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Associations between the Serum Triglyceride Level and Kidney Outcome in Patients with Chronic Kidney Disease: The Fukuoka Kidney disease Registry Study

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Aims: Hypertriglyceridemia is a risk factor for chronic kidney disease (CKD). However, whether or not it predicts the risk of CKD progression is unknown. This study evaluated the association between serum triglyceride (TG) levels and kidney disease progression in patients with non-dialysis-dependent CKD.

Methods: The Fukuoka Kidney disease Registry (FKR) study was a multicenter, prospective longitudinal cohort study. In total, 4,100 patients with CKD were followed up for 5 years. The primary outcome was the incidence of CKD progression, defined as a ≥ 1.5 -fold increase in serum creatinine level or the development of end-stage kidney disease. The patients were divided into quartiles according to baseline serum TG levels under non-fasting conditions: Q1 < 87 mg/dL; Q2, 87–120 mg/dL; Q3, 121–170 mg/dL, and Q4 > 170 mg/dL.

Results: During the 5-year observation period, 1,410 patients met the criteria for CKD progression. The multivariable-adjusted Cox proportional hazards model showed a significant association between high serum TG level and the risk of CKD progression in the model without macroalbuminuria as a covariate (multivariable hazard ratio[HR] for Q4 versus Q1, 1.20; 95% CI, 1.03–1.41; $P=0.022$), but the significance disappeared after adjusting for macroalbuminuria (HR for Q4 versus Q1, 1.06; 95% CI, 0.90–1.24; $P=0.507$).

Conclusions: The present findings suggest that individuals with high serum TG levels are more likely to develop CKD progression than those without; however, whether or not higher serum TG levels reflect elevated macroalbuminuria or lead to CKD progression via elevated macroalbuminuria is unclear.

Key words: Triglyceride, Chronic kidney disease, Dyslipidemia, Kidney disease progression, Body Mass Index, Albuminuria

Introduction/Aim

The prevalence of chronic kidney disease (CKD) has been increasing worldwide. CKD progression can lead to end-stage kidney disease (ESKD), which imposes a health burden on individuals and an economic burden on healthcare providers^{1–4}.

Therefore, prevention of CKD progression is important from both medical and economic perspectives. Currently, CKD progression is controlled by managing known risk factors, such as hypertension, diabetes mellitus, hyperuricemia, obesity, smoking, and anemia^{5–7}. However, CKD progression and development of ESKD cannot be decreased^{1–4},

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suggesting that there may be untreated residual risk factors for CKD progression that remain to be identified.

Dyslipidemia, characterized by high triglyceride (TG) and low high-density lipoprotein (HDL)-cholesterol levels, which are common in CKD patients⁸⁻¹⁰), may be a residual risk factor. In the general population, metabolic syndrome and hypertriglyceridemia, a component of metabolic syndrome, have been identified as risk factors for CKD development¹¹⁻¹⁴). Furthermore, high serum TG levels were recently reported to be a residual risk factor for atherosclerotic cardiovascular disease (CVD) in patients with CKD^{15, 16}). However, despite these associations and the fact that most risk factors for atherosclerotic CVD are common for CKD progression¹⁷⁻²⁰), the findings from studies on the relationship between hypertriglyceridemia and CKD progression have been inconclusive.

One reason for the conflicting results in these studies may be the CKD populations that were examined. Although several studies using data from healthcare checkup programs or medical records²¹⁻²⁵) have included patients with CKD, the patients were either in the early stages of CKD or represented only a small number of participants. A large cohort study on US Veterans, which included approximately 40,000 CKD patients, had the limitation of notable sex bias, with 95% of the participants being male²⁶). Given the need for residual risk factor management in patients with CKD, it is important to determine causality in the relationship between serum TG levels and kidney prognosis in a relevant population. However, to achieve this, prospective community-based studies with appropriate sample sizes and follow-up durations are required in patients with advanced CKD.

Prospective cohort studies have been conducted in patients with CKD^{27, 28}), particularly the Chronic Renal Insufficiency Cohort (CRIC) study, which is a large prospective cohort study of CKD patients. However, the CRIC study has the limitation of being restricted to patients with an estimated glomerular filtration rate (eGFR) of 20–70 mL/min/1.73 m², age <75 years old, and specific causes of kidney disease. The Fukuoka Kidney disease Registry (FKR) Study is a Japanese prospective cohort study involving almost 4,500 non-dialysis-dependent CKD patients, reflecting a more real-world population than previous studies because it is not limited by the age, kidney function, or cause of kidney disease.

In addition, non-fasting TG levels have recently attracted attention²⁹⁻³¹). Conventionally, serum lipids have been measured under fasting conditions, and serum TG levels have been found to be greatly affected

by fasting time. However, it was recently shown that non-fasting TG levels are equally^{30, 31}), and sometimes more strongly²⁹), associated with the risk of CVD development and mortality. Although several global guidelines have set targets for non-fasting TG levels³²⁻³⁴), there are few reports on the relationship between non-fasting TG levels and the kidney prognosis.

The present study evaluated the relationship between non-fasting serum TG levels and the kidney prognosis using data from the FKR Study.

Methods

Study Population

The FKR Study is a multicenter, longitudinal, observational study of non-dialysis-dependent CKD outpatients under the care of nephrologists. Details of the FKR Study design have been described previously³⁵). A total of 4,476 outpatients ≥ 16 years old with CKD were enrolled from January 2013 to March 2017 at 12 outpatient sites in Fukuoka Prefecture in the northern region of Kyushu Island. CKD was defined as abnormalities of the kidney structure or function that persisted for over three months, in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines³⁶). Patients were followed until death or withdrawal of consent, initiation of kidney replacement therapy, or five years from the start of observation, whichever came first. Of the 4,476 patients, excluding those who withdrew consent ($n=2$) and those who never visited after giving consent ($n=22$), 4,452 were followed up. Among them, 4,100 patients were included in this study after excluding 352 patients with missing baseline data. None of the patients had missing outcomes.

The study protocol was approved by the Institutional Review Board of the Clinical Research Ethics Committee of Kyushu University (Approval Number. 469-09), and registered in the clinical trial registry (University Hospital Medical Information Network, UMIN000000556). Written informed consent was obtained from all patients before participation in the study. This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical research.

Outcomes and Covariates

The primary outcome was CKD progression, defined as a ≥ 1.5-fold increase in the serum creatinine level from baseline or the development of ESKD. ESKD is defined as the need for kidney replacement therapy (maintenance hemodialysis, peritoneal

dialysis, or kidney transplantation) or death due to kidney disease.

The main exposure was baseline non-fasting serum TG levels. Patients were divided into quartiles (Q1–Q4) based on baseline serum TG levels as follows: Q1 ($n=1,009$), <87 mg/dL; Q2 ($n=1,030$), $87–120$ mg/dL; Q3 ($n=1,019$), $121–170$ mg/dL; and Q4 ($n=1,042$), >170 mg/dL. Data on age, sex, cause of CKD, height, and weight were collected from the patients' clinical records at baseline. The history of cardiovascular events and information on medications were collected from clinical records and questionnaires at baseline. Serum and urinary biochemical parameters, such as creatinine, albumin, HDL cholesterol, TG, C-reactive protein (CRP), urinary albumin, and urinary creatinine, were measured in the central laboratory. Blood and urine samples were collected at baseline under non-fasting conditions; the eGFR was calculated in patients <18 years old using the Schwartz formula and in patients ≥ 18 years old using the formula appropriate for Japanese patients: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ in females)^{37–39}. The body mass index (BMI) was calculated as follows: $\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} \div (\text{height (m)})^2$. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Low-density lipoprotein (LDL) cholesterol was determined using the Friedewald formula or the direct measurement method for patients with TG concentrations <400 and ≥ 400 mg/dL, respectively. The cause of kidney disease was classified as primary chronic glomerulonephritis (CGN) proven by a kidney biopsy, clinically diagnosed CGN without a kidney biopsy, hypertensive nephrosclerosis, diabetic nephropathy, or other causes. A history of CVD events included a history of ischemic heart disease, congestive heart failure, stroke (brain infarction or hemorrhaging), peripheral artery disease, thoracic aortic aneurysm, or abdominal aortic aneurysm. Macroalbuminuria was defined as a urine albumin-to-creatinine ratio of ≥ 300 mg/g. Obesity was defined as a BMI ≥ 25.0 kg/m², according to the “Guidelines for the Management of Obesity Disease” published by the Japanese Society for the Study of Obesity (2020)⁴⁰.

Statistical Analysis

All continuous variables were described as medians and interquartile ranges, and categorical variables were described as the number of patients and percentages. The distribution of baseline characteristics across baseline serum TG levels was compared using the following trend analyses: the Jonckheere–Terpstra test for continuous variables and the Cochran–Armitage test for categorical variables.

The event-free survival rate for CKD progression based on the quartile of baseline serum TG levels was evaluated using Kaplan–Meier curves and log-rank tests. Unadjusted, sex- and age-adjusted, and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcomes based on baseline serum TG levels were estimated using a Cox proportional hazards risk model. The assumption of proportional hazards was evaluated using the Schoenfeld residuals. Multivariable-adjusted analyses were performed using the following plausible risk factors based on previous studies of kidney disease progression: age; sex; BMI; systolic blood pressure; use of TG-lowering drugs, polyunsaturated fatty acids, or fibrates; use of renin-angiotensin-aldosterone system (RAAS) blockers; cause of CKD; history of CVD; blood hemoglobin level; serum albumin level; log-transformed CRP level; eGFR (model 2); and presence of macroalbuminuria (added in model 3). As both increases and decreases in the BMI and SBP were considered to be associated with a poor kidney prognosis, these two factors were categorized into quartiles.

Subgroup analyses were performed to estimate the heterogeneity according to the subgroups of risk factors. For the sensitivity analysis, we performed three types of analyses. First, we evaluated hazard ratios using a Fine-Gray regression model by setting all-cause death as a competing risk. Second, we performed the analysis after excluding individuals followed for ≤ 12 months to account for the influence of rapidly progressing kidney disease or rapidly worsening complications. In addition, we performed several analyses to evaluate the relationship between serum TG levels and CKD progression by modifying and adding covariates.

In all analyses, a two-tailed P -value of <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

The baseline characteristics according to quartiles of baseline serum TG levels were shown in [Table 1](#). Serum TG and CRP levels were not normally distributed and were, therefore, log-transformed when treated as continuous variables. Patients with higher TG levels were more likely to be male ($P<0.001$) and more likely to have diabetic nephropathy ($P<0.001$) as the cause of CKD than those with lower levels.

Table 1. Baseline characteristics according to baseline serum triglyceride quartiles ($n=4,100$)

	Baseline serum triglyceride levels, mg/dL				<i>P</i> for trend
	Q1 (<87) <i>n</i> =1,009	Q2 (87–120) <i>n</i> =1,030	Q3 (121–170) <i>n</i> =1,019	Q4 (>170) <i>n</i> =1,042	
Basic information					
Age, years	66.0 (47.0–76.0)	68.0 (57.0–77.0)	68.0 (59.5–76.0)	65.0 (52.3–73.0)	0.586
Sex, male, <i>n</i> (%)	494 (49.0)	570 (55.3)	563 (55.3)	657 (63.1)	<0.001
Cause of CKD, <i>n</i> (%)					
CGN without biopsy	150 (14.9)	147 (14.3)	151 (14.8)	137 (13.1)	0.342
Biopsy proven primary CGN	405 (40.1)	337 (32.7)	345 (33.9)	369 (35.5)	0.056
Diabetic nephropathy	75 (7.4)	121 (11.7)	107 (10.5)	151 (14.5)	<0.001
Hypertensive nephrosclerosis	195 (19.3)	233 (22.6)	213 (20.9)	221 (21.2)	0.498
Others	184 (18.2)	192 (18.6)	203 (19.9)	164 (15.7)	0.239
Presence of diabetes, <i>n</i> (%)	202 (20.0)	283 (27.5)	289 (28.4)	347 (33.3)	<0.001
History of CVD, <i>n</i> (%)	197 (19.5)	256 (24.9)	238 (23.4)	245 (23.5)	0.078
Current drinking, <i>n</i> (%)	506 (63.6)	516 (61.5)	471 (56.1)	547 (64.5)	0.753
Current smoker, <i>n</i> (%)	69 (8.0)	91 (9.9)	101 (10.9)	151 (16.0)	<0.001
Past smoker, <i>n</i> (%)	331 (56.2)	366 (55.0)	415 (60.7)	427 (57.7)	0.243
Never smoker, <i>n</i> (%)	469 (54.5)	469 (51.2)	422 (45.5)	381 (40.3)	<0.001
BMI, kg/m ²	21.3 (19.5–23.5)	22.7 (20.5–25.0)	23.1 (21.0–25.6)	24.7 (22.3–27.3)	<0.001
Systolic blood pressure, mmHg	128.0 (116.0–140.0)	130.0 (119.0–142.0)	130.0 (120.0–142.0)	130.8 (120.0–142.0)	<0.001
Presence of macro albuminuria, <i>n</i> (%)	356 (35.4)	430 (41.7)	439 (43.1)	544 (52.3)	<0.001
Laboratory tests					
Hemoglobin, g/dL	12.6 (11.2–13.8)	12.6 (11.2–14.0)	12.7 (11.4–14.1)	13.2 (11.8–14.8)	<0.001
Serum albumin, g/dL	4.1 (3.8–4.3)	4.0 (3.8–4.3)	4.1 (3.8–4.3)	4.1 (3.8–4.3)	0.798
Serum creatinine, mg/dL	1.1 (0.8–1.9)	1.3 (0.9–2.1)	1.4 (0.9–2.2)	1.4 (0.9–2.1)	<0.001
eGFR, mL/min/1.73m ²	46.5 (26.3–69.1)	40.2 (22.9–58.9)	37.2 (21.9–55.0)	38.3 (24.2–55.6)	<0.001
Serum total cholesterol, mg/dL	186.0 (160.0–212.0)	187.0 (165.0–210.0)	193.0 (170.0–218.0)	202.0 (179.0–231.0)	<0.001
Serum HDL-cholesterol, mg/dL	68.0 (56.0–82.0)	60.0 (49.0–71.0)	54.0 (45.0–64.8)	46.0 (39.0–56.0)	<0.001
Serum LDL-cholesterol, mg/dL	100.0 (81.8–119.8)	105.4 (85.9–125.6)	108.2 (88.8–128.8)	105.8 (84.0–130.3)	<0.001
Serum non-HDL-cholesterol, mg/dL	113.0 (95.0–133.0)	126.0 (107.0–146.0)	136.0 (117.0–158.0)	153.0 (132.0–180.0)	<0.001
Serum C-reactive protein, mg/dL	0.04 (0.01–0.09)	0.04 (0.02–0.12)	0.05 (0.02–0.13)	0.07 (0.03–0.16)	<0.001
Medications					
Use of triglyceride-lowering drugs, <i>n</i> (%)	16 (1.6)	31 (3.0)	53 (5.2)	102 (9.8)	<0.001
Use of statin, <i>n</i> (%)	328 (32.5)	391 (38.0)	436 (42.8)	513 (49.2)	<0.001
Use of ezetimibe, <i>n</i> (%)	16 (1.6)	38 (3.7)	37 (3.6)	74 (7.1)	<0.001
Use of RAAS blockers, <i>n</i> (%)	654 (64.8)	739 (71.7)	719 (70.6)	790 (75.8)	<0.001

Baseline data are expressed as the median (interquartile range) or number (%). The Cochran–Armitage test was used to determine *P* for a trend of categorical variables. The Jonckheere–Terpstra test was used to determine *P* for a trend of continuous variables. A two-tailed *P*-value <0.05 was considered statistically significant.

Abbreviations: BMI, body mass index; CGN, chronic glomerulonephritis; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quartiles based on baseline serum triglyceride values; RAAS, renin-angiotensin-aldosterone system.

Higher TG levels were associated with a higher prevalence of diabetes mellitus and macroalbuminuria (both $P<0.001$) and a higher frequency of current smoking ($P<0.001$). In addition, the BMI, systolic blood pressure, blood hemoglobin levels, serum creatinine, eGFR, serum total cholesterol, serum non-HDL cholesterol, LDL-cholesterol, and CRP levels were significantly higher (all $P<0.001$) in patients

with higher TG levels than in those with lower levels. Serum HDL-cholesterol levels were significantly lower in patients with higher TG levels than in those with lower levels ($P<0.001$). Finally, the use of TG-lowering drugs and RAAS blockers was more frequent in patients with higher TG levels than in those with lower levels (both $P<0.001$).

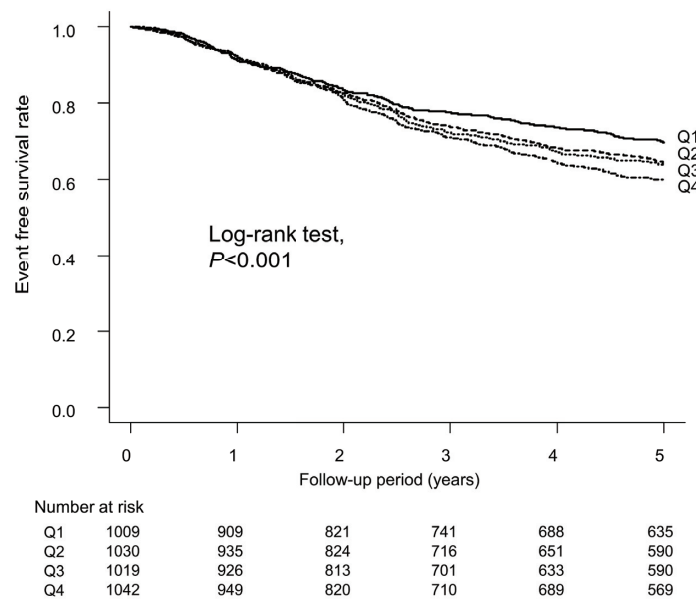


Fig. 1. Kaplan–Meier curves for the incidence of CKD progression during the 5-year observational period according to quartiles of baseline serum TG level

A two-tailed P -value < 0.05 was considered statistically significant. CKD, chronic kidney disease; TG, triglyceride; Q, quartiles based on baseline serum triglyceride values.

Table 2. Hazard ratios for CKD progression according to quartiles and 1-SD increment of serum triglyceride levels

Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	P -value	P for trend	HR (95% CI)	P -value	P for trend	HR (95% CI)	P -value	P for trend
Q1 (<87 mg/dL)	293/1,009	1.00 (reference)		<0.001	1.00 (reference)		0.020	1.00 (reference)		0.435
Q2 (87–120 mg/dL)	353/1,030	1.10 (0.94–1.28)	0.249		0.98 (0.84–1.15)	0.836		0.92 (0.79–1.08)	0.291	
Q3 (121–170 mg/dL)	356/1,019	1.09 (0.94–1.28)	0.255		0.99 (0.85–1.16)	0.917		0.91 (0.77–1.07)	0.235	
Q4 (>170 mg/dL)	408/1,042	1.13 (1.13–1.52)	<0.001		1.20 (1.03–1.41)	0.022		1.06 (0.90–1.24)	0.507	
Per 1SD higher in lnTG levels		1.12 (1.06–1.18)	<0.001		1.08 (1.02–1.15)	0.005		1.03 (0.97–1.09)	0.292	

^aModel 1: adjusted for age; sex

^bModel 2: adjusted for age; sex; BMI(categorized in quartiles); systolic blood pressure(categorized in quartiles); cause of CKD; history of CVD; presence of diabetes mellitus; blood hemoglobin; albumin; log-transformed serum C-reactive protein; estimated glomerular filtration rate; use of TG-lowering drugs; use of RAAS blockers.

^cModel 3: adjusted for Model 2 factors and presence of macroalbuminuria.

A two-tailed P -value < 0.05 was considered statistically significant.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; lnTG, log-transformed TG; Q, quartile of serum triglyceride level; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; TG, triglyceride.

Associations between Baseline Serum TG Levels and CKD Progression

During a median observational period of 5 years (interquartile range: 2.5–5.0 years), 1,410 patients met the criteria for CKD progression, 793 of whom developed ESKD. Kaplan–Meier curves showed higher probabilities of CKD progression in the higher quartiles of serum TG levels than in the lower quartiles (Fig. 1). In the multivariable-adjusted Cox proportional hazards model, the risk of CKD progression was 1.20-fold (95% CI, 1.03–1.41;

$P=0.022$) higher in the highest quartile (Q4) than in the lowest quartile (Q1) (Table 2, model 2). The HR for a 1-standard deviation (SD) increase in log-transformed serum TG level was 1.08 (1.02–1.15; $P=0.005$). However, when macroalbuminuria was added to the relevant Cox model, the association between serum TG levels and CKD progression was not significant (Table 2, Model 3). The assumption of proportional hazard was assessed by Schoenfeld residuals but was not maintained during the observational period ($P=0.02$). Therefore, we

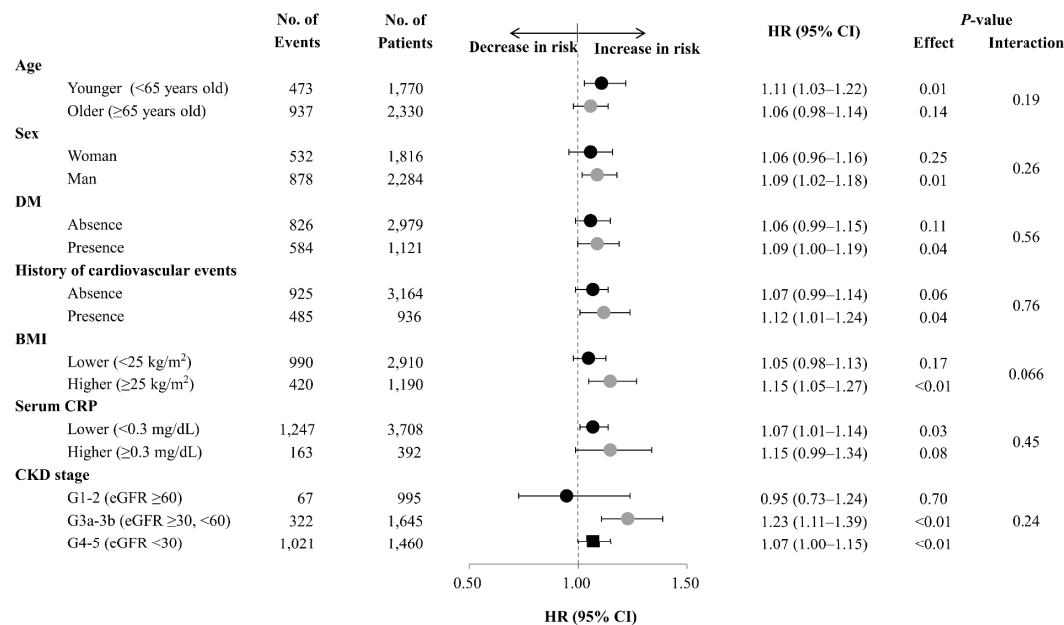


Fig. 2. Multivariable-adjusted HRs and 95% CIs for the incidence of CKD progression according to each increase of 1-SD higher in the log-transformed serum TG

A subgroup analysis by baseline characteristics. Black circles, gray circles, and black squares indicate the point estimate of the HRs, and the error bars represent the 95% CIs. The multivariable-adjusted model was adjusted for the age, sex, BMI (categorized in quartiles), systolic blood pressure (categorized in quartiles), cause of CKD, history of CVD, presence of diabetes mellitus, blood hemoglobin, albumin, log-transformed serum C-reactive protein, estimated glomerular filtration rate, use of TG-lowering drugs, and use of RAAS blockers. Variables relevant to the subgroups were excluded from each model. BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Q, quartiles based on baseline serum triglyceride values; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; TG, triglyceride.

considered the results from the Cox proportional hazards model as an average hazard risk over the entire observation period rather than a constant hazard risk throughout the observation period.

Subgroup Analyses Stratified by Baseline Characteristics

The results of the subgroup analysis are shown in **Fig. 2**. There was no significant difference in the multivariable-adjusted HR of serum TG for CKD progression among the risk factor subgroups (P for interaction >0.06). However, the association between serum TG and CKD progression tended to be stronger in obese patients ($\text{BMI} \geq 25 \text{ kg/m}^2$) than in non-obese patients ($\text{BMI} < 25 \text{ kg/m}^2$) (P for interaction $=0.066$). Patients were divided into 2 groups of $\text{BMI} \geq 25 \text{ kg/m}^2$ and $< 25 \text{ kg/m}^2$, and HRs for CKD progression were determined for each quartile of baseline TG, with the lowest quartile (Q1) as the reference (**Fig. 3**). In the $\text{BMI} \geq 25 \text{ kg/m}^2$ group, HRs increased with increasing baseline TG (P for trend < 0.001), with an HR of 1.96 (1.35–2.84) for Q4. This relationship was not significant in the $\text{BMI} < 25 \text{ kg/m}^2$ group (P for trend $=0.51$). The covariates in this

multivariable analysis were the same as those in Model 2 of the main analysis, which did not include the presence of macroalbuminuria but excluded the BMI. The results were similar when the presence of macroalbuminuria was added as a covariate, and the results are shown in **Supplementary Fig. 1**.

Sensitivity Analyses

For sensitivity analyses, we performed three types of analyses. First, we evaluated the association between serum TG levels and CKD progression using a Fine-Gray regression model, with all-cause death as a competing risk. These results were not substantially altered in this analysis (**Supplementary Table 1**).

In the second sensitivity analysis, cases followed up for ≤ 12 months were excluded to account for patients with rapidly progressing kidney disease or rapidly worsening fatal complications. The association between serum TG levels and CKD risk progression did not substantially change (**Supplementary Fig. 2 and Supplementary Table 2**). The assumption of proportional hazards was assessed by Schoenfeld residuals, and the hazard ratio remained constant throughout the observational period from one year to

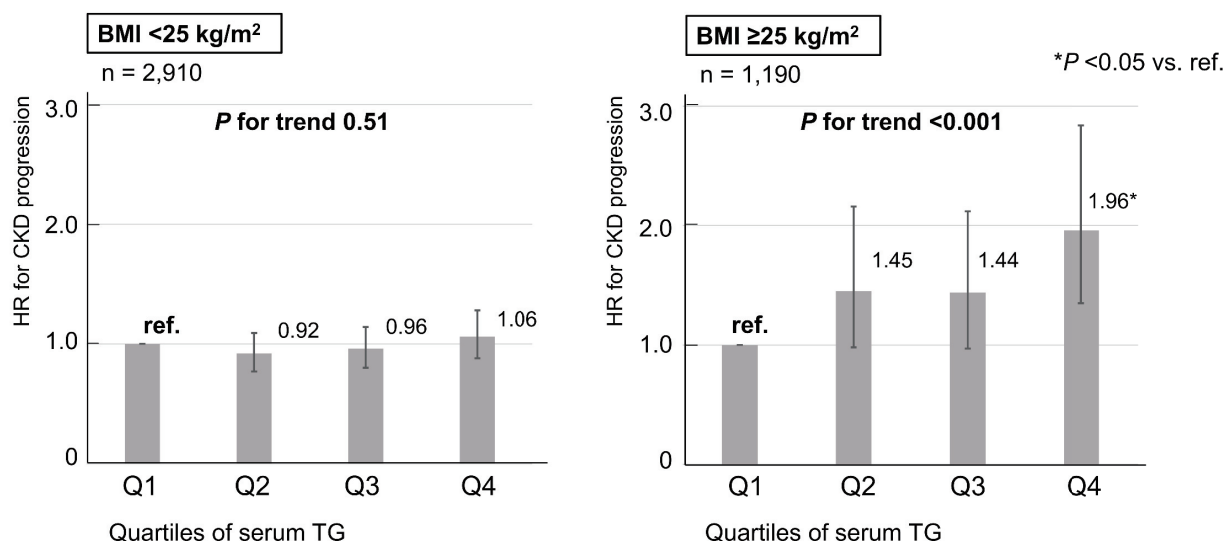


Fig. 3. Multivariable-adjusted HRs and 95% CIs for incidence of CKD progression for each quartile of serum TG vs. Q1 as a reference, stratified by the presence of obesity (BMI ≥ 25 kg/m²)

Multivariable analyses were adjusted for the age, sex, BMI (categorized into quartiles), systolic blood pressure (categorized into quartiles), cause of CKD, history of CVD, presence of diabetes mellitus, blood hemoglobin, serum albumin, log-transformed serum C-reactive protein, estimated glomerular filtration rate, use of TG-lowering drugs, and use of RAAS blockers. BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Q, quartiles based on baseline serum triglyceride values; RAAS, renin-angiotensin-aldosterone system; TG, triglyceride.

five years.

We also performed several analyses, adjusting for covariates based on prior reports and previous FKR Study Collaboration Group reports⁴¹⁻⁴⁶. First, in the population with available smoking data ($n=3,648$), we conducted an analysis with smoking status (past and current smoking) added as a covariate ([Supplementary Table 3](#)). We further conducted analyses with the addition of HDL-C quartiles as covariates and individual factors in the history of CVD events (a history of ischemic heart disease, congestive heart failure, brain infarction, brain hemorrhaging, peripheral artery disease, thoracic aortic aneurysm, or abdominal aortic aneurysm) as independent covariates ([Supplementary Table 3](#)). Finally, we performed analyses with factors that might be expected to influence CKD progression based on previous FKR Study Collaboration Group reports⁴¹⁻⁴⁶, such as hematuria, constipation, and the Charlson comorbidity index, as covariates ([Supplementary Table 3](#)). In all of these analyses, there were no significant changes in the association between serum TG levels and CKD progression.

Discussion

In this multicenter, prospective, longitudinal cohort study, we evaluated the association between

baseline non-fasting serum TG levels and CKD progression based on a multivariable-adjusted Cox proportional hazards model. In the multivariable-adjusted model, increased baseline serum TG levels were significantly associated with CKD progression; however, this significant association disappeared when macroalbuminuria was included in the relevant model. In the subgroup analyses, the association between high baseline TG levels and the risk of CKD progression tended to be stronger in the higher BMI group than in the lower BMI group. The present findings suggest that individuals with high serum TG levels are more likely to develop CKD progression than those without such high levels, possibly due to elevated macroalbuminuria. These findings also imply the importance of paying particular attention to patients with obesity.

The relationship between hypertriglyceridemia (elevated serum TG levels) and CKD progression has been the subject of conflicting research. Several retrospective observational studies have shown a significant association between this factor and CKD progression^{22, 26}. For example, data from a US veteran cohort revealed a significant association between hypertriglyceridemia and risk of CKD progression, particularly in non-CKD and CKD stage G3 patients²⁶. However, the study had limited data on albuminuria, and the main analysis was not adjusted

for albuminuria. Similarly, the Japanese Annual Health Examination Program found a significant association with the rate of eGFR decline in patients with CKD²²⁾. However, these studies primarily focused on early CKD and were not adjusted for proteinuria or albuminuria.

In contrast, the CRIC study²⁸⁾, a prospective cohort study involving patients with a wider range of eGFRs (20–70 mL/min/1.73 m²), found a significant association between serum TG levels and CKD progression when unadjusted, but the significance disappeared after adjusting for several variables, including 24-h excretion proteinuria, similar to the findings in the present study. The present study is unique in that it is a prospective cohort study involving a wide spectrum of patients with CKD from the early to advanced stages. The results of the study revealed that the significance of the association between hypertriglyceridemia and CKD progression changed depending on whether or not macroalbuminuria was included as a covariate in the multivariate-adjusted model, which is consistent with previous studies. Although the results of previous studies may have been affected by differences in the sample size and subject characteristics, it is also possible that the results may have been significantly affected by whether or not the analyses were adjusted for albuminuria or proteinuria.

In the multivariable-adjusted Cox proportional hazards model, a significant association between higher baseline serum TG levels and the risk of CKD progression disappeared after macroalbuminuria was included in the relevant model. This finding suggests that macroalbuminuria is a confounding factor leading to CKD progression through elevated TG levels. This is supported by previous findings that increased albuminuria can trigger mechanisms such as accelerated lipoprotein synthesis in the liver and decreased lipoprotein metabolism^{47–49)}. Although most of these reports were related to nephrotic syndrome, these mechanisms have been reported to be caused by an increase in albuminuria rather than a decrease in serum albumin⁴⁹⁾, and similar mechanisms might exist in patients with a low degree of albuminuria. However, since albuminuria has been acknowledged to be a risk factor for CKD progression, it is possible that high serum TG levels or insulin resistance related to elevated serum TG levels may be involved in CKD progression through the deterioration of albuminuria.

Animal studies have demonstrated associations between high TG levels and intracellular lipid accumulation in the kidney, leading to mesangial cell expansion, glomerulosclerosis, and injury of podocytes leading to the elevation of proteinuria^{50, 51)}. In addition,

dyslipidemia, including hypertriglyceridemia, induces systemic vascular atherosclerosis and may promote proteinuria through the following factors: oxidative stress, endoplasmic reticulum stress, and activation of the renin-angiotensin-aldosterone system⁵²⁾. Insulin resistance may also play an important role. Individuals with high serum TG levels often have a background of insulin resistance⁵³⁾, which is a known risk factor for albuminuria⁵⁴⁾. Therefore, individuals with high serum TG levels in a background of insulin resistance may have contributed to CKD progression via elevated albuminuria. The present study could not determine whether higher serum TG levels simply reflected higher albuminuria levels or were associated with the exacerbation of albuminuria; however, we may be able to conclude that individuals with high serum TG levels were more likely to develop CKD progression than those without. Further studies are required to determine the role of macroalbuminuria in the association between high serum TG levels and CKD progression.

In our subgroup analyses, there was a stronger association between hypertriglyceridemia and CKD progression in obese patients (BMI ≥ 25 kg/m²) than in nonobese patients, although the statistical power of this tendency was insufficient to show a significant difference in the effects. In the non-obese group, CKD progression risk was the same, regardless of serum TG level; however, in the obese group, the risk of CKD progression was almost twice as high in the highest serum TG group compared with the lowest group. The possible effects of obesity on CKD progression include glomerular hyperfiltration, increased inflammatory cytokine levels, oxidative stress, insulin resistance, and activation of the renin-angiotensin-aldosterone system^{55, 56)}. Although these mechanisms are based on studies examining the effect of obesity on the CKD onset, the same mechanisms are likely to exist in CKD progression. In addition, increased inflammatory cytokine levels and oxidative stress, as well as activation of the renin-angiotensin-aldosterone system, in obese patients⁵⁵⁾ may synergistically amplify the effect of hypertriglyceridemia-induced kidney injury. The present findings suggest that improving both obesity and the conditions that cause hypertriglyceridemia may have a synergistic effect in preventing CKD progression. However, further investigations are needed to determine whether or not controlling the conditions that cause hypertriglyceridemia and obesity can prevent CKD progression.

In a sensitivity analysis that excluded patients followed for ≤ 12 months, the difference in the event-free survival among the TG quartile groups was more

apparent, and the assumption of proportional hazards was maintained in the sensitivity analysis. This may have arisen because patients followed up for ≤ 12 months included those close to having ESKD or with rapidly worsening CKD, so their exclusion may have attenuated the association between hypertriglyceridemia and CKD progression. This finding may indicate that hypertriglyceridemia is a residual risk factor for CKD progression, similar to recent reports that hypertriglyceridemia is a residual risk factor for atherosclerotic cardiovascular events in patients with CKD^{15, 57}.

Our study has several strengths. First, the follow-up rate was very high (97.5%), and the determination of outcomes was based on primary records and was thus highly reliable. In addition, the study population included a wide range of patients with different ages, CKD stages, and CKD causes; therefore, the selection bias was likely to be low. However, our study also had several limitations. First, serum TG levels and covariates were only measured at baseline, which may have led to misclassification if TG levels, and covariates changed during the follow-up period. Second, unknown or unmeasured confounders may have existed. Third, blood samples were collected only in a non-fasting state, and some parameters may have differed if measured in a fasting state, meaning that we may have missed some associations. Furthermore, we did not evaluate insulin resistance. Finally, the study was limited to Japanese patients under the care of nephrologists, and the results may not be generalizable to other patient groups.

Conclusion

In conclusion, the present study found that individuals with high serum TG levels are more likely to develop CKD progression than those without high levels among Japanese patients with non-dialysis-dependent CKD. However, whether higher TG levels simply reflect albuminuria levels or they are associated with CKD progression via exacerbation of albuminuria is unclear. Furthermore, the risk tended to be particularly pronounced in obese patients. Further studies are needed to assess whether or not intensive intervention can prevent CKD progression in these patients.

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Authors' Contributions

Mai Seki contributed to the study design, statistical analysis, data interpretation, and manuscript drafting. Toshiaki Nakano contributed to the study design, data acquisition, data interpretation, and drafting of the manuscript, and supervised the study. Shigeru Tanaka contributed to the study design, data acquisition, statistical analysis, data interpretation, and manuscript drafting. Hiromasa Kitamura contributed to study design, data acquisition, statistical analysis, data interpretation, and drafting of the manuscript. Hiroto Hiyamuta contributed to data acquisition and manuscript drafting. Toshiharu Ninomiya contributed to critical revision of the manuscript and supervised the study. Kazuhiko Tsuruya contributed to critical revision of the manuscript and supervised the study. Takanari Kitazono critically revised and supervised the study. All authors critically reviewed the draft and

approved the final version for submission.

Conflict of Interest:

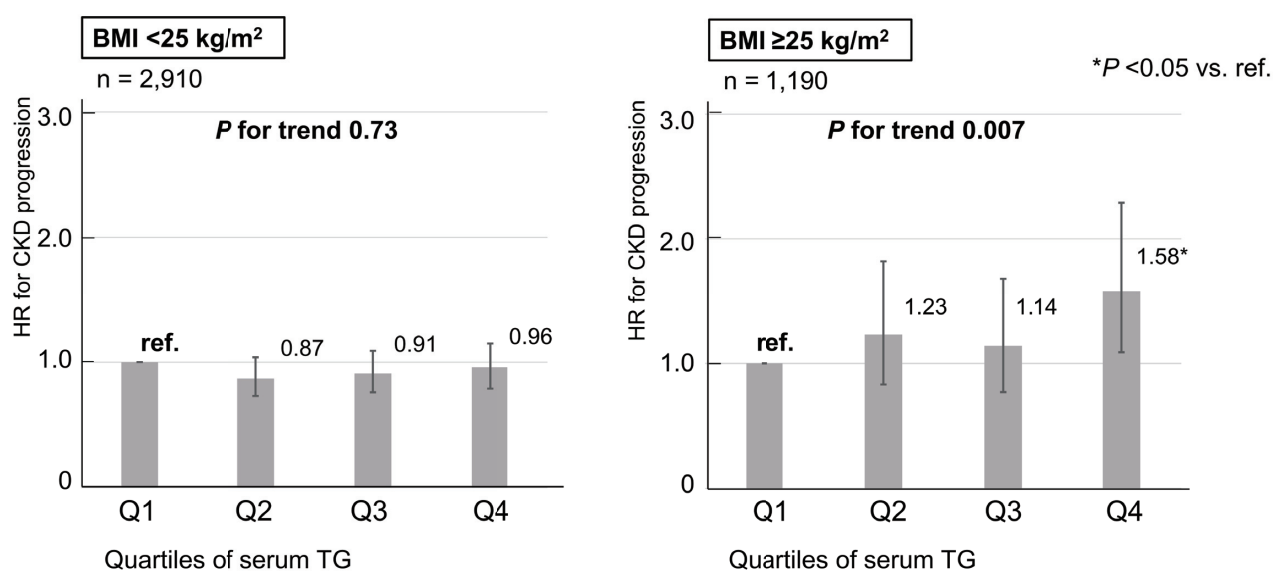
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References

- Webster AC, Nagler EV, Morton RL and Masson P: Chronic Kidney Disease. *Lancet*, 2017; 389: 1238-1252
- Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, Gu H, Hirth RA, Hutton D, Jin Y, Kapke A, Kurtz V, Li Y, McCullough K, Modi Z, Morgenstern H, Mukhopadhyay P, Pearson J, Pisoni R, Repeck K, Schaubel DE, Shamraj R, Steffick D, Turf M, Woodside KJ, Xiang J, Yin M, Zhang X and Shahinian V: US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*, 2020; 75: A6-A7
- Johansen KL, Chertow GM, Gilbertson DT, Herzog CA, Ishani A, Israni AK, Ku E, Li S, Li S, Liu J, Obrador GT, O'Hare AM, Peng Y, Powe NR, Roetker NS, St Peter WL, Saeed F, Snyder J, Solid C, Weinhandl ED, Winkelmayer WC and Wetmore JB: US Renal Data System 2021 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*, 2022; 79: A8-A12
- Borg R, Carlson N, Søndergaard J and Persson F: The Growing Challenge of Chronic Kidney Disease: An Overview of Current Knowledge. *Int J Nephrol*, 2023; 2023: 9609266
- Shlipak MG, Tummalaipalli SL, Boulware LE, Grams ME, Ix JH, Jha V, Kengne AP, Madero M, Mihaylova B, Tangri N, Cheung M, Jadoul M, Winkelmayer WC and Zoungas S: The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*, 2021; 99: 34-47
- Eckardt KU, Delgado C, Heerspink HJL, Pecoits-Filho R, Ricardo AC, Stengel B, Tonelli M, Cheung M, Jadoul M, Winkelmayer WC and Kramer H: Trends and perspectives for improving quality of chronic kidney disease care: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*, 2023;
- Drawz PE, Beddhu S, Kramer HJ, Rakotz M, Rocco MV and Whelton PK: Blood Pressure Measurement: A KDOQI Perspective. *Am J Kidney Dis*, 2020; 75: 426-434
- Vaziri ND: Lipotoxicity and impaired high density lipoprotein-mediated reverse cholesterol transport in chronic kidney disease. *J Ren Nutr*, 2010; 20: S35-43
- Noels H, Lehrke M, Vanholder R and Jankowski J: Lipoproteins and fatty acids in chronic kidney disease: molecular and metabolic alterations. *Nat Rev Nephrol*, 2021; 17: 528-542
- Nakano T, Tanaka S, Tsuruya K and Kitazono T: Relationship between serum lipid concentrations and impaired renal function in patients with chronic kidney disease: the Fukuoka Kidney Disease Registry Study. *Clin Exp Nephrol*, 2021; 25: 385-393
- Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW and Levy D: Predictors of new-onset kidney disease in a community-based population. *JAMA*, 2004; 291: 844-850
- Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP and Navaneethan SD: Metabolic syndrome and kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*, 2011; 6: 2364-2373
- McMahon GM, Preis SR, Hwang SJ and Fox CS: Mid-adulthood risk factor profiles for CKD. *J Am Soc Nephrol*, 2014; 25: 2633-2641
- Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, Hirakata H and Iida M: Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. *Am J Kidney Dis*, 2006; 48: 383-391
- Bajaj A, Xie D, Cedillo-Couvert E, Charleston J, Chen J, Deo R, Feldman HI, Go AS, He J, Horwitz E, Kallem R, Rahman M, Weir MR, Anderson AH and Rader DJ: Lipids, Apolipoproteins, and Risk of Atherosclerotic Cardiovascular Disease in Persons With CKD. *Am J Kidney Dis*, 2019; 73: 827-836
- Tian X, Chen S, Wang P, Zhang Y, Zhang X, Xu Q, Wu S and Wang A: Association of Multitrajectories of Lipid Indices With Premature Cardiovascular Disease: A Cohort Study. *J Am Heart Assoc*, 2023; 12: e029173
- Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ and Coresh J: Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol*, 2003; 14: 2934-2941
- Bash LD, Erlinger TP, Coresh J, Marsh-Manzi J, Folsom AR and Astor BC: Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*, 2009; 53: 596-605
- Erlinger TP, Tarver-Carr ME, Powe NR, Appel LJ, Coresh J, Eberhardt MS and Brancati FL: Leukocytosis, hypoalbuminemia, and the risk for chronic kidney disease in US adults. *Am J Kidney Dis*, 2003; 42: 256-263
- Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB and Stamler J: Blood pressure and end-stage renal disease in men. *N Engl J Med*, 1996; 334: 13-18
- Navaneethan SD, Schold JD, Kirwan JP, Arrigain S, Jolly SE, Poggio ED, Beddhu S and Nally JV, Jr.: Metabolic syndrome, ESRD, and death in CKD. *Clin J Am Soc Nephrol*, 2013; 8: 945-952
- Tsuruya K, Yoshida H, Nagata M, Kitazono T, Iseki K, Iseki C, Fujimoto S, Kenta T, Moriyama T, Yamagata K, Narita I, Kimura K, Kondo M, Asahi K, Ohashi Y and Watanabe T: Association of Hypertriglyceridemia With the Incidence and Progression of Chronic Kidney Disease and Modification of the Association by Daily Alcohol Consumption. *J Ren Nutr*, 2017; 27: 381-394
- Chawla V, Greene T, Beck GJ, Kusek JW, Collins AJ, Sarnak MJ and Menon V: Hyperlipidemia and long-term outcomes in nondiabetic chronic kidney disease. *Clin J*

- Am Soc Nephrol, 2010; 5: 1582-1587
- 24) Syrjänen J, Mustonen J and Pasternack A: Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. *Nephrol Dial Transplant*, 2000; 15: 34-42
 - 25) Muntner P, Coresh J, Smith JC, Eckfeldt J and Klag MJ: Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int*, 2000; 58: 293-301
 - 26) Soohoo M, Hashemi L, Hsiung JT, Moradi H, Budoff MJ, Kovesdy CP, Kalantar-Zadeh K and Streja E: Association of Serum Triglycerides and Renal Outcomes among 1.6 Million US Veterans. *Nephron*, 2022; 146: 457-468
 - 27) Bash LD, Astor BC and Coresh J: Risk of incident ESRD: a comprehensive look at cardiovascular risk factors and 17 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*, 2010; 55: 31-41
 - 28) Rahman M, Yang W, Akkina S, Alper A, Anderson AH, Appel LJ, He J, Raj DS, Schelling J, Strauss L, Teal V and Rader DJ: Relation of serum lipids and lipoproteins with progression of CKD: The CRIC study. *Clin J Am Soc Nephrol*, 2014; 9: 1190-1198
 - 29) Iso H, Imano H, Yamagishi K, Ohira T, Cui R, Noda H, Sato S, Kiyama M, Okada T, Hitsumoto S, Tanigawa T and Kitamura A: Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Atherosclerosis*, 2014; 237: 361-368
 - 30) Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT and Gudnason V: Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*, 2007; 115: 450-458
 - 31) Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M and Komachi Y: Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol*, 2001; 153: 490-499
 - 32) Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Jr., Virani SS, Williams KA, Sr., Yeboah J and Ziaien B: 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, 2019; 140: e596-e646
 - 33) 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis*, 2019; 290: 140-205
 - 34) Okamura T, Tsukamoto K, Arai H, Fujioka Y, Ishigaki Y, Koba S, Ohmura H, Shoji T, Yokote K, Yoshida H, Yoshida M, Deguchi J, Dobashi K, Fujiyoshi A, Hamaguchi H, Hara M, Harada-Shiba M, Hirata T, Iida M, Ikeda Y, Ishibashi S, Kanda H, Kihara S, Kitagawa K, Kodama S, Koseki M, Maezawa Y, Masuda D, Miida T, Miyamoto Y, Nishimura R, Node K, Noguchi M, Ohishi M, Saito I, Sawada S, Sone H, Takemoto M, Wakatsuki A and Yanai H: Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2022. *J Atheroscler Thromb*, 2023;
 - 35) Tanaka S, Ninomiya T, Fujisaki K, Yoshida H, Nagata M, Masutani K, Tokumoto M, Mitsui K, Hirakata H, Fujimi S, Kiyohara Y, Kitazono T and Tsuruya K: The Fukuoka Kidney disease Registry (FKR) Study: design and methods. *Clin Exp Nephrol*, 2017; 21: 465-473
 - 36) Andrassy KM: Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. *Kidney Int*, 2013; 84: 622-623
 - 37) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H and Hishida A: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*, 2009; 53: 982-992
 - 38) Schwartz GJ, Brion LP and Spitzer A: The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am*, 1987; 34: 571-590
 - 39) Schwartz GJ, Haycock GB, Edelmann CM, Jr. and Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics*, 1976; 58: 259-263
 - 40) Japan Society for the Study of Obesity. (2020). "Guidelines for the Management of Obesity Disease." Tokyo, Japan: Life Science Publishing Co.Ltd.
 - 41) Kitamura H, Tanaka S, Hiayamuta H, Shimamoto S, Tsuruya K, Nakano T and Kitazono T: Cardiovascular Risk Factor Burden and Treatment Control in Patients with Chronic Kidney Disease: A Cross-Sectional Study. *J Atheroscler Thromb*, 2023; 30: 1210-1288
 - 42) Nakagawa K, Tanaka S, Tsuruya K, Kitazono T and Nakano T: Association between microscopic hematuria and albuminuria in patients with chronic kidney disease caused by diabetes and hypertension: the Fukuoka Kidney disease Registry Study. *Clin Exp Nephrol*, 2023; 27: 227-235
 - 43) Yamada S, Tanaka S, Arase H, Hiayamuta H, Kitamura H, Tokumoto M, Mitsui K, Tsuruya K, Kitazono T and Nakano T: Association between prevalence of laxative use and history of bone fractures and cardiovascular diseases in patients with chronic kidney disease: the Fukuoka Kidney disease Registry (FKR) study. *Clin Exp Nephrol*, 2023; 27: 151-160
 - 44) Shukuri T, Nakai K, Tanaka S, Yamada S, Tokumoto M, Tsuruya K, Nakano T and Kitazono T: Angiotensin II receptor blockers and bone fracture in chronic kidney disease patients: the Fukuoka kidney disease Registry Study. *Clin Exp Nephrol*, 2023; 27: 919-927
 - 45) Tsuda S, Nakayama M, Tanaka S, Haruyama N, Yoshitomi R, Fukui A, Tsuruya K, Nakano T and Kitazono T: The Association of Controlling Nutritional Status Score and Prognostic Nutritional Index with Cardiovascular Diseases: the Fukuoka Kidney Disease Registry Study. *J Atheroscler Thromb*, 2023; 30: 390-407
 - 46) Tanaka S, Nakano T, Hiayamuta H, Tsuruya K and Kitazono T: Association between Multimorbidity and Kidney Function among Patients with Non-Dialysis-Dependent CKD: The Fukuoka Kidney Disease Registry Study. *J Atheroscler Thromb*, 2022; 29: 1249-1264
 - 47) Vaziri ND: Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. *Kidney Int*, 2016; 90: 41-52

- 48) Joven J, Villabona C, Vilella E, Masana L, Albertí R and Vallés M: Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. *N Engl J Med*, 1990; 323: 579-584
- 49) Agrawal S, Zaritsky JJ, Fornoni A and Smoyer WE: Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. *Nat Rev Nephrol*, 2018; 14: 57-70
- 50) Sun L, Halaihel N, Zhang W, Rogers T and Levi M: Role of sterol regulatory element-binding protein 1 in regulation of renal lipid metabolism and glomerulosclerosis in diabetes mellitus. *J Biol Chem*, 2002; 277: 18919-18927
- 51) Joles JA, Kunter U, Janssen U, Kriz W, Rabelink TJ, Koomans HA and Floege J: Early mechanisms of renal injury in hypercholesterolemic or hypertriglyceridemic rats. *J Am Soc Nephrol*, 2000; 11: 669-683
- 52) Ruan XZ, Varghese Z and Moorhead JF: An update on the lipid nephrotoxicity hypothesis. *Nat Rev Nephrol*, 2009; 5: 713-721
- 53) Eckel RH, Grundy SM and Zimmet PZ: The metabolic syndrome. *Lancet*, 2005; 365: 1415-1428
- 54) Ninomiya T and Kiyohara Y: Albuminuria and chronic kidney disease in association with the metabolic syndrome. *J Cardiometab Syndr*, 2007; 2: 104-107
- 55) Szeto HH, Liu S, Soong Y, Alam N, Prusky GT and Seshan SV: Protection of mitochondria prevents high-fat diet-induced glomerulopathy and proximal tubular injury. *Kidney Int*, 2016; 90: 997-1011
- 56) Ruan X and Guan Y: Metabolic syndrome and chronic kidney disease. *J Diabetes*, 2009; 1: 236-245
- 57) Ambrosy AP, Yang J, Sung SH, Allen AR, Fitzpatrick JK, Rana JS, Wagner J, Philip S, Abrahamson D, Granowitz C and Go AS: Triglyceride Levels and Residual Risk of Atherosclerotic Cardiovascular Disease Events and Death in Adults Receiving Statin Therapy for Primary or Secondary Prevention: Insights From the KP REACH Study. *J Am Heart Assoc*, 2021; 10: e020377



Supplementary Fig. 1. Multivariable-adjusted HRs and 95% CIs for incidence of CKD progression for each quartile of serum TG vs. Q1 as a reference, stratified by the presence of obesity (BMI ≥ 25 kg/m²)

Multivariable analyses were adjusted for age, sex; BMI(categorized in quartiles), systolic blood pressure(categorized in quartiles), cause of CKD, history of CVD, presence of diabetes mellitus, blood hemoglobin, serum albumin, log-transformed serum C-reactive protein, estimated glomerular filtration rate, use of TG-lowering drugs, use of RAAS blockers and presence of macroalbuminuria.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Q, quartiles based on baseline serum triglyceride values; RAAS, renin-angiotensin-aldosterone system; TG, triglyceride.

Supplementary Table 1. Hazard ratios for CKD progression according to quartiles and 1-SD increment of serum triglyceride levels by Fine-Gray regression model with all cause of death as a competing risk

Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend
Q1 (<87 mg/dL)	290/1,006	1.00 (reference)		<0.001	1.00 (reference)		0.017	1.00 (reference)		0.20
Q2 (87–120 mg/dL)	353/1,030	1.11 (0.95–1.30)	0.19		0.96 (0.81–1.14)	0.63		0.90 (0.75–1.08)	0.27	
Q3 (121–170 mg/dL)	356/1,019	1.12 (0.96–1.31)	0.17		1.00 (0.85–1.19)	0.97		0.94 (0.79–1.12)	0.49	
Q4 (>170 mg/dL)	408/1,042	1.34 (1.15–1.56)	<0.001		1.21 (1.02–1.44)	0.027		1.09 (0.92–1.31)	0.33	
Per 1SD higher in lnTG levels		1.12 (1.07–1.18)	<0.001		1.09 (1.02–1.15)	0.006		1.05 (0.98–1.11)	0.15	

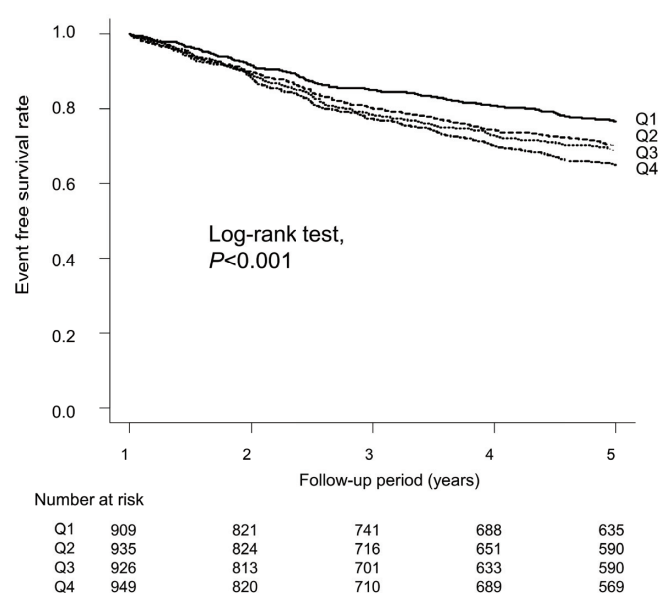
^a Model 1: adjusted for age; sex

^b Model 2: adjusted for age; sex; BMI(categorized in quartiles); systolic blood pressure(categorized in quartiles); cause of CKD; history of CVD; presence of diabetes mellitus; blood hemoglobin; albumin; log-transformed serum C-reactive protein; estimated glomerular filtration rate; use of TG-lowering drugs; and use of ACE-I or ARB.

^c Model 3: adjusted for Model 2 factors and the presence of macroalbuminuria.

Multivariable-adjusted HRs were analyzed by the Fine-Gray regression model with all cause of death as a competing risk. A two-tailed P-value < 0.05 was considered statistically significant.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; lnTG, log-transformed TG; Q, quartile of serum triglyceride level; SD, standard deviation; TG, triglyceride.



Supplementary Fig. 2. Kaplan–Meier curves for the incidence of CKD progression during the 1 to 5-year observational period according to the quartiles of baseline serum TG levels exclude individuals followed for ≤ 12 months

A two-tailed P -value < 0.05 was considered to be statistically significant.

Abbreviations: CKD, chronic kidney disease; TG, triglyceride; Q, quartiles based on baseline serum triglyceride values.

Supplementary Table 2. Hazard ratios for CKD progression according to quartiles and 1-SD increment of serum triglyceride levels by Cox proportional hazard model except for the patients followed for ≤ 12 months

Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	P -value	P for trend	HR (95% CI)	P -value	P for trend	HR (95% CI)	P -value	P for trend
Q1 (<87 mg/dL)	205/909	1.00 (reference)		<0.001	1.00 (reference)		0.002	1.00 (reference)		0.082
Q2 (87–120 mg/dL)	271/935	1.21 (1.00–1.45)	0.044		1.07 (0.89–1.29)	0.462		1.00 (0.83–1.21)	0.985	
Q3 (121–170 mg/dL)	277/926	1.21 (1.01–1.46)	0.036		1.07 (0.89–1.29)	0.452		0.98 (0.82–1.19)	0.866	
Q4 (>170 mg/dL)	324/949	1.50 (1.26–1.79)	<0.001		1.34 (1.12–1.62)	0.002		1.18 (0.98–1.42)	0.084	
Per 1SD higher in lnTG levels		1.18 (1.11–1.25)	<0.001		1.13 (1.06–1.20)	0.002		1.07 (1.00–1.15)	0.034	

^aModel 1: adjusted for age; sex

^bModel 2: adjusted for age; sex; BMI(categorized in quartiles); systolic blood pressure(categorized in quartiles); cause of CKD; history of CVD; presence of diabetes mellitus; blood hemoglobin; albumin; log-transformed serum C-reactive protein; estimated glomerular filtration rate; use of TG-lowering drugs; and use of ACE-I or ARB.

^cModel 3: adjusted for Model 2 factors and the presence of macroalbuminuria.

Multivariable-adjusted HRs were analyzed by the Cox proportional hazard risk model. A two-tailed P -value < 0.05 was considered statistically significant.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; lnTG, log-transformed TG; Q, quartile of serum triglyceride level; SD, standard deviation; TG, triglyceride.

Supplementary Table 3. Hazard ratios for CKD progression according to quartiles and 1-SD increment of serum triglyceride levels

A. Analysis in patients with available data of smoking status (<i>n</i> = 3,648)										
Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend
Q1 (<87 mg/dL)	252/860	1.00 (reference)		0.006	1.00 (reference)		0.061	1.00 (reference)		0.954
Q2 (87–120 mg/dL)	321/916	1.14 (0.96–1.34)	0.132		1.04 (0.88–1.23)	0.656		0.97 (0.83–1.15)	0.765	
Q3 (121–170 mg/dL)	318/928	1.08 (0.91–1.27)	0.378		1.00 (0.85–1.19)	0.979		0.89 (0.75–1.06)	0.201	
Q4 (>170 mg/dL)	364/944	1.29 (1.10–1.51)	0.00202		1.19 (1.01–1.41)	0.043		1.02 (0.86–1.21)	0.797	
Per 1SD higher in lnTG levels		1.11 (1.05–1.17)	<0.001		1.07 (1.01–1.14)	0.025		1.01 (0.95–1.08)	0.733	
B. Analysis with each factor of the history of CVD events treated as an independent covariate (<i>n</i> = 4,099)										
Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend
Q1 (<87 mg/dL)	293/1,009	1.00 (reference)		<0.001	1.00 (reference)		0.028	1.00 (reference)		0.529
Q2 (87–120 mg/dL)	353/1,030	1.10 (0.94–1.28)	0.249		0.98 (0.84–1.15)	0.849		0.92 (0.79–1.08)	0.300	
Q3 (121–170 mg/dL)	356/1,019	1.09 (0.94–1.28)	0.255		0.99 (0.85–1.17)	0.938		0.90 (0.77–1.06)	0.213	
Q4 (>170 mg/dL)	408/1,041	1.13 (1.13–1.52)	<0.001		1.19 (1.01–1.39)	0.032		1.05 (0.89–1.23)	0.593	
Per 1SD higher in lnTG levels		1.12 (1.06–1.18)	<0.001		1.08 (1.02–1.14)	0.006		1.03 (0.97–1.09)	0.333	
C. Analysis with HDL-cholesterol quartiles as covariate (<i>n</i> = 4,094)										
Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend
Q1 (<87 mg/dL)	290/1,006	1.00 (reference)		<0.001	1.00 (reference)		0.009	1.00 (reference)		0.536
Q2 (87–120 mg/dL)	353/1,030	1.10 (0.94–1.29)	0.214		1.00 (0.85–1.17)	0.984		0.92 (0.78–1.07)	0.273	
Q3 (121–170 mg/dL)	356/1,018	1.11 (0.95–1.29)	0.210		1.02 (0.87–1.20)	0.836		0.90 (0.77–1.06)	0.224	
Q4 (>170 mg/dL)	407/1,040	1.32 (1.14–1.54)	<0.001		1.24 (1.05–1.47)	0.010		1.04 (0.88–1.23)	0.624	
Per 1SD higher in lnTG levels		1.12 (1.06–1.18)	<0.001		1.10 (1.04–1.17)	0.001		1.03(0.97–1.09)	0.349	
D. Analysis added following factors as covariates, hematuria, constipation, and the Charlson comorbidity index (<i>n</i> = 3,051)										
Serum TG level quartiles	No. of events/ No. of patients	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend	HR (95% CI)	<i>P</i> -value	<i>P</i> for trend
Q1 (<87 mg/dL)	225/768	1.00 (reference)		<0.001	1.00 (reference)		0.041	1.00 (reference)		0.501
Q2 (87–120 mg/dL)	261/756	1.11 (0.93–1.33)	0.247		1.04 (0.87–1.25)	0.661		0.98 (0.82–1.18)	0.832	
Q3 (121–170 mg/dL)	276/748	1.17 (0.98–1.39)	0.089		1.03 (0.86–1.24)	0.736		0.94 (0.78–1.12)	0.487	
Q4 (>170 mg/dL)	311/779	1.33 (1.12–1.58)	0.001		1.22 (1.02–1.46)	0.033		1.08 (0.90–1.29)	0.434	
Per 1SD higher in lnTG levels		1.13 (1.06–1.20)	<0.001		1.08 (1.02–1.15)	0.014		1.03 (0.96–1.10)	0.437	

^aModel 1: adjusted for age; sex^bModel 2: adjusted for age; sex; BMI(categorized in quartiles); systolic blood pressure(categorized in quartiles); cause of CKD; history of CVD; presence of diabetes mellitus; blood hemoglobin; albumin; log-transformed serum C-reactive protein; estimated glomerular filtration rate; use of TG-lowering drugs; use of RAAS blockers.

In addition, the following factors were added in each analysis.

Analysis A; Smoking Status

Analysis B; each component of history of CVD (history of ischemic heart disease, congestive heart failure, brain infarction, brain hemorrhage, peripheral artery disease, thoracic aortic aneurysm, or abdominal aortic aneurysm), instead of history of CVD

Analysis C; HDL-cholesterol quartile

Analysis D; presence of hematuria, constipation, Charlson comorbidity index

^cModel 3: adjusted for Model 2 factors and the presence of macroalbuminuria.A two-tailed *P*-value <0.05 was considered statistically significant.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; lnTG, log-transformed TG; Q, quartile of serum triglyceride level; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; TG, triglyceride.