BMC Public Health

RESEARCH

Open Access

Interaction of proteinuria and diabetes on the risk of cardiovascular events: a prospective cohort CKD-ROUTE study

Shahi Kishor[1,2,3,4†], Jianrong Chen[1,2,3,4†], Yan Zhang[1,2,3,4], Wei Liu[1,2,3,4], Lingyan Zhu[1,2,3,4], Jixiong Xu[1,2,3,4*] and Jiancheng Wang[1,2,3,4*]

Abstract

Objective We evaluated the interaction of urinary protein-to-creatinine ratio (UPCR) with diabetes on the risk of cardiovascular events in a cohort study.

Methods The study population consisted of 639 participants with chronic kidney disease (CKD) stages 2–5, enrolled between 2010 and 2011 in Japan. Cox proportional hazards models were used to evaluate the independent and combined effects of the UPCR and diabetes on cardiovascular events.

Results During a median follow-up of 3 years, 59 participants developed cardiovascular events during follow-up. A notably higher risk of cardiovascular events was found in participants with proteinuria [hazards ratio (HR): 2.16, 95% confidence interval (95% CI): 1.17–3.97] compared to those without proteinuria at UPCR levels. In addition, the participants with diabetes had a higher risk of cardiovascular events (HR: 2.53, 95% CI: 1.49–4.30) than those without diabetes. Moreover, an interaction was found between UPCR and diabetes on cardiovascular events (*P* for interaction = 0.04). Participants with both proteinuria (UPCR ≥ 0.5 g/gCr) and diabetes had a 4.09 times higher risk of cardiovascular events (HR: 4.09, 95% CI: 1.97–8.47) compared with those without proteinuria (UPCR < 0.5 g/gCr) and diabetes.

Conclusions In summary, among participants with CKD stages 2–5, proteinuria and diabetes were found to independently and jointly affect the risk of cardiovascular events. Participants with proteinuria and diabetes had the highest risk of cardiovascular events compared with other groups.

Keywords Urinary protein-to-creatinine ratio, Diabetes, Proteinuria, Chronic kidney disease, Cardiovascular disease

†Shahi Kishor and Jianrong Chen contributed equally to this work.

*Correspondence:
Jixiong Xu
Jixiong.Xu@ncu.edu.cn
Jiancheng Wang
Jason095@ncu.edu.cn

[1]Department of Endocrinology and Metabolism, First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, People's Republic of China
[2]Jiangxi Clinical Research Center for Endocrine and Metabolic Disease, Nanchang 330006, People's Republic of China
[3]Jiangxi Branch of National Clinical Research Center for Metabolic Disease, Nanchang 330006, People's Republic of China
[4]Department of Endocrinology and Metabolism, People's Hospital of Jiangxi Province, Jingan 330600, People's Republic of China

Introduction

Cardiovascular disease (CVD) is the leading cause of death, and its incidence is rapidly increasing in every region of the world [1, 2]. Diabetes is known to be a major risk factor for CVD, and patients with diabetes have a 2–3 fold increased risk of dying from CVD compared with those who do not have diabetes [3, 4]. Several risk factors, including smoking, hypertension, and hyperlipidemia, have also been shown to contribute to the development of CVD [5]. Controlling hyperglycemia, hypertension, and dyslipidemia reduces CVD in patients with diabetes and chronic kidney disease (CKD); despite strict control, a high residual risk remains [6, 7].

Proteinuria is an important predictor of CVD in diabetic populations. Individuals with massive proteinuria have a CVD risk that is four to five times that of diabetic individuals without proteinuria [8]. Similarly, a population-based study conducted by Liu et al. on American Indian participants also confirmed that albuminuria is significantly associated with left ventricular systolic and diastolic dysfunction in type 2 diabetes mellitus [9]. Moreover, Valmadrid and his colleagues [10] showed that diabetic patients with an older age of onset and microalbuminuria or gross proteinuria have a higher risk of death from CVD in a prospective study. Thus, the coexistence of proteinuria and diabetes may have additive and, at times, multiplicative effects on CVD risk. However, there is limited evidence about the combination of proteinuria and diabetes with CV events, especially in patients with CKD.

Our primary interest was to investigate the hypothesis that the relationship between proteinuria and CVD risk might be modified by diabetes. The results from this study will significantly contribute to addressing crucial data gaps. More importantly, it will provide a more accurate method for predicting and preventing cardiovascular events in participants with CKD stages 2–5.

Methods

Study population and design

Details regarding the study design and major results of the Chronic Kidney Disease Research of Outcomes in Treatment and Epidemiology (CKD-ROUTE) have been reported elsewhere [11]. Briefly, the CKD-ROUTE was a prospective, observational, multicenter cohort study conducted from 2006 to 2011 and followed up until December 2012 in Japan. The data were kindly shared by the original authors, Soichiro Iimori et al. [12], from the Dryad repository. A total of 1138 participants diagnosed with CKD stages 2–5, as classified by the Kidney Disease Improving Global Outcomes (KDIGO) classification, were recruited from the Tokyo Medical and Dental University Hospital and its affiliated hospitals in the Tokyo metropolitan area. These participants were not on dialysis at the time of recruitment. The baseline characteristics of the study population were established at the initial medical examination, and follow-up data were collected every six months. The study followed all participants until the outcome was reached or until two years after enrollment. Researchers are allowed to utilize these data for secondary analysis in accordance with the Dryad Terms of Service, without infringing on the author's rights. Since informed consent and research ethics approval were obtained in the original study [11], they are not required for this secondary study. A total of 639 participants were included in the present study, with the requirement that they had no history of cardiovascular disease, had recorded baseline urinary protein-to-creatinine ratio (UPCR) levels, and were followed for at least 6 months (Figure S1).

Data collection

The variables employed in this study included age, sex, body mass index (BMI), UPCR, systolic blood pressure (SBP), hemoglobin, serum albumin, serum creatinine (Scr), causes of CKD, diabetes, hypertension, antihypertensive therapies including renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers (CCBs), and diuretics, years of follow-up, and cardiovascular events at follow-up. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation modified for Japanese subjects [13]: $eGFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times (0.739, \text{if female})$. Proteinuria was assessed through both the dipstick test and the UPCR.

Study outcomes

The outcome was CV events, including ischemic heart disease (angina pectoris or myocardial infarction), congestive heart failure, peripheral arterial disease (necrosis, amputation, or revascularization surgery of the extremities), and stroke (cerebral infarction, transient ischemic attack, cerebral hemorrhage, or subarachnoid hemorrhage).

Statistical analysis

Baseline characteristics are presented as means and standard deviations or median (interquartile range [IQR]) for continuous variables and proportions for categorical variables by baseline proteinuria categories and diabetes status. The differences in population characteristics were compared using two-sample t-tests or χ^2 tests, accordingly.

Cox proportional hazards models were used to test the independent and combined effects of UPCR and diabetes on the CV events, with and without adjustments for age, sex, BMI, SBP, eGFR, hypertension, use of calcium channel blockers, use of RAAS inhibitors, and use of

diuretics. As additional exploratory analyses, possible modifications of the association between UPCR and CV events were also evaluated by stratified analyses and interaction testing. In addition to stratified analyses, possible modifications of the association between UPCR and CV events were also assessed for the following variables: age (<60 vs. ≥ 60 years), sex, BMI (<24 vs. ≥ 24 kg/m^2), SBP (<140 vs. ≥ 140 mmHg), or eGFR levels (<30 vs. ≥ 30 mL/min/1.73 m^2). Heterogeneity across subgroups was assessed using Cox proportional hazards models, and interactions between subgroups and UPCR were tested using likelihood ratio tests.

A 2-tailed $P<0.05$ was considered to be statistically significant in all analyses. R software version 3.4.1 (http://www.r-project.org) was used for all statistical analyses. The "epicalc" and "survival" packages of R were used in our statistical analyses.

Results

Study participants and baseline characteristics

As shown in Table S1, 639 participants with a mean age of 69.0 (IQR, 58.0–76.0) years were included in this analysis. The median UPCR of those participants was 1.8 (IQR, 0.1–2.1) g/gCr. The clinical characteristics of the study participants, categorized by clinical categories of UPCR and diabetes status, are listed in Table 1. Participants with higher baseline UPCR were more likely to have a history of hypertension and diabetic nephropathy. They had higher levels of Scr, SBP, and a higher antihypertensive drug usage rate, as well as lower levels of hemoglobin, eGFR and serum albumin at baseline. Compared with nondiabetic patients, diabetic patients had higher BMI, UPCR, Scr, SBP, and a higher antihypertensive drug usage rate, and lower levels of eGFR, hemoglobin, and serum albumin.

Independent effect of UPCR and diabetes on the risk of CV events

During a median follow-up of 3 years, 59 participants developed CV events. Overall, there was a significant positive association between UPCR concentrations and the occurrence of CV events. Per 1-g/gCr increase in UPCR levels was associated with a 1.25 times higher adjusted risk of CV events (hazards ratio [HR]: 1.25, 95% confidence interval [95% CI]: 1.17–1.33; $P<0.001$). Consistently, when UPCR was assessed in clinical categories, a significantly higher risk of CV events was found in those with proteinuria (2.16, 95% CI: 1.17–3.97; $P<0.014$) compared with participants without proteinuria. Similar results were observed when UPCR was assessed using

Table 1 Characteristics of the study participants according to baseline UPCR concentrations or diabetes status*

	UPCR, g/gCr			Diabetes status		
Characteristics	**Normal (<0.5)**	**Proteinuria (≥0.5)**	***P* value**	**No**	**Yes**	***P* value**
No. of participants	306	333		438	201	
Age, year	70.0 (61.0–77.0)	68.0 (56.0–75.0)	0.027	69.0 (57.0–76.0)	69.0 (61.0–75.0)	0.366
BMI, kg/m^2	23.0 (21.0-25.5)	23.4 (21.2–26.4)	0.113	22.9 (20.8–25.2)	24.7 (21.6–27.4)	<0.001
Systolic blood pressure, mmHg	130.0 (120.0-147.5)	143.0 (130.5–160.0)	<0.001	136.0 (123.0-150.0)	140.0 (129.0-160.0)	0.004
Gender, No. (%)			0.228			
Male	214 (69.9)	218 (65.5)		291 (66.4)	141 (70.1)	0.352
Female	92 (30.1)	115 (34.5)		147 (33.6)	60 (29.9)	
Etiology of CKD, No. (%)			<0.001			<0.001
Diabetic nephropathy	23 (7.5)	102 (30.6)		7 (1.6)	118 (58.7)	
Nephrosclerosis	160 (52.3)	91 (27.3)		201 (45.9)	50 (24.9)	
Glomerulonephritis	40 (13.1)	101 (30.3)		121 (27.6)	20 (10.0)	
Other	83 (27.1)	39 (11.7)		109 (24.9)	13 (6.5)	
Hypertension, *n* (%)	240 (78.4)	318 (95.5)	<0.001	364 (83.1)	194 (96.5)	<0.001
Laboratory results						
Hemoglobin, g/dL	128.3 ± 19.5	118.3 ± 22.5	<0.001	125.1 ± 21.9	118.7 ± 20.7	<0.001
Serum albumin, g/dL	43.0 (40.0–45.0)	38.0 (33.0–41.0)	<0.001	41.0 (38.0–44.0)	39.0 (33.0–42.0)	<0.001
Serum creatinine, mg/dL	125.5 (105.2–160.0)	205.0 (135.0-310.0)	<0.001	135.5 (108.0-221.8)	180.0 (136.0-263.0)	0.012
eGFR, ml/min per 1.73 m^2	42.6 (30.5–52.5)	24.6 (15.2–38.4)	<0.001	37.8 (22.0–51.0)	27.8 (18.7–38.9)	<0.001
UPCR, g/gCr	0.1 (0.0-0.2)	2.1 (1.0-4.4)	<0.001	0.4 (0.1–1.4)	1.3 (0.2–4.6)	<0.001
Medication use, No. (%)						
Use of RAAS inhibitor	159 (52.0)	236 (70.9)	<0.001	240 (54.8)	155 (77.1)	<0.001
Use of calcium channel blocker	94 (30.7)	188 (56.5)	<0.001	169 (38.6)	113 (56.2)	<0.001
Use of diuretics	47 (15.4)	117 (35.1)	<0.001	88 (20.1)	76 (37.8)	<0.001

*Continuous variables are presented as mean (standard deviation) or median (interquartile range), categorical variables are presented as numbers (percentages)

Abbreviations: UPCR, urinary protein-to-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; RASS, renin-angiotensin-aldosterone system; CCB, calcium channel blocker

Table 2 Independent effect of baseline UPCR concentrations and diabetes on the risk of CV events

		HR (95% CI)		
Variables	**Events/*N* (%)**	**Crude model**	**Adjusted model***	***P* value**
UPCR				
Per 1-g/gCr increase	59/639 (9.2)	1.18 (1.13, 1.24)	1.25 (1.17, 1.33)	< 0.001
Clinical categories				
Normal (< 0.5)	17/355 (4.8)	Ref (1.00)	Ref (1.00)	
Proteinuria (≥ 0.5)	42/413 (10.2)	2.76 (1.57, 4.85)	2.16 (1.17, 3.97)	0.014
Medians				
Median 1 (< 0.6)	17/315 (5.4)	Ref (1.00)	Ref (1.00)	
Median 2 (≥ 0.6)	42/324 (13.0)	3.01 (1.71, 5.29)	2.42 (1.32, 4.45)	0.004
Diabetes status				
Categories				
No	27/438 (6.2)	Ref (1.00)	Ref (1.00)	
Yes	32/201 (15.9)	3.10 (1.85, 5.18)	2.53 (1.49, 4.30)	< 0.001

*Adjusted for age, sex, body mass index, systolic blood pressure, estimated glomerular filtration rate, history of hypertension, and use of calcium channel blocker, use of renin-angiotensin-aldosterone system inhibitor, as well as use of diuretics

Abbreviations: HR, hazards ratio; CI, confidence interval; UPCR, urinary protein-to-creatinine ratio; CV, cardiovascular

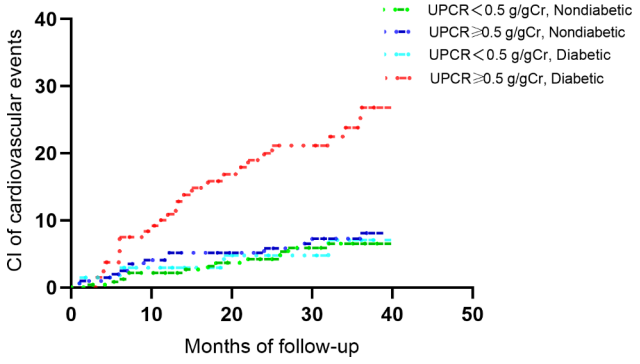

Fig. 1 Kaplan–Meier curves of cumulative hazards of CV events by baseline urinary protein-to-creatinine ratio (<0.5, ≥ 0.5 g/gCr) and diabetes status (yes, no) on the risk of CV events

median categories. After adjustment for confounding factors, participants with diabetes had a significantly increased risk of CV events (HR: 2.53, 95% CI: 1.49–4.30; $P<0.001$) than those without diabetes (Table 2).

Interaction between UPCR and diabetes on the risk of CV events

In Cox regression analyses, a statistically significant interaction between baseline UPCR and diabetes was observed for CV events (P for interaction = 0.04) (Fig. 1). The hazard ratios (HRs) for CV events were approximately 4.09 times higher in participants with proteinuria (UPCR ≥ 0.5 g/gCr) and diabetes compared to those without proteinuria (UPCR < 0.5 g/gCr) and without diabetes (HR: 4.09, 95% CI: 1.97–8.47) (Table 3; Fig. 2). Additionally, similar results were observed when UPCR was assessed using median categories (Table S2, Figure S2).

Stratified analyses by other important covariables

Stratified analyses were performed to further assess the association between UPCR and CV events in various subgroups. The following variables did not significantly modify the association between UPCR and CV events: age (< 60 vs. ≥ 60 years; P for interaction = 0.358), sex (P for interaction = 0.823), BMI (< 24 vs. ≥ 24 kg/m^2; P for interaction = 0.108), systolic blood pressure (< 140 vs. ≥ 140 mmHg; P for interaction = 0.243), and eGFR levels (< 30 vs. ≥ 30 mL/min/1.73 m^2; P for interaction = 0.580) (Table S3).

Discussion

Our current study demonstrated that proteinuria and diabetes had independent and combined effects on cardiovascular events among participants with CKD stages

Table 3 Interaction of baseline UPCR concentrations (< 0.5, ≥ 0.5 g/gCr) and diabetes (yes, no) on the risk of CV events

			HR (95% CI)		
Diabetes	**UPCR, g/gCr**	**Events/*N* (%)**	**Unadjusted**	**Adjusted***	***P* for interaction***
No	Normal (< 0.5)	13/238 (5.5)	Ref (1.00)	Ref (1.00)	0.04
	Proteinuria (≥ 0.5)	14/200 (7.0)	1.42 (0.67, 3.03)	1.15 (0.52, 2.54)	
Yes	Normal (< 0.5)	4/68 (5.9)	1.09 (0.36, 3.34)	0.91 (0.29, 2.82)	
	Proteinuria (≥ 0.5)	28/133 (21.1)	5.59 (2.88, 10.84)	4.09 (1.97, 8.47)	

*Adjusted for age, sex, body mass index, systolic blood pressure, estimated glomerular filtration rate, history of hypertension, and use of calcium channel blocker, use of renin-angiotensin-aldosterone system inhibitor, as well as use of diuretics

Abbreviations: HR, hazards ratio; CI, confidence interval; UPCR, urinary protein-to-creatinine ratio; CV, cardiovascular

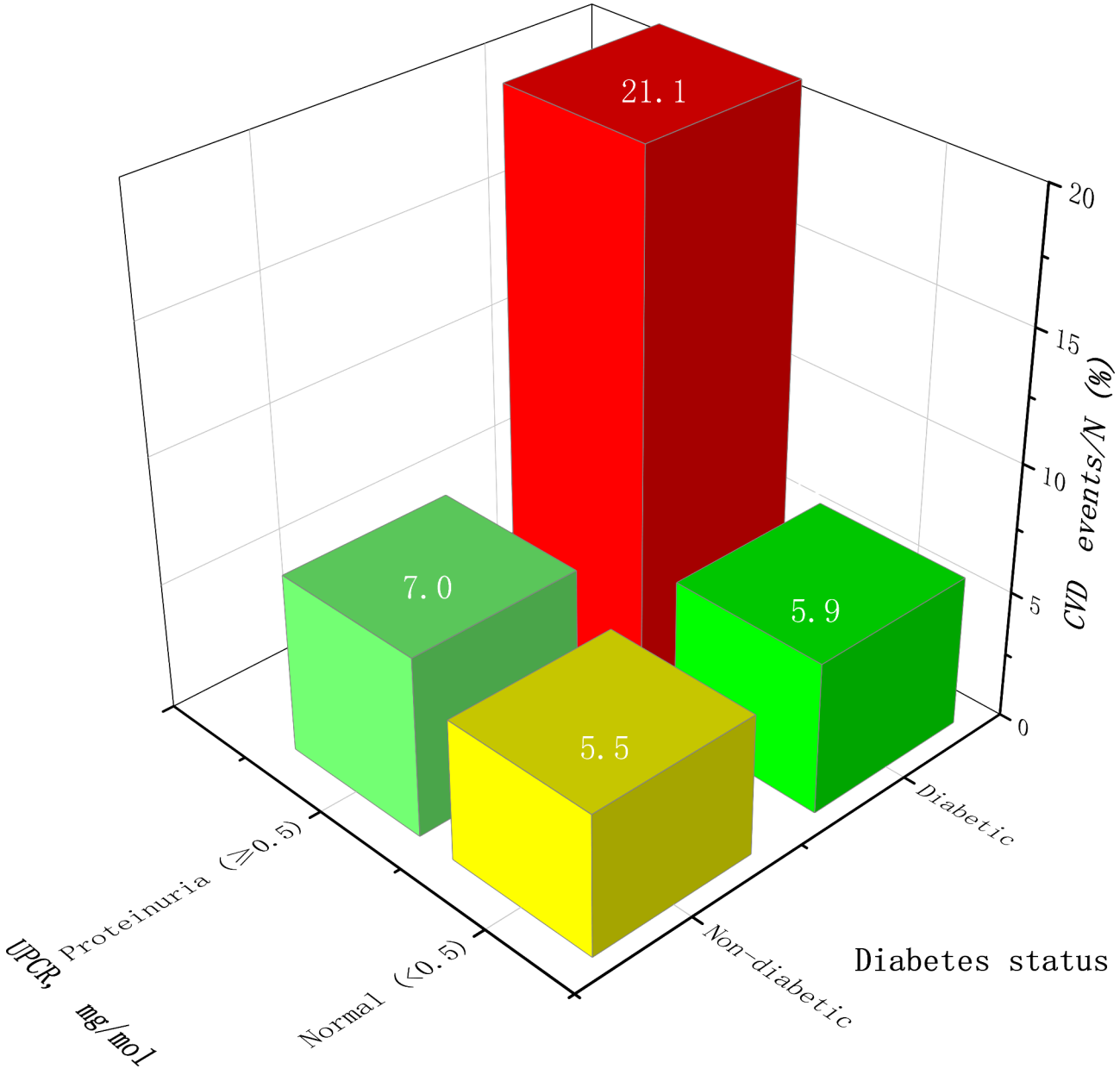

Fig. 2 CV events after 3 years of follow-up by categories of UPCR (<0.5, ≥0.5 g/gCr) and diabetes status (yes, no) at baseline

2–5. Participants with both proteinuria (UPCR≥0.5 g/gCr) and diabetes had a 4.09-fold increased risk of cardiovascular events at the 3 years follow-up compared to those without proteinuria (UPCR<0.5 g/gCr) and diabetes, after adjusting for potential confounding factors.

Numerous studies have shown that proteinuria has a significant association with CV events and mortality in patients with diabetes [14–17], but not for patients with both diabetes and CKD. Reductions in albuminuria have been shown to have cardioprotective effects in patients with type 1 and type 2 diabetes [18, 19]. In our study, we found that proteinuria accounted for an increase in the risk of CV events by a factor of 2.16 (Proteinuria vs Normal). Moreover, patients with proteinuria and diabetes had a 4.09-fold greater risk of CV events than those without proteinuria and without diabetes. Consistent with the present findings, prospective data from the Strong Heart study demonstrated that diabetic individuals with macroalbuminuria were associated with four to five times the CVD risk compared with those without albuminuria [20]. However, in the AdDIT study, Marcovecchio and colleagues [21] reported that ACR at the higher end of the normal range is associated with an increased risk of future CV events, independently of the HbA1c level. This discrepancy may be partly due to differences in patient characteristics and research design

among these studies. First, our study has different baseline proteinuria levels compared to the AdDIT study. The median baseline UPCR was 0.6 g/gCr (68.2 mg/mmol) in our study, much higher than the mean of 1.28 mg/mmol in the AdDIT study. Another possible explanation is that our study included participants with CKD, and diabetic patients with decreased renal function have a higher prevalence of several CVD risk factors, including hypertension, dyslipidemia, and proteinuria, as well as other complications [22–24]. It is noteworthy that demonstrating this relationship in the CKD population is particularly valuable because this population has a high cardiovascular risk and is well suited for regular health screening.

Our study is the first to show that proteinuria and diabetes have an interactive effect on CV events in patients with CKD. This finding is supported by a Hong Kong cohort study, which showed that the coexistence of proteinuria and glycated hemoglobin ≥ 6.2% in patients results in a higher risk of ischemic stroke than the isolated occurrence of either risk factor alone [25]. A secondary sub-analysis of the SUPPORT trial investigated the prognostic significance of impaired glucose tolerance with reference to albuminuria in patients with chronic heart failure and reported that impaired glucose tolerance is associated with a poor prognosis when complicated by albuminuria in chronic heart failure patients [26]. Accordingly, screening and intervention for elevated glucose levels and the management of proteinuria may reduce CV events and mortality risks.

There are several potential mechanisms that may explain the synergistic effect of proteinuria and diabetes on cardiovascular events. Firstly, diabetic patients with proteinuria exhibit a higher prevalence of various CVD risk factors, including hypertension and dyslipidemia, as well as complications. The simultaneous presence of these risk factors significantly accelerates endothelial dysfunction, thereby elevating the risk of CVD [27, 28]. Secondly, the RAAS is central to the pathogenesis of macrovascular and microvascular disease; hyperglycemia can activate the RAAS, leading to increased angiotensin II levels, which can cause vasoconstriction, inflammation, and proteinuria—all of which contribute to the development of atherosclerosis [29, 30]. Thirdly, diabetes, a leading cause of decreased renal function, is also associated with proteinuria, which reflects widespread vascular damage and is a risk factor for CVD [22, 31]. In addition, decreased renal function may further impair islet function and raise blood glucose levels [32], which may also increase the risk of CVD.

Potential limitations should be noted. First, the participants were enrolled at Tokyo Medical and Dental University Hospital and its 15 affiliated clinical centers in Japan. Whether the results can be extrapolated to other populations requires further verification. Second, because this was a secondary data analysis, variables not included in the data set cannot be adjusted, such as fasting plasma glucose, glycosylated hemoglobin, and low-density lipoprotein levels. Third, this study includes only a single measurement of UPCR and lacks data assessing current glycemic control. Finally, the participants enrolled in this study were patients with CKD stages 2–5 (most of whom have significant proteinuria); therefore, for patients with CKD stage 1 or without CKD, the relationship between proteinuria, diabetes, and CVD needs to be further explored.

The findings of the present study may have important clinical implications. A particularly notable finding is that proteinuria and diabetes synergistically increase the risk of CVD. Therefore, increased monitoring of proteinuria and blood glucose in clinical practice could lead to better prognostication and intensified interventions in patients with CKD. Moreover, considering that the combination of proteinuria and diabetes leads more rapidly to CVD, combination therapy is recommended to reduce risk. Novel therapies for proteinuria and diabetes may also improve cardiovascular outcomes. Recent outcome trials have shown a significant impact on CVD risk reduction in patients with CKD and diabetes after treatment with sodium-glucose co-transporter 2 (SGLT2) inhibitors [33].

In conclusion, this prospective, multicenter cohort study shows an association between proteinuria and diabetes status with a higher risk of CV events in participants with CKD stages 2–5. The results illustrate the importance of managing the combined early stages of proteinuria and diabetes in the prevention and treatment of CVD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20715-2.

Supplementary Material 1

Acknowledgements

As this is a secondary analysis, the data and method description are mainly derived from the following research. We are grateful to all the authors of the study.

Author contributions

Jiancheng Wang, and Jixiong Xu conceived and/or designed the study; Shahi Kishor, and Jianrong Chen acquired data; Jiancheng Wang, Shahi Kishor, Jianrong Chen, Yan Zhang, Wei Liu, Lingyan Zhu, and Jixiong Xu played an important role in interpreting the results; Shahi Kishor, and Jianrong Chen drafted or revised the manuscript; Jiancheng Wang and Jixiong Xu approved the final version.

Funding

The study was supported by funding from the following: the National Natural Science Foundation of China (No. 82160139), the Science and Technology Project of the Education Department of Jiangxi Province (No. GJJ190059), and the Clinical Cultivation Program of the First Affiliated Hospital of Nanchang University (No.YFYLCYJPY202308).

Data availability
The readers can access the data that support the findings of this study through the Dryad repository (DOI: 10.5061/dryad.kq23s).

Declarations

Ethics approval and consent to participate
In the previously published article, Iimori S et al. [12] has clearly stated that: This study was approved by the ethical committees of Tokyo Medical and Dental University, School of Medicine (No. 883) and all institutions participating in the study and was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 9 March 2024 / Accepted: 12 November 2024
Published online: 18 November 2024

References

1. Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1–25.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 update: a Report from the American Heart Association. Circulation. 2023;147(8):e93–621.
3. Huxley R, Barzi F, Woodward M, et al. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006;332(7533):73–8.
4. An Y, Zhang P, Wang J, et al. Cardiovascular and all-cause Mortality over a 23-Year period among Chinese with newly diagnosed diabetes in the Da Qing IGT and Diabetes Study. Diabetes Care. 2015;38(7):1365–71.
5. Watkins PJ. Cardiovascular disease, hypertension, and lipids. BMJ. 2003;326(7394):874–6.
6. Giugliano D, Maiorino M, Bellastella G, et al. Glycemic control in type 2 diabetes: from medication nonadherence to residual vascular risk. Endocrine. 2018;61(1):23–7.
7. Morales J, Handelsman Y. Cardiovascular outcomes in patients with diabetes and kidney disease: JACC Review topic of the Week. J Am Coll Cardiol. 2023;82(2):161–70.
8. Howard BV, Magee MF. Diabetes and cardiovascular disease. Curr Atheroscler Rep. 2000;2(6):476–81.
9. Liu JE, Robbins DC, Palmieri V, et al. Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: the strong heart study. J Am Coll Cardiol. 2003;41(11):2022–8.
10. Valmadrid CT, Klein R, Moss SE, et al. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med. 2000;160(8):1093–100.
11. Iimori S, Noda Y, Okado T, et al. Baseline characteristics and prevalence of cardiovascular disease in newly visiting or referred chronic kidney disease patients to nephrology centers in Japan: a prospective cohort study. BMC Nephrol. 2013;14:152.
12. Iimori S, Naito S, Noda Y, et al. Prognosis of chronic kidney disease with normal-range proteinuria: the CKD-ROUTE study. PLoS ONE. 2018;13(1):e0190493.
13. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
14. Wang A, Sun Y, Liu X, et al. Changes in proteinuria and the risk of myocardial infarction in people with diabetes or pre-diabetes: a prospective cohort study. Cardiovasc Diabetol. 2017;16(1):104.
15. Scirica BM, Mosenzon O, Bhatt DL, et al. Cardiovascular outcomes according to urinary albumin and kidney disease in patients with type 2 diabetes at High Cardiovascular Risk: observations from the SAVOR-TIMI 53 Trial. JAMA Cardiol. 2018;3(2):155–63.
16. Chauhan S, Ghosh M, Agrawal P, et al. Prevalence of silent myocardial ischemia in type 2 diabetes mellitus with microalbuminuria. Int J Adv Med. 2017;4(1):40–6.
17. Fukui M, Kitagawa Y, Nakamura N, et al. Association between urinary albumin excretion and serum dehydroepiandrosterone sulfate concentration in male patients with type 2 diabetes: a possible link between urinary albumin excretion and cardiovascular disease. Diabetes Care. 2004;27(12):2893–7.
18. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145–53.
19. Zeeuw DE, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;110(8):921–7.
20. Howard BV, Lee ET, Cowan LD, et al. Rising tide of cardiovascular disease in American indians. The strong heart study. Circulation. 1999;99(18):2389–95.
21. Marcovecchio ML, Chiesa ST, Armitage J, et al. Renal and Cardiovascular Risk according to Tertiles of urinary albumin-to-creatinine ratio: the adolescent type 1 diabetes cardio-renal intervention trial (AdDIT). Diabetes Care. 2018;41(9):1963–9.
22. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015;1:15018.
23. Aso Y. Cardiovascular disease in patients with diabetic nephropathy. Curr Mol Med. 2008;8(6):533–43.
24. Sheer R, Nair R, Pasquale MK, et al. Predictive risk models to identify patients at high-risk for severe clinical outcomes with chronic kidney disease and type 2 diabetes. J Prim Care Community Health. 2022;13:21501319211063726.
25. Yang X, Ko GTC, So WY, et al. Additive interaction of hyperglycemia and albuminuria on risk of ischemic stroke in type 2 diabetes: Hong Kong Diabetes Registry. Diabetes Care. 2008;31(12):2294–300.
26. Nochioka K, Sakata Y, Miura M, et al. Impaired glucose tolerance and albuminuria in patients with chronic heart failure: a subanalysis of the SUPPORT trial. ESC Heart Fail. 2019;6(6):1252–61.
27. Wong WT, Wong SL, Tian XY, et al. Endothelial dysfunction: the common consequence in diabetes and hypertension. J Cardiovasc Pharmacol. 2010;55(4):300–7.
28. Kim JA, Montagnani M, Chandrasekran S, et al. Role of lipotoxicity in endothelial dysfunction. Heart Fail Clin. 2012;8(4):589–607.
29. Steckelings UM, Rompe F, Kaschina E, et al. The evolving story of the RAAS in hypertension, diabetes and CV disease: moving from macrovascular to microvascular targets. Fundam Clin Pharmacol. 2010;23(6):693–703.
30. Rahman A, Sherajee SJ, Rafiq K, et al. The angiotensin II receptor-neprilysin inhibitor LCZ696 attenuates the progression of proteinuria in type 2 diabetic rats. J Pharmacol Sci. 2020;142(3):124–6.
31. Feldt-Rasmussen B. Microalbuminuria, endothelial dysfunction and cardiovascular risk. Diabetes Metab. 2000;26(Suppl 4):64–6.
32. Koppe L, Nyam E, Vivot K, et al. Urea impairs β cell glycolysis and insulin secretion in chronic kidney disease. J Clin Invest. 2016;126(9):3598–612.
33. Tuttle KR, Brosius FC, Cavender MA, et al. SGLT2 inhibition for CKD and Cardiovascular Disease in Type 2 diabetes: report of a Scientific Workshop Sponsored by the National Kidney Foundation. Diabetes. 2021;70(1):1–16.

Publisher's note