseline data; therefore, data from 4365 patients were analyzed in the present study. The study was approved by the Clinical Research Ethics Committee of the Institutional Review Board of Kyushu University (approval number 469-04) and the ethics committees of all participating institutions; the study was registered in the University Hospital Medical Information Network clinical trials registry (UMIN000007988) and was conducted in accordance with the principles of the Declaration of Helsinki and its amendments.

### Clinical parameters

Baseline demographic and clinical data were recorded at the time of enrollment. We obtained age, sex, height, body weight, blood pressure, and heart rate for all the participants. Clinical biochemical parameters [urinary protein and creatinine; hemoglobin concentration; and serum albumin, LDL-C, HDL-C, triglyceride, and C-reactive protein (CRP) concentrations] were determined by measurement in a central laboratory. Information regarding each participant's health, the presence of diabetes, their history of CVD, and any treatments were collected from the patient medical records using a structured data format by clinical research coordinators in our research network. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. Patients were not required to fast when blood samples were collected.

### Classification of CKD

CKD was defined and classified according to the patient's estimated glomerular filtration rate (eGFR) using the KDIGO guidelines [16–18]. eGFR was calculated in patients age  $< 18$  years using the Schwartz formula and in patients age  $\geq 18$  years using the following formula:  $eGFR (\text{mL}/\text{min}/1.73 \text{ m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ for women})$  [18]. CKD was categorized as stages G1–G5, according to the KDIGO guidelines.

### Definition of dyslipidemia

Dyslipidemia was defined according to Japan Atherosclerosis Society guidelines [19]. Non-HDL-C was calculated by subtracting HDL-C from total cholesterol. Hyper-LDL-cholesterolemia, hyper-non-HDL-cholesterolemia, and hypertriglyceridemia were defined as concentrations of LDL-C  $\geq 140$  mg/dL, non-HDL-C  $\geq 170$  mg/dL, and triglyceride  $\geq 150$  mg/dL, or use of lipid-lowering drugs, respectively. Hypo-HDL-cholesterolemia was defined as a concentration of HDL-C  $< 40$  mg/dL. Dyslipidemia was diagnosed when a patient had hyper-LDL-cholesterolemia, hypertriglyceridemia, or hypo-HDL-cholesterolemia, or was taking medication for dyslipidemia.

### Classification of proteinuria

Proteinuria was classified according to the KDIGO 2012 clinical practice guideline [20]. Proteinuria was evaluated by urinary protein/creatinine ratio (UpUCr). UpUCr was calculated by dividing the urinary protein values by the

urinary creatinine concentrations. Proteinuria was categorized as < 0.15, 0.15–0.50, and  $\geq$  0.50 g/gCr.

## Statistical analyses

Data are presented as mean  $\pm$  standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and percentage for categorical variables. To evaluate trends in continuous and categorical values, we used the Jonckheere–Terpstra and Cochran–Armitage tests, respectively. Logistic regression analysis was used to calculate age- and sex-adjusted, and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the relationships between CKD stage and the presence of dyslipidemia. The multivariable-adjusted model was adjusted for age, sex, the presence of diabetes, a history of CVD, systolic blood pressure, heart rate, BMI, hemoglobin concentration, serum albumin concentration, log-CRP, and urinary protein/creatinine ratio. Sensitivity analyses were performed to examine the odds ratio of hypertriglyceridemia using the American

Heart Association/American College of Cardiology Foundation (AHA/ACC) guidelines 2018 [21] and to confirm the odds ratio after excluding the patients taking lipid-lowering drugs. Statistical analyses were conducted using IBM SPSS version 22 (IBM Corp., Armonk, NY, USA) and R version 3.5.2 (<http://www.r-project.org>). A two-tailed *P* value of < 0.05 was deemed to indicate statistical significance.

## Results

### Study participants and baseline characteristics

The clinical characteristics of participants at each stage of CKD are shown in Table 1. Advanced CKD stages were positively associated with age, male sex, the presence of diabetes, a history of CVD, high systolic blood pressure, high diastolic blood pressure, high CRP concentration, high urinary protein/creatinine ratio, and the use of lipid-lowering drugs but negatively associated with hemoglobin and serum albumin concentrations.

**Table 1** Baseline characteristics according to CKD stage

	CKD G1 (254)	CKD G2 (808)	CKD G3a (822)	CKD G3b (909)	CKD G4 (1057)	CKD G5 (515)	<i>P</i> for trend
Age, years	34 (26–45)	56 (44–67)	65 (55–73)	70 (62–78)	73 (64–80)	72 (64–79)	< 0.01
Male, %	39.3	45.7	54.0	63.0	61.1	59.2	< 0.01
Diabetes, %	6.7	16.2	19.6	27.7	37.1	46.8	< 0.01
History of cardiovascular disease, %	2.0	6.9	13.4	21.9	33.2	32.3	< 0.01
Body mass index	21.3 (19.6–24.0)	22.9 (20.4–25.8)	23.2 (21.0–25.9)	23.1 (20.9–25.8)	22.8 (20.5–25.4)	22.8 (20.4–25.0)	0.73
Systolic blood pressure, mmHg	119 (109–127)	125 (115–137)	130 (120–140)	130 (120–142)	132 (122–145)	135 (126–147)	< 0.01
Diastolic blood pressure, mmHg	70 (63–79)	75 (68–83)	76 (70–84)	74 (68–82)	73 (65–81)	72 (65–80)	< 0.01
Heart rate, /min	81 (70–87)	73 (65–82)	74 (67–80)	72 (63–82)	74 (66–81)	72 (65–84)	0.29
Hemoglobin, g/dL	13.8 (13.1–15.0)	13.9 (12.9–15.0)	13.7 (12.6–14.8)	12.8 (11.6–14.1)	11.6 (10.7–12.7)	10.8 (10.1–11.7)	< 0.01
Albumin, g/dL	4.3 (4.0–4.6)	4.2 (4.0–4.4)	4.2 (3.9–4.4)	4.1 (3.8–4.3)	3.9 (3.7–4.2)	3.8 (3.6–4.1)	< 0.01
C-reactive protein (mg/dL)	0.03 (0.01–0.08)	0.04 (0.02–0.09)	0.05 (0.02–0.11)	0.06 (0.03–0.13)	0.06 (0.03–0.15)	0.06 (0.02–0.16)	< 0.01
Urinary protein/creatinine ratio (g/gCr)	0.12 (0.06–0.43)	0.17 (0.07–0.56)	0.17 (0.07–0.66)	0.30 (0.10–1.03)	0.68 (0.26–1.88)	1.80 (0.92–3.60)	< 0.01
Use of statins (%)	16.5	36.6	40.7	45.8	42.8	43.0	< 0.01
Use of ezetimibe (%)	0.8	3.7	3.7	4.4	4.4	4.7	0.02
Use of unsaturated fatty acids (%)	2.0	2.1	3.1	3.3	5.0	4.3	< 0.01
Use of fibrates (%)	0.0	1.0	1.6	3.0	1.2	0.7	< 0.01

CKD chronic kidney disease

### Relationship between CKD stage and serum lipid concentrations after adjustment of confounding factors

To adjust for patients' nutritional status and background, we investigated whether progression of CKD was associated with a high prevalence of dyslipidemia using logistic regression models (Tables 2, 3, 4, 5). CKD stage G3a was

associated with the highest odds of hyper-LDL-cholesterolemia, but CKD stages were not associated with a trend of hyper-LDL-cholesterolemia (Table 2). CKD stages G3a, G3b, G4 and G5 were associated with higher odds of hypertriglyceridemia [OR 2.16 (95% CI 1.03–4.56), OR 2.24 (95% CI 1.04–4.84), OR 2.62 (95% CI 1.19–5.78), and OR 2.47 (95% CI 1.04–5.88) for CKD stages G3a, G3b, G4, and G5, respectively) in comparison with CKD stage G1

**Table 2** Association between CKD stage and the risk of hyper-low-density lipoprotein cholesterolemia

	No. of events/patients	Age and sex adjusted			Multivariate-adjusted <sup>a</sup>		
		OR (95% CI)	P value	P for trend	OR (95% CI)	P value	P for trend
CKD G1	80/254	1.00 (reference)		0.47	1.00 (reference)		0.93
CKD G2	418/808	2.31 (1.17–4.56)	0.02		2.01 (0.99–4.08)	0.06	
CKD G3a	466/822	3.03 (1.50–6.15)	<0.01		2.27 (1.08–4.77)	0.03	
CKD G3b	540/909	2.55 (1.24–5.24)	0.01		2.08 (0.97–4.45)	0.06	
CKD G4	589/1057	2.64 (1.29–5.42)	<0.01		2.01 (0.92–4.41)	0.08	
CKD G5	276/515	2.35 (1.12–4.94)	0.02		1.56 (0.66–3.68)	0.31	

CKD chronic kidney disease; OR odds ratio; CI confidence interval

<sup>a</sup>Adjusted for age, sex, diabetes, history of cardiovascular disease, systolic blood pressure, heart rate, body mass index, hemoglobin concentration, serum albumin concentration, log-C-reactive protein, and urinary protein/creatinine ratio

**Table 3** Association between CKD stage and the risk of hypertriglyceridemia

	No of events/patients	Age and sex adjusted			Multivariate adjusted <sup>a</sup>		
		OR (95% CI)	P value	P for trend	OR (95% CI)	P value	P for trend
CKD G1	83/254	1.00 (reference)		0.02	1.00 (reference)		0.03
CKD G2	432/808	1.95 (1.00–3.81)	0.05		1.65 (0.81–3.37)	0.17	
CKD G3a	503/822	2.94 (1.46–5.92)	<0.01		2.16 (1.03–4.56)	0.04	
CKD G3b	606/909	2.65 (1.30–5.41)	<0.01		2.24 (1.04–4.84)	0.04	
CKD G4	652/1057	3.01 (1.47–6.15)	<0.01		2.62 (1.19–5.78)	0.02	
CKD G5	321/515	2.91 (1.39–6.09)	<0.01		2.47 (1.04–5.88)	0.04	

CKD chronic kidney disease; OR odds ratio; CI confidence interval

<sup>a</sup>Adjusted for age, sex, diabetes, history of cardiovascular disease, systolic blood pressure, heart rate, body mass index, hemoglobin concentration, serum albumin concentration, log-C-reactive protein, and urinary protein/creatinine ratio

**Table 4** Association between CKD stage and the risk of hyper-non-high-density lipoprotein cholesterolemia

	No. of events/patients	Age and sex adjusted			Multivariate adjusted <sup>a</sup>		
		OR (95% CI)	P value	P for trend	OR (95% CI)	P value	P for trend
CKD G1	75/254	1.00 (reference)		0.08	1.00 (reference)		0.30
CKD G2	398/808	2.78 (1.38–5.61)	<0.01		2.47 (1.18–5.17)	0.02	
CKD G3a	477/822	4.23 (2.04–8.78)	<0.01		3.30 (1.53–7.12)	<0.01	
CKD G3b	547/909	3.78 (1.79–7.97)	<0.01		3.23 (1.46–6.83)	<0.01	
CKD G4	594/1057	3.86 (1.84–8.13)	<0.01		3.03 (1.34–6.83)	<0.01	
CKD G5	279/515	3.43 (1.59–7.37)	<0.01		2.32 (0.95–5.63)	0.06	

CKD chronic kidney disease; OR odds ratio; CI confidence interval

<sup>a</sup>Adjusted for age, sex, diabetes, history of cardiovascular disease, systolic blood pressure, heart rate, body mass index, hemoglobin concentration, serum albumin concentration, log-C-reactive protein, and urinary protein/creatinine ratio

**Table 5** Association between CKD stage and the risk of hypo-high-density lipoprotein cholesterolemia

	No. of events/patients	Age and sex adjusted			Multivariate adjusted <sup>a</sup>		
		OR (95% CI)	<i>P</i> value	<i>P</i> for trend	OR (95% CI)	<i>P</i> value	<i>P</i> for trend
CKD G1	56/254	1.00 (reference)		<0.01	1.00 (reference)		<0.01
CKD G2	351/808	2.13 (1.04–4.38)	0.04		1.98 (0.92–4.25)	0.08	
CKD G3a	422/822	3.25 (1.54–6.82)	<0.01		2.79 (1.27–6.14)	0.01	
CKD G3b	545/909	3.88 (1.81–8.29)	<0.01		3.31 (1.47–7.45)	<0.01	
CKD G4	597/1057	3.93 (1.84–8.39)	<0.01		3.03 (1.32–6.95)	<0.01	
CKD G5	319/515	4.95 (2.26–10.86)	<0.01		3.62 (1.47–8.90)	<0.01	

CKD chronic kidney disease; OR odds ratio; CI confidence interval

<sup>a</sup>Adjusted for age, sex, diabetes, history of cardiovascular disease, systolic blood pressure, heart rate, body mass index, hemoglobin concentration, serum albumin concentration, log-C-reactive protein, and urinary protein/creatinine ratio

(Table 3). CKD stages were also associated with a trend of hypertriglyceridemia (*P* = 0.03, Table 3). CKD stages G2, G3a, G3b, and G4 were associated with high odds of hyper-non-HDL-cholesterolemia [OR 2.47 (95% CI 1.18–5.17), OR 3.30 (95% CI 1.53–7.12), OR 3.23 (95% CI 1.46–6.83), and OR 3.03 (95% CI 1.34–6.83) for CKD stage G2, G3a, G3b, and G4, respectively] compared with CKD stage G1, but there was no significant trend for the odds of hyper-non-HDL-cholesterolemia across all stages of CKD (Table 4). CKD stages G3a, G3b, G4 and G5 were associated with higher odds of hypo-HDL-cholesterolemia [OR 2.79 (95% CI, 1.27–6.14) OR 3.31 (95% CI 1.47–7.45), OR 3.03 (95% CI 1.32–6.95), and OR 3.62 (95% CI 1.47–8.90) for CKD

stages G3a, G3b, G4, and G5, respectively] in comparison with CKD stage G1 (Table 5). CKD stages were also associated with a trend of hypo-HDL-cholesterolemia (*P* < 0.01, Table 5).

**Relationship between proteinuria and serum lipid concentrations**

Proteinuria also affects dyslipidemia in patients with CKD. We, therefore, investigated the relationship between proteinuria and dyslipidemia, including hyper-LDL-cholesterolemia, hyper-non-high-density lipoprotein (HDL)-cholesterolemia, hypertriglyceridemia, and

**Table 6** Association between proteinuria and the risk of dyslipidemia

	No. of events/patients	Age and sex adjusted			Multivariate adjusted <sup>a</sup>		
		OR (95% CI)	<i>P</i> value	<i>P</i> for trend	OR (95% CI)	<i>P</i> value	<i>P</i> for trend
<b>Risk of hyper-low-density lipoprotein cholesterolemia</b>							
UpUCr < 0.15	647/1327	1.00 (reference)		<0.01	1.00 (reference)		0.04
0.15 ≤ UpUCr < 0.5	542/1064	1.43 (1.01–2.03)	0.04		1.39 (0.96–2.01)	0.08	
0.5 ≤ UpUCr	1176/1964	1.51 (1.12–2.04)	<0.01		1.50 (1.03–2.17)	0.03	
<b>Risk of hypertriglyceridemia</b>							
UpUCr < 0.15	721/1327	1.00 (reference)		<0.01	1.00 (reference)		0.07
0.15 ≤ UpUCr < 0.5	586/1064	1.47 (1.04–2.08)	0.03		1.34 (0.92–1.94)	0.12	
0.5 ≤ UpUCr	1285/1964	1.73 (1.29–2.34)	<0.01		1.43 (0.98–2.08)	0.07	
<b>Risk of hyper-non-high-density lipoprotein cholesterolemia</b>							
UpUCr < 0.15	646/1327	1.00 (reference)		<0.01	1.00 (reference)		<0.01
0.15 ≤ UpUCr < 0.5	530/1064	1.55 (1.10–2.20)	0.01		1.51 (1.04–2.18)	0.03	
0.5 ≤ UpUCr	1190/1964	1.75 (1.30–2.35)	<0.01		1.68 (1.16–2.47)	<0.01	
<b>Risk of hypo-high-density lipoprotein cholesterolemia</b>							
UpUCr < 0.15	605/1327	1.00 (reference)		<0.01	1.00 (reference)		0.07
0.15 ≤ UpUCr < 0.5	511/1064	1.42 (1.01–2.01)	0.05		1.34 (0.92–1.94)	0.12	
0.5 ≤ UpUCr	1170/1964	1.80 (1.34–2.43)	<0.01		1.42 (0.98–2.08)	0.07	

UpUCr urinary protein/creatinine ratio; OR odds ratio; CI confidence interval

<sup>a</sup>Adjusted for age, sex, diabetes, history of cardiovascular disease, systolic blood pressure, heart rate, body mass index, hemoglobin concentration, serum albumin concentration, log-C-reactive protein, and category of CKD stages

hypo-HDL-cholesterolemia, after adjustment for potentially confounding factors in patients with CKD (Table 6 and Supplementary Table 1). Proteinuria was associated with a trend of hyper-LDL-cholesterolemia ( $P=0.04$ ) and hyper-non-HDL-cholesterolemia ( $P<0.01$ ), but was not associated with a trend of hypertriglyceridemia ( $P=0.07$ ) and hypo-HDL-cholesterolemia ( $P=0.07$ ).

### Sensitivity analysis of odds ratios for hypertriglyceridemia using the 2018 AHA/ACC guideline

In this study, we measured triglyceride in a non-fasting state. Although the Japan Atherosclerosis Society guidelines did not mention the definition of hypertriglyceridemia in a non-fasting state [19], the 2018 AHA/ACC guideline proposed a cutoff of 175 mg/dL for a non-fasting triglyceride [21]. We conducted a sensitivity analysis of odds ratios for hypertriglyceridemia using the 2018 AHA/ACC guideline (Supplementary Table 2). CKD stages G2, G3a, G3b, G4, and G5 were associated with high odds of hypertriglyceridemia [OR 2.51 (95% CI 1.18–5.34), OR 3.01 (95% CI 1.38–6.60), OR 3.08 (95% CI 1.37–6.90), OR 3.74 (95% CI 1.63–7.68), and OR 3.12 (95% CI 1.27–7.68) for CKD stage G2, G3a, G3b, G4, and G5, respectively] compared with CKD stage G1 (Supplementary Table 2). The result was similar to that obtained using the Japan Atherosclerosis Society guidelines (Table 3).

### Sensitivity analyses of patients not taking lipid-lowering drugs

Since lipid-lowering therapy improves dyslipidemia, we reanalyzed the ORs of dyslipidemia only in patients not taking lipid-lowering drugs in a sensitivity analysis (Supplementary Tables 3, 4, 5, 6). CKD stages in patients not on lipid-lowering therapy were also associated with a trend of hypertriglyceridemia ( $P=0.01$ , Supplementary Table 4) and a trend of hypo-HDL-cholesterolemia ( $P<0.01$ , Supplementary Table 6). There was no significant trend in the odds of hyper-LDL-cholesterolemia or hyper-non-HDL-cholesterolemia across all CKD stages (Supplementary Tables 3 and 5). No essential difference was seen with respect to characteristics of the lipid profile in CKD without lipid-lowering drugs.

### Analysis of subgroups created according to baseline clinical characteristics

To evaluate interactions between the prevalence of dyslipidemia and patient characteristics, we evaluated the effects of patient stratification on the prevalence of hypertriglyceridemia and hypo-HDL-cholesterolemia (Supplementary

Tables 7 and 8). Advanced CKD stage appeared to be associated with hypertriglyceridemia and hypo-HDL-cholesterolemia in patients age  $<65$  years (both  $P<0.01$ ), but there was no significant difference in prevalence between patients age  $<65$  years and those age  $\geq 65$  years ( $P=0.30$  and  $P=0.26$  for interaction, Supplementary Tables 7 and 8). Finally, patients with CKD who had no history of CVD were more likely to have hypo-HDL-cholesterolemia ( $P<0.01$ , Supplementary Table 8).

## Discussion

In this cohort study of 4476 patients with CKD, CKD stages were significantly associated with hypertriglyceridemia and hypo-HDL-cholesterolemia after adjusting for confounding factors, but there were no linear relationships between abnormal LDL-C or non-HDL-C concentrations and CKD stage. CKD stage was significantly associated with hypo-HDL-cholesterolemia in patients who were  $<65$  years of age. To the best of our knowledge, this is the first study showing the characteristics of lipid profiles in patients with CKD using the Japan Atherosclerosis Society guidelines after adjustment for all confounding factors. In the present study, we showed that hypertriglyceridemia and hypo-HDL-cholesterolemia are the specific types of dyslipidemia that occur in patients with CKD.

The results of the recent CRIC study revealed that high triglyceride-rich lipoprotein concentrations and low HDL-C concentrations are associated with a higher risk of ASCVD whereas a high LDL-C concentration is not [14]. These findings differ from those of the ARIC study [11]. In the present study, over 40% of patients with CKD stages G3–5 were being treated with lipid-lowering therapy (Table 1). Statin treatment reduces serum LDL-C concentration; therefore, it is possible that the serum cholesterol concentrations of this recently enrolled cohort were lower than those of participants in previous studies. In addition, hypertriglyceridemia is difficult to treat safely in patients with CKD because fibrates occasionally induce rhabdomyolysis in patients with renal impairment. In the present study, hypertriglyceridemia was more common in patients with advanced CKD (Table 2), which might suggest that hypertriglyceridemia is a risk factor for ASCVD in patients with CKD.

Moreover, a recent sub-analysis of the SHARP (Study of Heart and Renal Protection) trial revealed that higher levels of triglycerides, LDL-C, and non-HDL-C, and a lower level of HDL-C had a significantly higher risk of ASCVD in 9270 patients with CKD [22]. That study also demonstrated that a higher level of LDL-C in simvastatin and ezetimibe groups did not have a higher risk of ASCVD, suggesting that the risk of ASCVD from higher LDL-C may possibly be suppressed by statins and ezetimibe. We presume from this

result that hypertriglyceridemia and hypo-HDL-cholesterolemia might be residual risks for ASCVD in CKD patients.

Plasma triglyceride concentrations have been reported to increase during the early stages of CKD [3, 4]. Degradation of triglyceride-rich VLDL is not high in patients with CKD [23], plasma lipoprotein lipase activity has been reported to be low [9], and patients with CKD also demonstrate low hepatic triglyceride lipase activity [9]. Alterations in the activity of these lipases cause the accumulation of triglyceride-rich lipoproteins in patients with CKD. In the present study, hypertriglyceridemia was a feature of advanced CKD (Table 2) and the use of fibrates was uncommon because of their side effects (Table 1). However, a recent report showed that pemafibrate, a new type of fibrate, did not significantly increase serum creatinine kinase activity in patients with advanced CKD [24]. Therefore, pemafibrate may be a useful means of reducing the risk of ASCVD in patients with CKD.

HDL-C plays an important role in reverse cholesterol transport; however, in the present study, hypo-HDL-cholesterolemia was more common in advanced CKD (Table 5). The conversion of HDL has been reported to be lower in CKD because lecithin–cholesterol acyltransferase activity is lower in these patients [3]. The lower ability of HDL particles to carry cholesterol causes impairment of reverse cholesterol transport, which promotes atherosclerosis. The CRIC study revealed that a low HDL-C concentration is associated with a high risk of ASCVD in CKD [14]; another study showed that an increase in HDL-C concentration induced by the inhibition of cholesteryl ester transfer protein does not reduce the risk of acute coronary syndrome [25]. Thus, there is no effective strategy to increase HDL-C concentration as a means of preventing ASCVD; this should be a priority of future research.

A previous study showed that the non-HDL-C concentration is superior to the LDL-C concentration for the prediction of myocardial infarction in patients receiving hemodialysis [26]. This can be explained by the fact that non-HDL-C includes all the cholesterol present in lipoprotein particles that is considered to be atherogenic, including LDL, lipoprotein(a), intermediate-density lipoprotein, and VLDL remnants [27]. In the present study, patients with CKD stages G3a and G4 were more likely to have a high non-HDL-C concentration (Table 4). Further investigation is needed to clarify whether high non-HDL-C concentrations are associated with a higher risk of ASCVD.

The present study has several limitations. First, we did not measure triglyceride concentration in the fasting state. However, a recent study showed that non-fasting triglyceride concentrations are related to the incidence of cardiovascular events [28], which implies that this measurement should also be useful. Second, all included patients were Japanese; thus, our findings might not be applicable to other ethnic groups. Third, given the cross-sectional

design of this study, we are unable to ascribe causality to the relationships between serum lipid concentrations and kidney function. We intend to observe this study prospectively and reveal these causal relationships. Finally, we did not evaluate the incidence of ASCVD; therefore, we are continuing to follow participants in a prospective study, and we will determine the relationship between dyslipidemia and the incidence of ASCVD in patients with CKD using this sample in the future.

## Conclusion

Patients with advanced CKD are more likely to have dyslipidemia, and especially to show hypertriglyceridemia and hypo-HDL-cholesterolemia, in comparison with those in the early stages of CVD. These serum lipid abnormalities might represent a risk for ASCVD; therefore, treatment for dyslipidemia should be considered in patients with CKD.

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## Compliance with ethical standards

**Conflict of interest** All the authors have declared no competing interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number UMIN000007988) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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