Original Paper

Dysglycemia Predicts Cardiovascular and Kidney Disease in the Kidney Early Evaluation Program

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The cardiometabolic syndrome has been associated with both chronic kidney disease (CKD) and cardiovascular disease (CVD). Using data from the National Kidney Foundation-Kidney Early Evaluation Program, the authors sought to investigate this association in a targeted CKD cohort. A total of 26,992 patients met eligibility criteria including age 18 years and older, diabetes, hypertension, or family history of CKD, diabetes, or hypertension and excluded those taking renal replacement therapy. Individuals were identified by Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) criteria (dysglycemia, hypertension, and dyslipidemia) and World Health Organization criteria (obesity and proteinuria). Univariate and multivariate analyses were used to evaluate increasing components of the cardiometabolic syndrome, CKD, and CVD. On multivariate analysis there was a graded relationship between increasing components with an increased prevalence of CKD and CVD. Additionally, there was a graded trend with the stage of dysglycemia (eg, normoglycemia, prediabetes, and overt diabetes) and increasing CKD. However, there was only an increased prevalence of CVD observed in the clinically diabetic group. This trend was also observed with increasing serum glucose levels and an increasing percent of CVD and CKD up to 160 mg/dL. However, prevalent CVD increased at >140 mg/dL and prevalent CKD at >180 mg/dL. Therefore, data support that increasing metabolic components and dysglycemia are strongly associated with an increased prevalence of CKD and CVD. J Clin Hypertens (Greenwich). *2010;12:51–58.* ©*2009 Wiley Periodicals, Inc.*

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The presence of multiple cardiometabolic risk factors including obesity, hypertension, insulin resistance/hyperinsulinemia, dyslipidemia, and microalbuminuria, all of which are components of the cardiometabolic syndrome, contribute to

increased cardiovascular disease (CVD) in the United States.[1–3] In this context, there are an estimated 64.4 million people in the United States that have CVD.[1–4] The interaction of genetic, environmental, metabolic, cardiovascular, and renal abnormalities increase the risk of chronic kidney disease (CKD) and CVD end points, such as stroke, congestive heart failure, and overall mortality.[3–8]

In recent years, an epidemiologic relationship between insulin resistance (eg, prediabetes), as well as other cardiometabolic components, and microalbuminuria has been established.[4,8,9] There are now data that support a direct association between the cardiometabolic components and CKD, independent of the contribution of diabetes alone.[10] An analysis of data from the National Health and Nutrition Examination Survey (NHANES) III in patients at least 20 years or older indicates that an increasing number of components was associated with increasing risk for CKD and microalbuminuria.[4] Furthermore, a recent report from the Atherosclerosis Risk in Communities (ARIC) study demonstrated a significant relationship between components of the cardiometabolic syndrome and CKD, independent of the presence of diabetes mellitus or hypertension.[8]

There is little information, however, on the relationship between stages of dysglycemia (normoglycemia, prediabetes, or overt diabetes) or serum levels of glucose and individual and composite components of the cardiometabolic syndrome with stage 3 to 5 CKD and/or CVD. Therefore, we sought to investigate the relationship between dysglycemia and cardiometabolic components for CKD and CVD in National Kidney Foundation (NKF) Kidney Early Evaluation Program (KEEP) participants, a highly representative CKD patient population. Individuals were identified by Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) criteria (dysglycemia, hypertension, dyslipidemia) and WHO criteria (obesity and proteinuria).

METHODS

NKF KEEP

The KEEP is a free community-based health screening program that targets a population of patients 18 years and older with a history of diabetes or hypertension or a first-order relative with diabetes, hypertension, or kidney disease. KEEP was officially launched in August of 2000. The KEEP database has been fully described in previous reports.[11,12]

From August 2000 through December 31, 2006, there was a total of 73,365 participants eligible for this study. After selecting individuals with measured fasting lipid panels and excluding individuals with missing data values for metabolic risk factors, the total study sample size was 26,992. The final sample size included in multivariate logistic regression was 24,118 after further excluding missing values in age, sex, race, education, and tobacco and alcohol use.

Definitions

Estimated glomerular filtration rate GFR (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) study equation[13] and serum creatinine was calibrated by the Cleveland Clinic Research Laboratory. Albumin to creatinine ratios were calculated from urine samples and recorded as <30 mg/g, 30 to 300 mg/g, or >300 mg/g. CKD was defined by an eGFR <60 mL/min/1.73 m^2. CVD was recorded as the composite of self-reported myocardial infarction, coronary artery bypass graft surgery, congestive heart failure (CHF), arrhythmia, or stroke.

The definitions included (1) dysglycemia: a fasting blood glucose (sugar) level >109 mg/dL (ATP III criteria) or a self-reported history of hyperglycemia, diabetes mellitus, or patients taking glucose-lowering medications; (2) hypertension: average systolic blood pressure >129 mm Hg or diastolic blood pressure >84 mm Hg (ATP III criteria) or a self-reported history of hypertension or patients taking blood pressure–lowering medication; (3) obesity: body mass index ≥ 30 kg/m^2 (WHO criteria); (4) dyslipidemia: triglyceride level >150 mg/dL or cholesterol >200 mg/dL (ATP III criteria); and (5) proteinura: albumin:creatinine ratio >29 mg/g (WHO criteria). Diabetes was defined as self-reported diabetes mellitus, retinopathy, and taking diabetic medications (including insulin). Prediabetes was defined as a fasting glucose >109 mg/dL among self-reported nondiabetics (per above). Total number of the components of the cardiometabolic syndrome (CMS) was also calculated for each individual.

Statistical Analysis

In addition to the univariate logistic regressions on the prevalence of CKD (eGFR <60 mL/min/1.73 m^2) and CVD for each risk factor, we also performed multivariate logistic regressions in estimating the individual associations with CKD and CVD and controlling for risk factors including age, sex, race, education and tobacco and alcohol use.

The multivariate regressions were also stratified by diabetes and level of glucose for the prevalence of CKD and CVD. To select the most important risk factor among the components of CMS in association with CVD events with multivariate adjustment, we performed forward selection analyses with multivariate logistic regressions using 2 criteria: −2 log likelihood and Wald chi-square value.

RESULTS

The eligible sample size included 26,992 participants (Table I). Of those participants, 20,062 (74.3%) were found to have hypertension or reported a history of hypertension or taking antihypertensive medications; 17,033 (63.1%) were found to have dyslipidemia or reported a history of taking medications for high cholesterol; 8720 (32.3%) with dysglycemia were found to have fasting hyperglycemia or reported a history of hyperglycemia or taking insulin or hypoglycemic medications; 11,823 (43.8%) had a body mass index of $\geq$30 kg/m^2; and 2908 (10.8%) had proteinuria. By number of CMS components, 1827 (6.8%) participants had no components, 5275 (19.5%) had 1 component, 8730 (32.3%) had 2 components, 7387 (27.4%) had 3 components, 3215 (11.9%) had 4 components, and 558 (2.1%) had 5 components of the CMS.

On forward selection analysis, the presence of dysglycemia was identified as the most important metabolic risk factor for prevalent CVD. Among the participants, there were 18,272 with normoglycemia, 7912 with overt diabetes, and 802 with prediabetes (Table II). We found similar demographic trends in the percentages of participants between those with diabetes, prediabetes, and normoglycemia in regards to age, sex, race, and education. Glycemia and triglyceride levels were increased in the diabetic population compared with their prediabetic and normoglycemic counterparts.

Among the participants, dysglycemia, hypertension, proteinuria, dyslipidemia, and obesity were associated with prevalent CKD on multivariate analysis (odds ratio [95% confidence interval]: 1.08 [1.01–1.17]; 1.40 [1.27–1.55]; 2.09 [1.89–2.31]; 1.23 [1.14–1.33]; and 1.29 [1.20–1.39], respectively) (Table III). Dysglycemia, hypertension, dysglycemia, proteinuria, and obesity conferred an increased odds for self-reported CVD (1.52 [1.43–1.62]; 1.43 [1.32–1.55]; 1.52 [1.39–1.67]; 1.15 [1.08–1.22], respectively). After adjustment on multivariate analysis, having 2, 3, 4, or 5 components of the cardiometabolic syndrome was associated with a graded increased prevalence of CKD. Having 3, 4, or 5 components of the cardiometabolic syndrome was associated with an increased prevalence of CVD.

In those participants with either normoglycemia, prediabetes, and diabetes there was a graded trend on univariate analysis with increasing components of the cardiometabolic syndrome and prevalent CKD (Table IV). After adjusting on multivariate analysis, there was still a graded trend in those having 2 to 4 components on multivariate analysis in all 3 groups, but significantly in the normoglycemic and diabetic groups. This trend continued with stages of dysglycemia and associated prevalent CKD between the two groups. However, conclusions in the prediabetic group may be limited due to the sample size. A similar graded relationship was observed in the diabetic group on prevalent CVD on univariate and multivariate analysis with increasing components and having 2 to 4 components of the cardiometabolic syndrome and prevalent CVD.

The graded association between increasing stage of dysglycemia held true with levels of glycemia. There was an increasing percent of CKD and CVD in study participants with increasing glucose level up to 160 mg/dL, with a prevalent CVD increasing at >140 mg/dL (Table V). However, increased prevalent CKD was only increased at glucose levels >180 mg/dL (1.18 [1.04–1.34]) after adjustments on multivariate analysis.

DISCUSSION

In this report of KEEP, we sought to determine the collective risk that multiple metabolic risk factors convey in a targeted CKD cohort on prevalent CKD stages 3 to 5 and CVD. Our observations are consistent with previous reports from KEEP and other reports regarding CVD prevalence in the CKD state.[7,14] Our observation that dysglycemia was the most significant factor for increased CKD and CVD prevalence is particularly pertinent. Further, our data suggest that, with increasing stage of dysglycemia (normoglycemia, prediabetes, vs overt diabetes) and level of glycemia there was an associated increased likelihood of CKD and CVD, is novel. Our data further complement previous investigations utilizing general population screenings such as the NHANES,[4,15,16] and extend our knowledge by demonstrating that the presence of multiple metabolic risk factors ($\geq$3) is required to increase prevalent CVD in those with diabetes and CKD. Our analysis is particularly comprehensive and novel due to the generalizable data of the KEEP

Table I. Baseline Characteristics of KEEP Participants (N=26,992)

							No. of Risk Factors				
	Control	Dysglycemia	Hypertension	Proteinuria	Dyslipidemia	Obesity[a]	1	2	3	4	5
No.	1827	8720	20,062	2908	17,033	11,823	5275	8730	7387	3215	558
Age, mean, y	41.1	59.0	57.9	58.3	55.9	53.6	51.0	56.4	57.1	58.3	58.4
Sex, %											
Male	21.6	32.2	33.5	32.5	31.0	27.9	32.8	32.5	31.5	29.2	32.3
Race, %											
White	50.0	51.3	53.2	46.8	55.3	48.5	52.8	53.0	51.2	53.8	48.4
Black	26.8	30.7	32.3	33.5	27.0	37.1	27.7	30.9	32.9	31.2	33.5
Other	23.2	18.0	14.6	19.7	17.8	14.4	19.5	16.1	15.9	15.0	18.1
Hispanic	13.1	10.7	9.4	11.5	11.9	10.9	12.0	10.1	10.7	10.5	12.7
Non-Hispanic	85.5	89.3	90.6	88.5	88.1	89.1	88.0	89.9	89.3	89.6	87.3
Socioeconomic characteristic, %											
>High school education	74.0	53.5	56.8	51.7	57.8	57.4	65.9	59.6	55.8	51.0	49.1
Current tobacco use	11.4	10.0	10.1	12.3	11.1	10.1	12.2	10.8	9.7	10.4	11.5
Current alcohol use	68.0	54.3	58.7	55.7	60.2	58.7	63.6	61.6	58.0	53.6	52.0
Clinical measures											
Systolic BP, mm Hg	111.8	135.6	138.8	140.0	134.1	135.6	123.7	133.8	137.9	140.7	145.7
Diastolic BP, mm Hg	70.2	78.5	81.7	80.8	80.0	81.4	75.6	79.8	81.7	81.7	82.1
Triglycerides, mg/dL	80.1	179.5	166.8	181.2	198.0	175.5	114.4	148.7	184.1	223.5	262.5
Total cholesterol, mg/dL	168.9	193.8	200.8	198.3	218.3	199.9	189.9	202.5	206.8	207.6	209.8
Glucose, mg/dL	96.0	147.3	119.8	140.5	119.0	123.6	101.5	109.0	121.1	152.0	182.6
Proteinuria, mg/g[b]											
BMI, kg/m^2	23.9	31.9	30.9	31.0	30.4	36.1	26.1	28.8	33.0	35.6	37.4
eGFR, mL/min/1.73 m^2	89.1	77.3	77.0	73.1	77.4	79.9	82.9	78.3	77.7	75.8	69.6

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate. Data are reported as means or percent (%) as indicated. Most missing values are due to missing dyslipidemia, which is available starting 2005. [a]Body mass index (BMI) ≥30 kg/m^2. [b]Not available to calculate mean values.

Table II. Baseline Demographics of KEEP Participants by Stage of Dysglycemia (N=26,992)

	Normoglycemic	Prediabetes	Diabetes
No.	18,272	802	7918
Age, mean, y	52.8	57.2	59.2
Sex, %			
Male	30.7	31.8	32.2
Race, %			
White	52.7	45.6	51.8
Black	30.6	33.4	30.4
Other	16.7	21.0	17.7
Hispanic	11.1	11.7	10.6
Non-Hispanic	88.9	88.3	89.4
Socioeconomic characteristic, %			
>High school education	62.4	50.8	53.8
Current tobacco use	11.2	11.0	9.9
Current alcohol use	63.2	56.7	54.1
Clinical measures			
Systolic BP, mm Hg	131.1	136.0	135.6
Diastolic BP, mm Hg	79.5	81.6	78.2
Triglycerides, mg/dL	148.2	148.3	182.6
Total cholesterol, mg/dL	202.5	208.5	192.3
Glucose, mg/dL	101.9	127.5	149.3
Proteinuria, mg/g[a]			
BMI, kg/m^2	29.2	30.3	32.0
eGFR, mL/min/1.73 m^2	80.2	80.5	77.0

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; KEEP, Kidney Early Evaluation Program. Values are expressed as means or percent. Body mass index (BMI) $\geq$30 kg/m^2. [a]Not available to calculate mean values.

Table III. Logistic Regressions for CKD and CVD Based on Metabolic Components

	CKD		CVD	
Variables	Univariate	Multivariate	Univariate	Multivariate
Metabolic components				
Dysglycemia	1.45 (1.35–1.55)	1.08 (1.01–1.17)	1.79 (1.69–1.90)	1.52 (1.43–1.62)
Hypertension	2.55 (2.33–2.8)	1.4 (1.27–1.55)	2.10 (1.95–2.27)	1.43 (1.32–1.55)
Proteinuria	2.36 (2.16–2.59)	2.09 (1.89–2.31)	1.69 (1.55–1.86)	1.52 (1.39–1.67)
Dyslipidemia	1.37 (1.28–1.47)	1.23 (1.14–1.33)	0.941 (0.89–1.00)	0.85 (0.8–0.91)
Obesity	1.01 (0.94–1.08)	1.29 (1.2–1.39)	1.04 (0.98–1.10)	1.15 (1.08–1.22)
Increasing components				
Control	1	1	1	1
One	1.88 (1.53–2.31)	1.05 (0.84–1.31)	1.41 (1.22–1.64)	0.99 (0.85–1.15)
Two	2.83 (2.33–3.45)	1.25 (2.33–3.45)	1.85 (1.61–2.13)	1.10 (0.95–1.27)
Three	3.22 (2.64–3.92)	1.44 (2.64–3.92)	2.06 (1.78–2.37)	1.22 (1.05–1.41)
Four	4.41 (3.59–5.43)	1.9 (1.52–2.37)	2.88 (2.47–3.35)	1.64 (1.40–1.93)
Five	7.64 (5.86–9.94)	3.65 (2.75–4.83)	3.84 (3.07–4.80)	2.27 (1.80–2.86)

Values are expressed in odds ratios (95% confidence intervals). Each metabolic risk factor for either chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) or cardiovascular disease (CVD) (recorded as the composite of self-reported MI, CABG, CHF, arrhythmia, or stroke) on crude (univariate) and adjusted (multivariate) analysis. N=24,118 after excluding missing values in age, sex, race, education and tobacco and alcohol use. On forward selection analysis, dysglycemia was the most important risk factor for CVD (highest Wald chi-square statistic) in patients with an eGFR <60 mL/min/1.73 m^2. Thereby risk components are presented in order of importance and depict increasing risk factor and collective odds for eGFR <60 mL/min/1.73 m^2 and CVD.

screening that other study populations (eg, NHANES and Atherosclerosis Risk in Communities [ARIC] study) have not been able to attain.

It is widely accepted that type 2 diabetes and hypertension are risk factors for CVD and progression of CKD.[6,7] The current report of the KEEP

Table IV. Logistic Regressions for CKD and CVD Based on Stages of Dysglycemia and Increasing Components of the Cardiometabolic Syndrome

	CKD		CVD	
Variables	Univariate	Multivariate	Univariate	Multivariate
Normoglycemia				
Control	1	1	1	1
1	1.94 (1.58–2.39)	1.1 (0.88–1.36)	1.4 (1.2–1.63)	0.98 (0.84–1.15)
2	2.91 (2.38–3.55)	1.36 (1.1–1.68)	1.73 (1.49–1.99)	1.05 (0.9–1.22)
3	3.13 (2.55–3.85)	1.64 (1.32–2.04)	1.65 (1.41–2.31)	1.04 (0.89–1.22)
4	4.56 (3.31–6.29)	2.76 (1.96–3.89)	1.72 (1.28–2.31)	1.14 (0.84–1.55)
Prediabetes				
Control	1	1	1	1
1	3.25 (0.41–25.59)	2.36 (0.26–21.37)	1.68 (0.6–4.66)	1.32 (0.45–3.87)
2	5.06 (0.67–38.05)	3.32 (0.39–28.45)	1.89 (0.71–5.08)	1.34 (0.48–3.79)
3	7.95 (1.06–59.86)	7.14 (0.83–61.79)	1.65 (0.6–4.51)	1.15 (0.4–3.29)
4	10.67 (1.14–99.46)	10.42 (0.92–118.22)	0.62 (0.11–3.56)	0.44 (0.07–2.64)
Diabetes				
Control	1	1	1	1
1	2.42 (1.53–3.82)	1.58 (0.98–2.57)	1.51 (1.13–2.04)	1.14 (0.84–1.55)
2	3.13 (2.01–4.88)	2.17 (1.36–3.47)	1.64 (1.24–2.18)	1.25 (0.93–1.67)
3	4.05 (2.59–6.31)	3.12 (1.95–10.54)	1.9 (1.43–2.52)	1.47 (1.09–1.97)
4	7.01 (4.37–11.26)	6.38 (3.86–10.54)	2.41 (1.74–3.35)	1.96 (1.4–2.75)

Values are expressed in odds ratios (95% confidence intervals). Analysis excludes diabetes from metabolic components. Stratification of dysglycemia into normoglycemia (N=16,394), prediabetes (n=709), and diabetes (n=7015) for chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) or cardiovascular disease (CVD) (recorded as the composite of self-reported myocardial infarction, coronary artery bypass graft surgery, congestive heart failure, arrhythmia, or stroke) on crude (univariate) and adjusted (multivariate) analysis. N=24,118 after excluding missing values in age, sex, race, education, and tobacco and alcohol use.

Table V. Logistic Regressions for Level of Glycemia and CKD and CVD

	CKD		CVD	
Glucose level, mg/dL	No. (% CKD)	Multivariate	No. (% CVD)	Multivariate
<110	14,900 (16.0)	1.00 (ref)	2378 (33.2)	1.00 (ref)
110 to <126	3763 (18.0)	0.97 (0.87–1.07)	677 (39.3)	1.18 (0.98–1.41)
126 to <140	1448 (20.9)	1.06 (0.92–1.22)	303 (39.9)	1.18 (0.92–1.52)
140 to <160	1181 (23.7)	1.16 (0.998–1.35)	280 (44.6)	1.40 (1.09–1.82)
160 to <180	705 (21.3)	0.96 (0.79–1.17)	150 (50.0)	1.66 (1.18–2.33)
≥180	1795 (22.0)	1.18 (1.04–1.34)	394 (45.9)	1.58 (1.27–1.98)

Values are expressed as odds ratio (95% confidence intervals) and are adjusted for age, sex, race, education, smoking, and drinking status. Percent of chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) (N=23,792) and cardiovascular disease (CVD) (recorded as the composite of self-reported myocardial infarction, coronary artery bypass graft surgery, congestive heart failure, arrhythmia, or stroke) (N=4182).

indicates that 2 other metabolic risk components, obesity and dyslipidemia, are also important for CVD and CKD.[1–4] Our finding that dysglycemia is the principal component to drive increased CKD and CVD prevalence extends our understanding of the relationship between metabolic risk and CKD. Importantly, we report a graded relationship between increasing stage of diabetes (normoglycemia, prediabetes, and overt diabetes) and increasing components of the cardiometabolic syndrome and CKD. Prevalent CVD was only increased in patients with overt diabetes. In addition, there was a graded relationship with increasing glycemia and prevalent CVD up to >160 mg/dL, while glycemia >180 mg/dL was associated with prevalent CKD.

The development of obesity is one of the principle contributors to insulin resistance and has long been thought to contribute to kidney disease.[17]

Indeed, increases in body mass index are associated with a reduced eGFR and CKD.[18,19] Thus our finding that dysglycemia, and not obesity, (ie, the last risk factor selected on forward selection analysis) support recent observations[15] and extend our understanding of the seminal importance of insulin resistance in context of metabolic risk for CKD and CVD.

The presence of insulin resistance has been associated with CKD in general population observational studies. In a study of 6453 nondiabetic NHANES III participants, risk for CKD increased as serum insulin, serum C-peptide, glycated hemoglobin A_{1c}, and insulin resistance increased.[15] In further evaluating the association between insulin resistance and CKD in NHANES, investigators examined this association in more than 6000 US adults. Each element of the cardiometabolic syndrome was noted to be associated with increased prevalence of CKD. The data also revealed a graded relationship between the number of risk factors present and the corresponding prevalence of CKD or microalbuminuria.[4] Additional evidence from a cohort including 10,096 nondiabetic patients with normal baseline kidney function in the ARIC study demonstrated that patients with metabolic risk factors have a likelihood for developing CKD.[8] Furthermore, after adjustment for the subsequent development of diabetes and hypertension during the 9 years of follow-up, participants at baseline still had a greater risk of developing CKD compared with those without it.

Our finding that the association between dysglycemia and CKD was increased with advancing stage of dysglycemia (normoglycemia to overt diabetes) and level of glycemia is novel in the metabolic literature. Thus, the composite findings from the current analysis of KEEP and prior reports of ARIC and NHANES show a strong and progressive relationship between increasing dysglycemia, cardiometabolic components, and CKD. Further, the current analysis of the KEEP database extends prior observations in demonstrating that multiple cardiometabolic components are strongly associated with an increased risk for CKD stage 3 to 5 and prevalent CVD in a targeted CKD cohort.

Another key observation is that a fasting glucose >140 mg/dL portended a greater prevalent CVD in those with an eGFR <60 mL/min/m^2. It is now largely accepted that tight glycemic control in patients with both type 1 and type 2 diabetes reduces the risk of developing microvascular complications in the general population.[17,20] Observational studies suggest that tighter glycemic control is associated with a reduced risk of these outcomes.[21–23] However, there are few data regarding glycemic control and CVD risk in the CKD stage 3 to 5 population.

CONCLUSIONS

The presence of increased multiple metabolic risks are associated with CKD stage 3 to 5 and CVD. Moreover, dysglycemia predicts CKD (eGFR <60 mL/min/1.73 m^2) and CVD and glucose levels >160 mg/dL are associated with an increased CVD and >180 mg/dL CKD prevalence. Because of the well-described association of the cardiometabolic syndrome and CKD in general population studies, our finding of increasing dysglycemia and metabolic components with CKD and CVD is particularly important within a targeted CKD population.

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