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Examining the factors contributing to the association between non-albuminuric CKD and a low rate of kidney function decline in diabetes

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Abstract

Background: Studies have shown that among people with diabetes, those with non-albuminuric chronic kidney disease (CKD) have a slower rate of reduction in renal function than do those with normal renal function. This suggests the presence of protective factors, the identification of which may open up targets for intervention. The aim of this study was to identify protective clinical factors and nonclinical biomarkers that contribute to the association between non-albuminuric CKD and the low rate of progression of CKD.

Methods: We tested for significant associations of several clinical factors and 33 nonclinical biomarkers with (1) normoalbuminuria and (2) a low rate of CKD progression among participants with diabetes and CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study in the United States. Factors significantly associated with both normoalbuminuria and a low rate of CKD progression were assessed in linear regression to estimate their potential contributions to the association between non-albuminuric CKD and rate of CKD progression.

Results: Systolic blood pressure (SBP), glycated A1c (HbA1c), estimated glomerular filtration rate (eGFR) and six biomarkers [β-trace protein (BTP), kidney injury molecule (KIM-1), fibrinogen, fractalkine, brain natriuretic peptide (BNP) and high-sensitivity troponin-T (hsTnT)] were associated with both normoalbuminuria and a low rate of eGFR decline. The univariate β-coefficient for normoalbuminuria was 0.93 [95% confidence interval (CI): 0.82, 1.05]. When all associated factors and biomarkers were included, the regression coefficient decreased to 0.54 (95% CI: 0.40, 0.67). The factors that contributed to the association between non-albuminuric CKD and low rate of eGFR were lower levels of SBP, HbA1c, BTP, KIM-1, hsTnT, BNP, fibrinogen and fractalkine.

Conclusion: Lower levels of SBP and biomarkers that have pro-inflammatory and vascular modulating features may explain up to 40% of the association between non-albuminuric CKD and low rate of CKD progression. Further investigation of these biomarkers may lead to therapeutic interventions.

Keywords: chronic kidney disease, normoalbuminuria, diabetes, biomarker, epidemiology

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Introduction

Albuminuric chronic kidney disease (CKD) is the most common form of CKD among people with diabetes and is associated with a significant risk of progression to end-stage kidney disease (ESKD), and with increased all-cause and cardiovascular mortality.[1–3] However, non-albuminuric CKD has recently been recognised as a common

manifestation of CKD in people with diabetes and is increasing in prevalence.[4,5] We have shown previously, in two separate cohorts of people with diabetes [the Chronic Renal Insufficiency Cohort (CRIC) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study], that the rate of decline of estimated glomerular filtration rate (eGFR) in people with non-albuminuric CKD not only slower than in albuminuric CKD but is also even slower than in people with normal kidney function.[6,7] This suggests the presence of reno-protective factors in people with non-albuminuric CKD. However, as of yet, there has been no identification of these reno-protective factors, although people with non-albuminuric CKD have lower levels of blood pressure and lower rates of smoking.[6–8] Characterisation of the reno-protective factors in non-albuminuric CKD may improve our understanding of the progression of CKD in diabetes and may help identify new targets for therapeutic interventions for both albuminuric and non-albuminuric CKD. Therefore, the aim of this study was to identify protective clinical factors and nonclinical biomarkers that contribute to the association between non-albuminuric CKD and the low rate of progression of CKD.

Materials and methods

Study design and participants

We obtained data from the CRIC study, which is a multicentre observational study in the United States that examined risk factors for the progression of CKD and cardiovascular disease (CVD) among people with mild to moderate renal insufficiency. A detailed description of the CRIC study has been previously reported.[9,10] The CRIC study was approved by the Institutional Review Boards of each study centres, and all study participants provided written informed consent forms. In brief, between 2003 and 2008, a total of 3939 ethnically diverse participants with an eGFR of 20–70 ml/min/1.73 m^2 were enrolled into this longitudinal study with >10 years of subsequent follow-up. Participants were invited annually for in-person follow-up visits, which included assessment of kidney function and other clinical parameters. Participants were also asked to provide information on clinical events (kidney transplant, dialysis, treatment for diabetes and cardiovascular events) and general health at the 6-month time-point between clinic visits. Nearly, 50% of the study participants had diabetes, defined as a fasting plasma glucose ⩾126 mg/dl or a non-fasting plasma glucose ⩾200 mg/dl, or self-report of glucose lowering medication use.[11] For this study, we included 1604 participants with diabetes after excluding those with a missing value for baseline albuminuria ($n = 95$) or fewer than three eGFR measurements during follow-up ($n = 209$).

Measurements

Detailed information about measurement methods for laboratory parameters has been presented in previous reports.[12–14] Different platforms were used for the measurement of each of the biomarkers, and data were available for 33 nonclinical biomarkers for the current analysis.

Measurement of urinary albumin was performed by an immunoturbidometric method and creatinine was determined using a kinetic colorimetric assay. Serum creatinine was determined annually by the Jaffe method on a Beckman Synchron System. eGFR was calculated using the CRIC Study-specific formula.[15] Serum lipids were measured using an enzymatic colorimetric assay. Sociodemographics, medical history, concomitant medications use and lifestyle behaviours were self-reported.

Statistical analyses

Baseline demographic and clinical characteristics of participants were presented as frequencies and percentages, means (standard deviations) or medians (25th–75th percentiles). Baseline characteristics were stratified by albuminuria status, which was classified as normoalbuminuria (urinary albumin<30 mg/24 h) or albuminuria (⩾30 mg/24 h).

To elucidate the potential protective clinical factors or nonclinical biomarkers and their relative contributions to the lower rate of eGFR decline in non-albuminuric CKD, we first identified clinical factors and biomarkers that had a statistically significant association with both normoalbuminuria and with a low rate of eGFR decline, using logistic regression. To perform the logistic regression, annual eGFR decline was classified into two categories: low (annual eGFR decline <1.0 ml/min/1.73 m^2/year) and medium-high (annual eGFR decline ⩾1.0 ml/min/1.73 m^2/year). An annual eGFR decline of< 1.0 ml/min/1.73 m^2/year was selected because the mean decline in

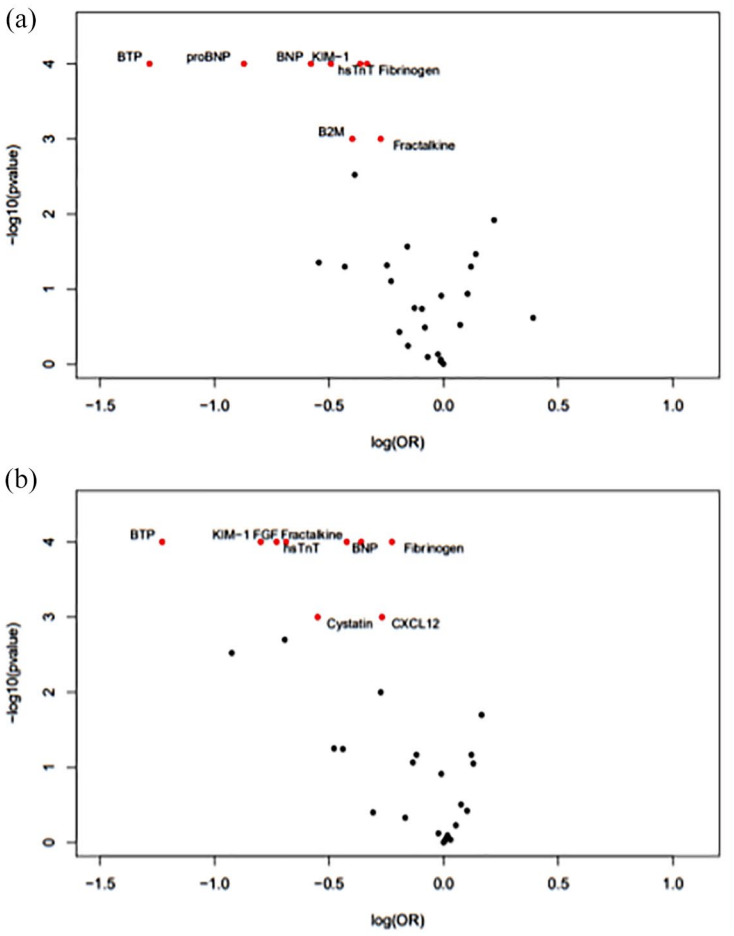

Figure 1. Volcano plot of association of nonclinical biomarkers with a low rate of decline in (a) eGFR and with (b) normoalbuminuria. Red circles correspond to statistically significant associations (at $p \leqslant 0.001$). Odds ratios are per one standard deviation change in the biomarker.
B2M, β2-microglobulin; BNP, brain natriuretic peptide; BTP, β-trace protein; CXCL12, C-X-C Motif Chemokine Ligand 12; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factors; hsTnT, high-sensitivity troponin-T; KIM-1, kidney injury molecule-1; proBNP, N-terminal pro b-type BNP.

eGFR in people with CKD and baseline urine albumin <50 mg/24 h was <1.0 ml/min/1.73 m^2/year (Supplementary Figure 1), which is consistent with the previous studies.[6,7] Annual rate of eGFR decline for each individual was estimated by calculating the absolute annual change in eGFR for each participant using a joint-longitudinal survival model,[16,17] then classified as low or medium-high for each individual. All clinical factors and nonclinical biomarkers were included as continuous variables as exposures in univariate logistic regression analyses (a complete list is presented in Tables S1 and S2), and factors that had a significant association (at $p \leqslant 0.001$) with both normoalbuminuria and a low rate of eGFR decline were included in further analyses (three clinical factors and six nonclinical biomarkers; Tables S1 and S2). This logistic regression analysis was adjusted for age, sex, baseline serum creatinine, race/ethnicity, education, smoking and renin–angiotensin–aldosterone system blockers (RAAS blockers) use.

All biomarkers had $<1\%$ of values missing, with the exceptions of urinary kidney injury molecule (KIM-1), urinary N-acetyl-beta-d-glucosaminidase (NAG), liver-type fatty acid-binding protein (L-FABP), asymmetric dimethylarginine (ADMA), soluble intercellular adhesion molecule-1 (siCAM-1) and sclerostin. Values were missing for $>30\%$ of people for these biomarkers. The remaining values were normally

distributed, and baseline characteristics of participants with and without these variables were similar (Table S3), suggesting participants with missing biomarkers measurements are not very different from those with complete measurements. Since KIM-1 is considered as one of the most important biomarkers of kidney injury in diabetic nephropathy,[18,19] the main analysis was restricted to those with available KIM-1 data ($n = 1092$). A sensitivity analysis was conducted including all the participants ($n = 1604$).

Following the initial logistic regression, linear regression analysis was used to assess the contribution of clinical factors and nonclinical biomarkers to the association between non-albuminuric CKD and rate of eGFR decline. We used standardised measures with standard deviations to facilitate comparison among factors and biomarkers. First, we conducted a series of separate linear regression models, adding each of the factors and biomarkers, individually, to a regression model of normoalbuminuria *versus* albuminuria (the exposure) and low eGFR decline (the outcome) to assess the change in the β-coefficient for normoalbuminuria *versus* albuminuria. Thus, a change in the β-coefficient for normoalbuminuria, on addition of the factor or biomarker, suggests that the factor or biomarker contributes to the association between non-albuminuric CKD and a low rate of eGFR decline. Then, to estimate the total contribution of all clinical factors and biomarkers to this association, we conducted multivariate linear regression analysis in stepwise fashion, adding one factor at a time (including only factors that changed the β-coefficient in the first analysis). In this case, the total change in the β-coefficient from the first to final model is indicative of the total contribution of these factors and biomarkers to the association between non-albuminuric CKD and a low rate of eGFR decline.

All statistical analyses were undertaken using Stata, version 15.1 (Stata, College Station, Texas) and R, Version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

We obtained de-identified data from the publicly available National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) Central Repository after approval from human research ethics committees of the Alfred Hospital and Monash University, Melbourne, Australia (41/20).

Results

Baseline characteristics of the study population by albuminuria status were shown in Table 1. Those with non-albuminuric CKD were older, had lower median glycated haemoglobin (HbA1c), systolic and diastolic blood pressures, had higher median eGFR and were more likely to be using RAAS blockers.

Univariate associations of clinical factors, nonclinical biomarkers and normoalbuminuria with eGFR decline

The median values of clinical factors and the 33 nonclinical biomarkers, stratified by albuminuria status and eGFR-decline category (low and medium-high), and their univariate associations with normoalbuminuria and eGFR decline (as a binary outcome of low *versus* medium-high) were shown in Tables S1 and S2, respectively, and the univariate logistic regression results were shown in Figure 1. Three clinical factors [systolic blood pressure (SBP), HbA1c and eGFR] and six nonclinical biomarkers [KIM-1, β-trace protein (BTP), fibrinogen, brain natriuretic peptide (BNP), high-sensitivity troponin-T (hsTnT) and fractalkine] were significantly associated with both normoalbuminuria and with a low rate of eGFR decline and were included in further analyses.

Regression analyses of albuminuria status and rate of eGFR decline

The results of the linear regression analyses were presented in Tables 2 and 3. The univariate β-coefficient for normoalbuminuria *versus* albuminuria was 0.93 [95% confidence interval (95% CI): 0.82, 1.05]. Addition of SBP, HbA1c, BTP, KIM-1, hsTnT, BNP, fibrinogen and fractalkine altered the β-coefficient for normoalbuminuria *versus* albuminuria, with the largest effects occurring with BTP, SBP, KIM-1 and hsTnT. Baseline eGFR, age and neutrophil gelatinase-associated lipocalin (NGAL) did not appear to contribute to this association. When the factors and biomarkers that individually reduced the β-coefficient for normoalbuminuria *versus* albuminuria were included in multivariate linear regression analysis, the β-coefficient for normoalbuminuria decreased to 0.54 (95% CI: 0.40, 0.67), ~40% reduction (Table 3).

In a sensitivity analysis that included all study participants, but excluded KIM-1, the association

Table 1. Baseline demographic and clinical characteristics of participants stratified by albuminuria status.

Variable	Albuminuria status, mg/24 h		Total	*p*-value
	<30	⩾30		
N	483	1121	1604	
Age [yr; M (SD)]	62.3 (53.4, 65.7)	60.3 (53.4, 65.7)	60.9 (54.3, 66.8)	<0.0001
Female [*n* (%)]	285 (59.0)	422 (37.6)	707 (44.1)	<0.0001
Race/ethnicity [*n* (%)]				<0.0001
Non-Hispanic White	215 (44.5)	374 (33.4)	589 (36.7)	
Non-Hispanic Black	201 (41.6)	510 (45.5)	711 (44.3)	
Hispanic	49 (10.1)	190 (16.9)	239 (14.9)	
Others	18 (3.8)	47 (4.2)	65 (4.11)	
Education [*n* (%)]				0.01
Less than high school	96 (19.9)	301 (26.9)	397 (24.8)	
High school graduate	90 (18.6)	223 (19.9)	313 (19.5)	
Some college	158 (32.7)	322 (28.7)	480 (29.9)	
College graduate or higher	139 (28.8)	275 (24.5)	414 (25.8)	
Current smoker [*n* (%)]	47 (9.7)	141 (12.6)	188 (11.7)	0.1
RAAS blockers use [*n* (%)]	403 (83.4)	883 (78.8)	1286 (80.2)	0.03
BMI [kg/m^2; median (IQR)]	33.5 (28.9, 39.1)	32.4 (28.1, 38.1)	32.9 (28.4, 38.3)	0.03
SBP [mmHg; M (SD) mmHg]	121.5 (18.3)	136.7 (21.6)	132.1 (21.8)	<0.0001
DBP [mmHg; M (SD)]	65.0 (11.2)	71.1 (12.4)	69.2 (12.4)	<0.0001
HbA1c [%; median (IQR)]	7.0 (6.2, 7.9)	7.5 (6.6, 8.6)	7.3 (6.5, 8.4)	<0.0001
eGFR [ml/min/m^2; median (IQR)]	46.1 (36.3, 57.8)	37.9 (29.6, 47.9)	40.4 (31.3, 51.4)	<0.0001

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range; RAAS blockers, renin–angiotensin–aldosterone system blockers; SBP, systolic blood pressure; SD, standard deviations; yr, year.

between non-albuminuric CKD and a low rate of eGFR decline was consistent with the main analysis [with the β-coefficient decreasing from 0.92 (95% CI: 0.82, 1.01) to 0.57 (95% CI: 0.46, 0.68); Table S4].

Discussion

In this study of people with diabetes and CKD, we found that ~40% of the low rate of CKD progression in non-albuminuric CKD could be explained by several key clinical factors and non-clinical biomarkers. The factors that appeared to contribute to the association between non-albuminuric CKD and a low rate of eGFR decline were lower levels of SBP, HbA1c, BTP, KIM-1, hsTnT, BNP, fibrinogen and fractalkine.

High blood pressure and HbA1c are well-known risk factors for CKD progression,[20,21] with high blood pressure and HbA1c, leading to kidney damage through an increase in intraglomerular

Table 2. Association of non-albuminuric *versus* albuminuric CKD and of clinical factors and biomarkers with decline in eGFR, in a series of bivariate linear regression models.

	β-coefficient (95% CI)	
	Added variable	**Normoalbuminuria *versus* albuminuria**
Normoalbuminuria *versus* albuminuria	NA	0.93 (0.82, 1.05)
SBP	−0.17(−0.23, −0.11)	0.80 (0.68, 0.93)
HbA1c	−0.08 (−0.14, −0.03)	0.89 (0.77, 1.02)
eGFR	−0.003 (−0.05, 0.05)	0.93 (0.81, 1.06)
BTP	−0.21 (−0.27, −0.14)	0.77 (0.65, 0.90)
KIM-1	−0.14 (−0.19, −0.08)	0.83 (0.71, 0.96)
hsTnT	−0.14 (−0.20, −0.08)	0.83 (0.68, 0.94)
BNP	−0.15 (−0.22, −0.10)	0.86 (0.75, 0.99)
Fibrinogen	−0.15 (−0.21, −0.10)	0.87 (0.76, 1.00)
Fractalkine	−0.09 (−0.15, −0.04)	0.90 (0.78, 1.02)

BNP, brain natriuretic peptide; BTP, B-trace protein; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; hsTnT, high-sensitivity troponin-T; KIM-1, kidney injury molecule-1; SBP, systolic blood pressure.
β-coefficients indicate the number of ml/min/1.73 m^2 of eGFR decline associated with a one standard deviation change in each of the clinical factors and biomarkers. Positive β-coefficients indicate an association with a slowing of eGFR decline, while negative values indicate an association with more rapid decline.

pressure, which causes injury of small vessels through mechanical stretch and cell damage which, in turn results in the activation of the RAAS and oxidative stress,[22,23] and may result in inflammation.[24,25]

We also found that a considerable proportion of the lower rate of CKD progression in non-albuminuric CKD was associated with lower levels of BTP and KIM-1. Both BTP (also known as lipocalin-type prostaglandin D) and KIM-1 are transmembrane proteins expressed by kidney cells, are known as potential biomarkers of kidney injury and are associated with inflammation in glomeruli and tubules.[26–28] Studies suggest that lower levels of these biomarkers are associated with normalisation of albuminuria, and a reduction of pro-inflammatory markers and kidney cell loss in diabetes and CKD.[18,28–31]

Other biomarkers that contributed to the association between non-albuminuric CKD and a low rate of eGFR decline were lower levels of BNP and fibrinogen. BNP has been studied extensively as a biomarker for CVD.[32,33] Elevation of BNP has been associated with endothelial dysfunction, progression of atherosclerosis, early changes in volume and cardiac stretch and venous congestion, all of which may contribute to kidney disease progression,[34] and lower levels of BNP may therefore prevent these deleterious effects. Fibrinogen is a glycoprotein that has pro-inflammatory, vascular and thrombosis modulating properties, with higher levels of this biomarker being reported in various disorders, including atherosclerosis, dementia and rheumatoid arthritis.[35–37] Furthermore, work using animal models have shown that inhibition or genetic ablation of fibrinogen is associated with reduced fibroblast infiltration into the kidney and attenuated kidney damage.[38] Indeed, the fact that fibrinogen was identified in this study may be a promising finding for the development of therapies that attenuate progression of CKD in both the albuminuric and non-albuminuric populations.

It is important to note that while the relative contribution of the factors to the rate of eGFR decline

Table 3. Hierarchical regression of factors contributing to the association between non-albuminuric CKD and rate of eGFR decline.

	β-coefficient (95% CI)								
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
Normoalbuminuria *versus* albuminuria	0.93 (0.82, 1.05)	0.80 (0.68, 0.93)	0.77 (0.65, 0.90)	0.63 (0.49, 0.76)	0.56 (0.43, 0.70)	0.54 (0.39, 0.67)	0.54 (0.40, 0.68)	0.54 (0.40, 0.67)	0.54 (0.40, 0.67)
SBP	–	−0.17 (−0.23, −0.11)	−0.17 (−0.23, −0.11)	−0.15 (−0.21, −0.09)	−0.14 (−0.21, −0.09)	−0.14 (−0.19, −0.07)	−0.12 (−0.18, −0.06)	−0.11 (−0.17, −0.04)	−0.11 (−0.17, −0.05)
HbA1c	–	–	−0.08 (−0.14, −0.03)	−0.09 (−0.14, −0.03)	−0.08 (−0.13, −0.03)	−0.08 (−0.14, −0.03)	−0.09 (−0.14, −0.04)	−0.09 (−0.14, −0.03)	−0.09 (−0.14, −0.03)
BTP	–	–	–	−0.20 (−0.26, −0.14)	−0.19 (−0.26, −0.11)	−0.17 (−0.24, −0.11)	−0.16 (−0.22, −0.09)	−0.14 (−0.20, −0.07)	−0.14 (−0.20, −0.06)
KIM-1	–	–	–	–	−0.11 (−0.16, −0.05)	−0.11 (−0.16, −0.05)	−0.11 (−0.16, −0.05)	−0.10 (−0.16, −0.04)	−0.11 (−0.16, −0.04)
hsTnT	–	–	–	–	–	−0.06 (−0.12, −0.09)	−0.04 (−0.10, 0.02)	−0.04 (−0.10, 0.03)	−0.04 (−0.10, 0.02)
BNP	–	–	–	–	–	–	−0.09 (−0.15, −0.09)	−0.09 (−0.15, −0.03)	−0.09 (−0.15, −0.03)
Fibrinogen	–	–	–	–	–	–	–	−0.09 (−0.15, −0.03)	−0.09 (−0.15, −0.03)
Fractalkine	–	–	–	–	–	–	–	–	−0.02 (−0.07, 0.04)

BNP, brain natriuretic peptide; BTP, B-trace protein; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; hsTnT, high-sensitivity troponin-T; KIM-1, kidney injury molecule-1; M, model; SBP, systolic blood pressure.
β-coefficients indicate the number of ml/min/1.73 m^2 of eGFR decline associated with one standard deviation change in each of the clinical factors and biomarkers. Positive β-coefficients indicate an association with a slowing of eGFR decline, while negative values indicate an association with more rapid decline.

may appear small, their potential utility as a treatment target to attenuate CKD progression is not. For example, while the β-coefficient for SBP was only −0.11 in the final adjusted linear regression for eGFR decline, intensive blood pressure lowering shows substantial benefits on the progression of CKD.[39,40]

The strengths of this study are large sample size and assessment of a range of serum and urinary nonclinical biomarkers that cover different pathophysiological pathways, including hemodynamic pathways, inflammation and fibrosis. In addition, the CRIC Study included a diverse group of participants with diabetes and CKD. However, there are also some limitations that warrant mention. The CRIC study included people with both type 1 and 2 diabetes, and we were unable to distinguish diabetes type. However, the majority of study participants had type 2 diabetes.[6] In addition, some nonclinical biomarkers, including KIM-1, in this study had >30% missing values. Furthermore, although we included 33 nonclinical biomarkers that cover various pathophysiological pathways mediating kidney damage, it should be noted that biomarkers that are more specific for oxidative stress and endothelial dysfunction were not evaluated in this study. It is possible that biomarkers of oxidative stress/anti-oxidant defence and endothelial dysfunction may contribute to the large proportion of the association between non-albuminuric CKD and a low rate of eGFR decline that was left unexplained in this study. Future research to explain this proportion is needed. Finally, it is possible that higher use of RAAS blockers in the normoalbuminuric group may have contributed to a slower rate of CKD progression.[41,42] However, we have previously shown that, within the non-albuminuric CKD group of the CRIC study, eGFR decline was unrelated to the use of RAAS blockers at baseline.[6] Nevertheless, quantifying the mediating effect of RAAS blockers on the slower decline in eGFR for people with normoalbuminuria, in addition to biomarkers, requires further study.

In conclusion, a considerable proportion of association between non-albuminuric CKD and a low rate of decline in kidney function could be explained by lower levels of SBP, HbA1c and lower levels of nonclinical biomarkers that exert pro-inflammatory effects and effects on vascular function. Further investigation of these and other related biomarkers in the pathogenesis of CKD in diabetes is warranted.

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Author contributions

Oyunchimeg Buyadaa: Conceptualisation; Data curation; Formal analysis; Methodology; Writing – original draft.

Agus Salim: Conceptualisation; Formal analysis; Investigation; Validation; Writing – review & editing.

Jedidiah I. Morton: Conceptualisation; Methodology; Writing – review & editing.

Karin Jandeleit-Dahm: Conceptualisation; Methodology; Writing – review & editing.

Dianna J. Magliano: Conceptualisation; Methodology; Supervision; Validation; Writing – review & editing.

Jonathan E. Shaw: Conceptualisation; Data curation; Methodology; Supervision; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Statement of ethics

This study is approved by the Human Research Ethics Committees of the Alfred Hospital and Monash University, Melbourne, Australia (41/20).

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Supplemental material

Supplemental material for this article is available online.

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