EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

Cystatin C– and Creatinine-Based Estimated Glomerular Filtration Rate, Vascular Disease, and Mortality in Persons With Diabetes in the U.S.

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OBJECTIVE

Serum cystatin C is an alternative to serum creatinine for estimating glomerular filtration rate (GFR), since cystatin C is less influenced by age and muscle mass. Among persons with diabetes, we compared the performance of GFR estimated using cystatin C (eGFR$_{cys}$) with that using creatinine (eGFR$_{cr}$) for the identification of reduced kidney function and its association with diabetes complications.

RESEARCH DESIGN AND METHODS

We analyzed data from adult participants from the 1999–2002 National Health and Nutrition Examination Survey with available cystatin C (N = 4,457). Kidney function was dichotomized as preserved (eGFR ≥60 mL/min/1.73 m^2) or reduced (eGFR <60 mL/min/1.73 m^2) using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C and the 2009 CKD-EPI creatinine equations.

RESULTS

Among 778 persons with diabetes, the prevalence of reduced kidney function was 16.5% using eGFR$_{cr}$ and 22.0% using eGFR$_{cys}$. More persons with diabetes were reclassified from preserved kidney function by eGFR$_{cr}$ to reduced kidney function by eGFR$_{cys}$ than persons without diabetes (odds ratio 3.1 [95% CI 1.9–4.9], $P <$ 0.001). The associations between lower eGFR and higher prevalence of albuminuria, retinopathy, peripheral arterial disease, and coronary artery disease were robust regardless of filtration marker. Similarly, the risk of all-cause mortality increased with lower eGFR$_{cr}$ and eGFR$_{cys}$. Only lower eGFR$_{cys}$ was significantly associated with cardiovascular mortality.

CONCLUSIONS

More persons with diabetes had reduced kidney function by eGFR$_{cys}$ than by eGFR$_{cr}$, and lower eGFR$_{cys}$ was strongly associated with diabetes complications. Whether eGFR$_{cys}$ is superior to eGFR$_{cr}$ in approximating true kidney function in a diabetic population requires additional study.

Diabetes is the leading cause of chronic kidney disease (CKD) in developed countries, including the U.S. (1,2). Diabetic kidney disease accounts for 40% of prevalent CKD and 50% of incident end-stage renal disease, and it has increased in direct proportion to the increasing prevalence of diabetes (2–4). People with diabetes often suffer from microvascular and macrovascular complications, including retinopathy, nephropathy, coronary artery disease, peripheral arterial disease, and stroke, as well as early mortality (5,6). Compared with persons with diabetes and preserved kidney function, those with diabetes and CKD face even higher risks of morbidity and mortality. Indeed, both reduced kidney function and albuminuria are independent predictors for cardiovascular disease as well as all-cause mortality (7,8). Accurate estimation of glomerular filtration rate (GFR) and identification of CKD are important.

In clinical practice, kidney function is estimated rather than measured. Glomerular filtration rate estimated using serum creatinine (eGFR$_{cr}$) is the most common approach; however, creatinine is influenced by age, muscle mass, sex, and race (9). Given these limitations, serum cystatin C has been proposed as an alternative filtration marker (10). Cystatin C, an endogenous protein believed to be produced by all nucleated cells, is less affected by age, race, and muscle mass and, in the general population, associates more strongly with all-cause and cardiovascular mortality than does serum creatinine (11,12). However, BMI, diabetes, and inflammation may affect cystatin C levels independent of kidney function (13). Given the high prevalence of obesity in the population with diabetes, as well as the suggestion that cystatin may perform differently in patients with diabetes, there is controversy as to whether cystatin C–based or creatinine-based estimated GFR (eGFR) equations should be used to estimate kidney function in this population (14,15). Furthermore, it is unknown whether the associations of diabetes complications with kidney function estimated using cystatin C (eGFR$_{cys}$) are similar to those observed using eGFR$_{cr}$.

Using nationally representative data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES), we estimated the prevalence of reduced kidney function (eGFR <60 mL/min/1.73 m^2) among persons with diabetes using the 2012 CKD-EPI cystatin C (16) and 2009 CKD-EPI creatinine (17) equations and investigated the discordance in CKD classification by the two filtration markers. We also compared the associations of eGFR$_{cr}$ and eGFR$_{cys}$ with prevalent complications of diabetes, including albuminuria, peripheral arterial disease, retinopathy, and coronary artery disease, as well as incident all-cause and cardiovascular mortality.

RESEARCH DESIGN AND METHODS

Study Population
NHANES is an ongoing cross-sectional, multistage, stratified, clustered probability sample of the U.S. civilian noninstitutionalized population conducted by the National Center for Health Statistics. Cystatin C concentrations were measured in a subsample of the NHANES 1999–2002 participants aged 12 years and older who were not missing serum creatinine (18). For the current study, we included all participants in the cystatin C subsample aged 20 years or older (N = 4,457; 778 of whom had diabetes). The ankle-brachial index (ABI), used to define peripheral arterial disease, was measured only in persons aged 40 years or older (N = 556 of the 778 participants with diabetes, 10 of whom with ABI >1.5 were excluded owing to concern for calcified atherosclerosis) (19,20).

Assessment of Diabetes and Kidney Function
We classified persons as having diabetes if they reported a physician diagnosis of diabetes, took antidiabetes pills or insulin injections, or had a glycated hemoglobin (HbA$_{1c}$) value of ≥6.5%. No distinction was made with regard to type of diabetes. Preserved/reduced kidney function was defined as eGFR ≥60 mL/min/1.73 m^2 / eGFR <60 mL/min/1.73 m^2, estimated using standardized creatinine and cystatin C values and the CKD-EPI 2009 and 2012 equations, respectively (16,17). The term

"advanced CKD" was used to indicate CKD stage 4 or 5 (eGFR <30 mL/min/1.73 m^2). Creatinine values from NHANES 1999–2000 were standardized [standard creatinine (mg/dL) = 0.147 + 1.013 × (NHANES 1999–2000 uncalibrated serum creatinine [mg/dL]), whereas no correction to the creatinine values in the 2001–2002 survey was needed (21,22). Cystatin C values were recalibrated and standardized to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standard: IFCC standard cystatin C (mg/L) = 1.12 × (cystatin C [mg/L] − 0.12) (22).

Other Variables of Interest
Hypertension was defined as mean systolic pressure ≥140 mmHg, mean diastolic pressure ≥90 mmHg, self-reported hypertension, or the use of an antihypertensive medication. Hyperlipidemia was defined as total cholesterol concentration ≥200 mg/dL. Low HDL was defined as serum HDL <40 mg/dL. Information on age, sex, race, and smoking was self-reported. Smoking status was determined using answers to the questions, "Have you smoked at least 100 cigarettes in your life?" and "Do you now smoke cigarettes?"

Prevalent Micro- and Macrovascular Outcomes
Coronary artery disease was defined on the basis of a self-reported history of coronary heart disease, angina, or previous heart attack. Albuminuria was defined as a urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g. Peripheral arterial disease was defined by an ABI <0.90 in either leg (23). Diabetic retinopathy was self-reported ("Has a doctor ever told you that diabetes has affected your eyes or that you had retinopathy?").

Mortality Follow-up
Information on all-cause and cardiovascular mortality was obtained using the linkage of NHANES data to death certificate data from the National Death Index (24). The underlying cause of death was coded according to the ICD-10. Outcomes of interest included all-cause and cardiovascular (ICD-10 code I00–I78) mortality. Length of follow-up for each participant was calculated as the date of

the NHANES examination to date of death or 31 December 2006 (whichever occurred first).

Statistical Analyses

All statistical analyses incorporated modified sampling weights, primary sampling units, and strata specific to the sample with available cystatin C in order to generate nationally representative estimates of the U.S. population (18). SEs were estimated using the Taylor series (linearization) method. Kidney function was analyzed both as a continuous measure using restricted cubic splines and as a categorical measure according to K/DOQI classification (eGFR <15, 15–29, 30–59, 60–89, and 90–200 mL/min/1.73 m^2) for both eGFR$_{cr}$ and eGFR$_{cys}$. Individuals with eGFR values >200 mL/min/1.73 m^2 were reassigned a value of 200 mL/min/1.73 m^2 (two persons with eGFR$_{cr}$ >200 mL/min/1.73 m^2).

Modified Poisson regression models were used to examine the relationship of eGFR with the prevalence of coronary artery disease, peripheral arterial disease, albuminuria, and retinopathy (25). Associations of eGFR and mortality were examined using multivariable Cox proportional hazards models. The proportional hazards assumption was tested using log-log plots by category of eGFR. All multivariable models were adjusted for age (years), female sex (yes, no), and race (non-Hispanic black, non-Hispanic white, Hispanic, other) as well as current smoking status (current, former, never), BMI (measured as weight in kilograms divided by the square of height in meters), hypercholesterolemia (yes, no), low HDL (yes, no), hypertension (yes, no), coronary artery disease (yes, no), and albuminuria (yes, no; only in analyses where albuminuria was not the outcome). Given the possible relationship between cystatin C and obesity, interactions between BMI, eGFR$_{cys}$, and adverse outcomes were tested in multivariable models. All analyses were conducted using Stata, version 12 (Stata, College Station, TX).

RESULTS

Study Population

The prevalence of diabetes among U.S. adults was 8.2% (95% CI 7.4–9.0).

Persons with diabetes were older, more likely to be black, and more likely to be male than those without diabetes (Table 1). Persons with diabetes also had poorer lipid profiles. Two-thirds of persons with diabetes had hypertension, which was nearly twice as prevalent compared with those without diabetes (63.8% vs. 33.4%). There was also a substantial difference in the distribution of BMI: 50% of the U.S. population with diabetes had a BMI >30 kg/m^2 compared with 28% without diabetes, and 28% of persons with diabetes had a BMI ≥35 kg/m^2 compared with 12% of those without diabetes. The prevalence of reduced kidney function was almost three times higher in persons with diabetes compared with those without diabetes (eGFR$_{cr}$ 16.5% vs. 5.8%, eGFR$_{cys}$ 22.0% vs. 7.9%).

Prevalence of Reduced Kidney Function in Persons With Diabetes by Filtration Marker

The trend of higher prevalence of reduced kidney function by eGFR$_{cys}$

persisted across subgroups of sex, race, age, and BMI (Supplementary Fig. 1). On the absolute scale, the discrepancy in eGFR$_{cys}$ versus eGFR$_{cr}$ was largest in older individuals. The absolute difference in reduced kidney function prevalence estimated by cystatin C versus creatinine was 6.9% in those aged 60–80 years and 10.3% in those aged 80 years and older. Similarly, the absolute difference was larger among persons with BMI >30 kg/m^2 (reduced kidney function by eGFR$_{cys}$ vs. eGFR$_{cr}$: 20.0% vs. 13.1%) than among those with BMI <30 kg/m^2 (reduced kidney function by eGFR$_{cys}$ vs. eGFR$_{cr}$: 21.3% vs. 16.9%).

Reclassification of Reduced Kidney Function by Filtration Marker

Discordance between eGFR$_{cr}$ and eGFR$_{cys}$ in the classification of reduced kidney function was 11.8% in persons with diabetes and 4.7% in persons without diabetes. In the population with diabetes, 10.4% of those classified as having preserved kidney function by eGFR$_{cr}$ (8.7% of the 83.6% with eGFR$_{cr}$

Table 1—Characteristics of U.S. adults aged ≥20 years by diabetes status: NHANES 1999–2002 cystatin C subsample (N = 4,457)

	No diabetes	Diabetes	P
n	3,679	778	
Age (years)	45.2 (0.4)	58.2 (1.1)	<0.001
Male, %	47.9 (1.2)	55.8 (3.2)	0.03
Race/ethnicity, %			<0.001
Non-Hispanic white	73.0 (2.1)	62.1 (3.8)	
Non-Hispanic black	10.2 (1.2)	17.2 (3.1)	
Mexican American	7.0 (0.9)	7.1 (1.5)	
Other	9.8 (1.9)	13.6 (3.6)	
Self-reported diabetes or medication use, %	—	79.5 (2.5)	
Hemoglobin A$_{1c}$ (mean, %)	5.3 (0.02)	7.7 (0.1)	<0.001
Hypertension, %	33.4 (1.4)	63.8 (3.8)	<0.001
Systolic blood pressure (mmHg), mean (SE)	122.8 (0.6)	132.9 (1.2)	<0.001
Diastolic blood pressure (mmHg), mean (SE)	72.2 (0.4)	71.0 (1.0)	0.3
BMI (kg/m^2), mean	27.8 (0.2)	31.6 (0.6)	<0.001
<25, %	37.7 (1.5)	18.6 (3.2)	<0.001
25–<30, %	34.2 (1.5)	31.4 (2.9)	
30–35, %	15.8 (0.7)	22.1 (2.8)	
>35, %	12.3 (1.1)	27.9 (3.2)	
Total cholesterol (mg/dL), mean (SE)	202.2 (1.2)	202.6 (2.8)	0.8
HDL (mg/dL), mean (SE)	51.5 (0.4)	45.7 (0.9)	<0.001
ACR (mg/g), mean (SE)	23.4 (3.0)	185.7 (30.3)	<0.001
eGFR$_{cr}$ (mL/min/1.73 m^2), mean (SE)	95.1 (0.6)	85.5 (1.7)	<0.001
eGFR$_{cys}$ (mL/min/1.73 m^2), mean (SE)	100.7 (0.8)	84.3 (2.6)	<0.001
eGFR$_{cr}$ <60 mL/min/1.73 m^2, %	5.8 (0.4)	16.5 (1.4)	<0.001
eGFR$_{cys}$ <60 mL/min/1.73 m^2, %	7.9 (0.6)	22.0 (2.1)	<0.001

$\geq$60 mL/min/1.73 m^2) were reclassified as having reduced kidney function by eGFR$_{cys}$ (Supplementary Table 1). In the population without diabetes, 3.6% of those classified as having preserved kidney function by eGFR$_{cr}$ (3.4% of the 94.2% with eGFR$_{cr}$ $\geq$60 mL/min/1.73 m^2) were reclassified as having reduced kidney function by eGFR$_{cys}$ (Supplementary Table 1). Within the overall population, diabetes status was significantly associated with reclassification from preserved kidney function by eGFR$_{cr}$ to reduced kidney function by eGFR$_{cys}$ (odds ratio [OR] 3.1 [95% CI 1.9–4.9], $P < 0.001$) (Supplementary Table 2). This association was attenuated but still significant after sequential adjustment for eGFR$_{cr}$ and BMI but not after further adjustment for age. In contrast, eGFR$_{cr}$, BMI, age, and albuminuria were all significantly associated with reclassification by eGFR$_{cys}$ in multivariable regression (eGFR$_{cr}$, OR 0.9 per 1 mL/min/1.73 m^2 increase, $P < 0.001$; BMI, OR 1.5 per 5 kg/m^2 increase, $P < 0.001$; age, OR 1.8 per decade increase, $P < 0.001$; ACR $>$30 mg/g, OR 2.2, $P = 0.01$).

Association of Kidney Function With Micro- and Macrovascular Complications by Filtration Marker

In the population with diabetes, the prevalence of albuminuria, retinopathy, coronary artery disease, and peripheral arterial disease was high, even among those with preserved kidney function (Fig. 1). The most common of these complications was albuminuria, present in 27.0% of those with eGFR$_{cr}$ $\geq$60 mL/min/1.73 m^2 and 55.9% of those with eGFR$_{cr}$ $<$60 mL/min/1.73 m^2. The prevalence of coronary artery disease, retinopathy, and peripheral artery disease was also two to three times higher among those with reduced kidney function than those with preserved kidney function. In general, the probability of microvascular and macrovascular complications increased with lower eGFR; above eGFR 90 mL/min/1.73 m^2, relationships between eGFR and vascular complications were more variable. The unadjusted relationships between eGFR, coronary artery disease, peripheral arterial disease, albuminuria, and retinopathy

were similar using eGFR$_{cr}$ and eGFR$_{cys}$, although there was suggestion of a "U-shape" (with higher risk at both higher and lower levels of GFR) in the association between albuminuria, retinopathy, and eGFR$_{cr}$ but not eGFR$_{cys}$ (Supplementary Fig. 2A–D).

After adjustment for demographic and traditional cardiovascular risk factors, the prevalence ratios for vascular complications (coronary artery disease, peripheral arterial disease, albuminuria, retinopathy) by eGFR category were similar using creatinine or cystatin C (Table 2). Compared with a reference group of eGFR 60–90 mL/min/1.73 m^2, persons with advanced CKD (eGFR 15–30 mL/min/1.73 m^2) had a higher prevalence of coronary artery disease, albuminuria, and retinopathy, regardless of filtration marker used. The adjusted relationships between eGFR category and peripheral arterial disease were similar in magnitude but not statistically significant. There were no significant interactions between BMI, eGFR$_{cys}$, and vascular complications.

All-Cause and Cardiovascular Mortality in Those With and Without Reduced Kidney Function

There were 153 deaths (63 from a cardiovascular cause) during a median follow-up of 5.3 years among the 778 participants with diabetes. The risk of both all-cause and cardiovascular mortality increased with lower eGFR, regardless of filtration marker used (Table 3). Compared with the reference group of eGFR 60–90 mL/min/1.73 m^2, persons with eGFR 15–30 mL/min/1.73 m^2 had a significantly higher risk of all-cause mortality (eGFR$_{cys}$, hazard ratio [HR] 3.8, $P = 0.007$; eGFR$_{cr}$, HR 2.6, $P = 0.04$). By contrast, eGFR 15–30 mL/min/1.73 m^2 was significantly associated with increased cardiovascular mortality when estimated by cystatin C (HR 5.3, $P = 0.007$) but not by creatinine (HR 2.0, $P = 0.3$). There were no significant interactions between BMI, eGFR$_{cys}$, and either all-cause or cardiovascular mortality.

CONCLUSIONS

This nationally representative study of persons with diabetes suggests that the use of cystatin C to estimate kidney function would result in a higher

prevalence of reduced kidney function than would estimates using serum creatinine. Reclassification from preserved kidney function using creatinine to reduced kidney function using cystatin C occurred more commonly among persons with diabetes than those without, but this observation was explained by differences in the distributions of eGFR, BMI, age, and albuminuria between the two populations: reclassification was significantly associated with lower eGFR$_{cr}$, higher BMI, older age, and ACR $>$30 mg/g. Lower eGFR as determined by either creatinine or cystatin was associated with higher odds of prevalent vascular complications; however, the shape of the relationship with albuminuria and retinopathy at higher levels of eGFR differed slightly by filtration marker in unadjusted analysis. Similarly, while low eGFR was robustly associated with all-cause mortality, only eGFR$_{cys}$ showed significant association with cardiovascular mortality.

Differences in eGFR$_{cr}$ and eGFR$_{cys}$ have been noted previously in the general population (26,27). In the U.S. noninstitutionalized civilian population, kidney function estimated using cystatin C resulted in a reduced kidney function prevalence of 8.7% compared with an estimated 6.5% using creatinine (26). In a cross-sectional study of 1,360 inhabitants of the Alpine region in Europe, Pattaro et al. (28) noted that the Lin concordance correlation coefficient of eGFR$_{cr}$ and eGFR$_{cys}$ was 0.56, with significant differences by age (0.57 in those $\geq$65 years old vs. 0.38 in those $<$65 years old) but not by diabetes status. Our results differ somewhat from those of this prior study; the presence of diabetes differentially affected kidney disease classification by eGFR$_{cr}$ and eGFR$_{cys}$, at least in univariable analysis—an observation that may be attributable to our larger sample size and distinct American population.

Neither creatinine nor cystatin C is a perfect marker of glomerular filtration; each has non-GFR determinants. Some have argued that neither marker can adequately estimate true GFR in persons with diabetes; however, this concern is primarily relevant for those
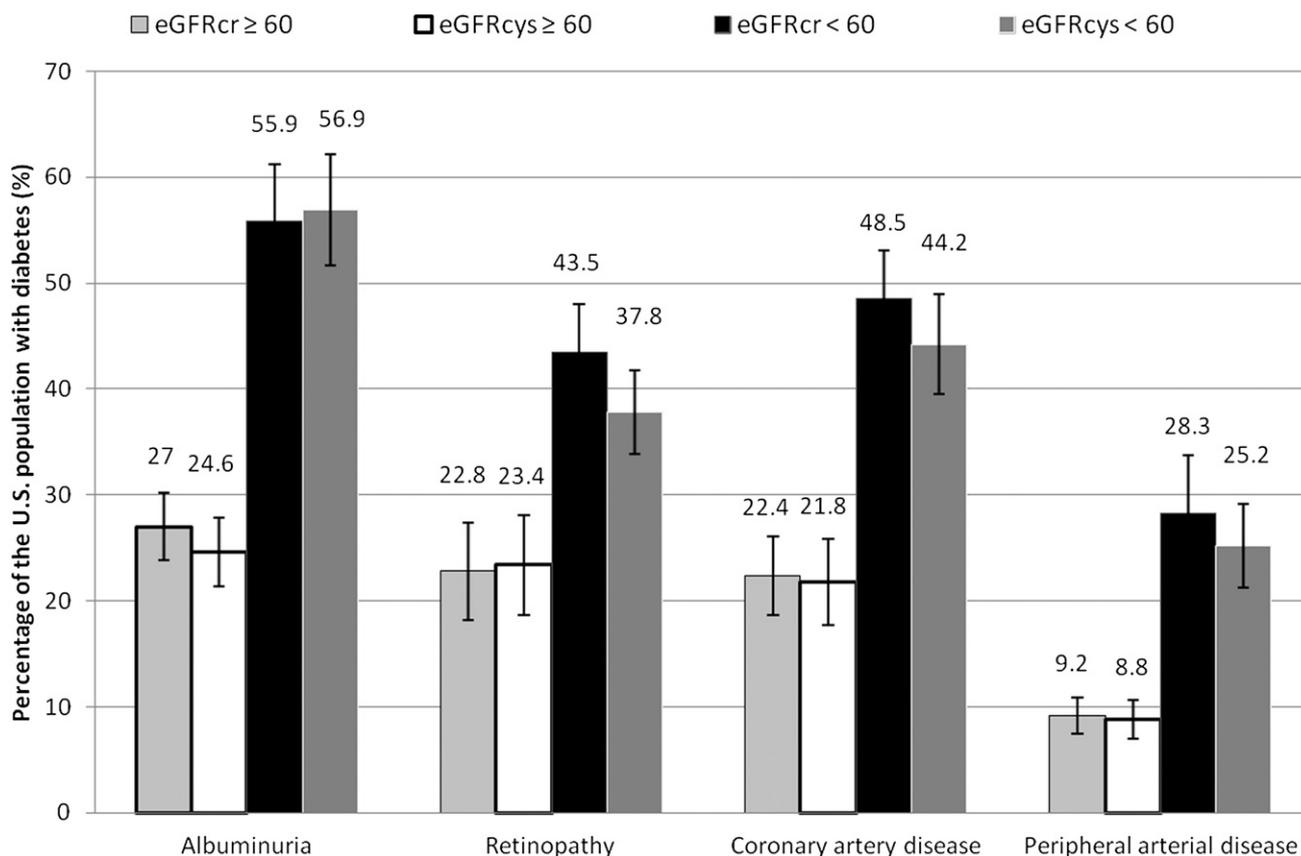
Figure 1—Prevalence of microvascular and macrovascular conditions among U.S. adults with diabetes according to the presence or absence of reduced kidney function (estimated using creatinine and cystatin C).

with high GFR—not reduced GFR as in the current study (29,30). The strong relationship between reclassification to reduced kidney function by eGFR$_{cys}$ and age may be due to inherent properties of the filtration markers. In the case of creatinine, muscle mass and diet are significantly associated with creatinine levels (31). Older persons may be sicker than their younger peers; thus, kidney function estimated using serum creatinine may be confounded by cachexia and muscle wasting. A similar explanation could apply to the differences seen with albuminuria (i.e., those with albuminuria are sicker than their peers without albuminuria). To our knowledge, the observation that reclassification by cystatin C occurs more frequently among those with albuminuria is novel; however, it is fully consistent with a recent study demonstrating that the decrement in eGFR$_{cys}$ associated with 24-h albuminuria >30 mg was greater than that of eGFR$_{cr}$ or measured GFR (27).

In the population with diabetes, both serum creatinine and cystatin C may have drawbacks. Serum creatinine may poorly estimate kidney function given

Table 2—Adjusted prevalence ratios (95% CI) for categories of kidney function with complications of diabetes, by filtration marker, among U.S. adults with diabetes (N = 778)*

	Coronary artery disease	Peripheral arterial disease**	Albuminuria†	Retinopathy
eGFR$_{cr}$ (mL/min/1.73 m^2)				
>90	1.1 (0.7–1.6)	0.9 (0.4–1.9)	0.97 (0.6–1.7)	1.8 (0.9–3.4)
60–90	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
30–60	1.4 (1.0–1.9)	1.7 (0.9–3.5)	1.7 (1.2–2.3)	1.9 (1.2–3.0)
15–30	2.8 (1.4–5.6)	2.7 (0.8–8.8)	2.3 (1.4–3.6)	3.9 (2.0–7.8)
eGFR$_{cys}$ (mL/min/1.73 m^2)				
>90	0.8 (0.4–1.5)	0.8 (0.3–2.1)	1.0 (0.6–1.7)	0.6 (0.3–1.4)
60–90	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
30–60	1.2 (0.8–1.6)	1.4 (0.7–2.8)	2.2 (1.5–3.2)	1.1 (0.6–1.9)
15–30	2.4 (1.4–4.1)	1.9 (0.5–7.3)	3.1 (2.0–4.8)	2.1 (1.2–3.9)

*All analyses adjusted for age, sex, race, hypercholesterolemia, low HDL, smoking, hypertension, BMI, and albuminuria, †except model of albuminuria. Insufficient numbers in eGFR <15 mL/min/1.73 m^2 category to accurately estimate. **Limited to adults aged ≥40 years with ABI measurements.

Table 3—Adjusted hazard ratios (95% CI) for categories of kidney function with all-cause and cardiovascular mortality, by filtration marker, among U.S. adults with diabetes (N = 778)*

	Number at risk	All-cause mortality (n = 153 events)	Cardiovascular mortality (n = 63 events)
eGFR$_{cr}$ (mL/min/1.73 m^2)			
>90	243	0.7 (0.2–3.5)	0.1 (0.0–0.8)
60–90	336	1.0 (ref.)	1.0 (ref.)
30–60	162	1.8 (1.0–3.2)	1.8 (0.6–5.4)
15–30	23	2.6 (1.1–6.4)	2.0 (0.5–7.9)
eGFR$_{cys}$ (mL/min/1.73 m^2)			
>90	241	0.5 (0.2–1.1)	0.7 (0.1–3.8)
60–90	289	1.0 (ref.)	1.0 (ref.)
30–60	191	1.5 (0.6–3.3)	1.3 (0.5–3.2)
15–30	39	3.8 (1.5–9.9)	5.3 (1.6–17.3)

*All analyses adjusted for age, sex, race, smoking, hypertension, coronary artery disease, hypercholesterolemia, low HDL, albuminuria, and BMI. Insufficient numbers in eGFR <15 mL/min/1.73 m^2 category to accurately estimate.

the tendency of persons with diabetes to have a lower than average muscle mass. Cystatin C may be directly affected by both BMI and diabetes (13,32,33). In obese individuals, cystatin C levels are higher, and eGFR$_{cys}$ significantly underestimates true kidney function (27,31). Indeed, our study suggests that much of the association between diabetes and cystatin C is driven by differences in the distribution of age and BMI. Additional work is needed to determine whether an approach using cystatin C or both filtration markers (the latter of which better approximates measured GFR in the overall population) would improve kidney function estimates in the population with diabetes (16).

Conventional wisdom is that, among persons with diabetes, kidney function decline and vascular complications go hand in hand. Certainly, our results support the association of prevalent complications with very low eGFR whether estimated by creatinine or cystatin C. Interestingly, in the upper ranges of preserved kidney function, the association between eGFR$_{cr}$ and retinopathy reversed, with higher levels of eGFR$_{cr}$ conferring increased odds of retinopathy, although this was not statistically significant in adjusted analysis. A similar pattern was seen in the univariate association of eGFR$_{cr}$ and albuminuria. These observations are consistent with previous studies demonstrating weaker-than-expected correlation between eGFR$_{cr}$,

albuminuria, and retinopathy (34). Because of the more monotonic relationship seen between eGFR$_{cys}$, albuminuria, and retinopathy, it is possible that kidney function based on cystatin C may prove a better predictor of diabetes complications than that based on creatinine. However, this may be more useful in defining a low-risk group than a high-risk group, given the larger differences in the upper ranges of eGFR. We also observed that the relationship between eGFR$_{cys}$ and all-cause and cardiovascular mortality was stronger than the corresponding relationship with eGFR$_{cr}$, similar to findings in the general population (11,12,35) and previous studies of persons with diabetes (36). Additional prospective studies are needed to determine whether eGFR$_{cys}$ provides better risk stratification for subsequent diabetes complications.

Our study has certain limitations. We relied on a single measurement of creatinine and cystatin; GFR is estimated from these filtration markers and not measured directly. As such, we cannot assess which filtration marker most closely approximates true kidney function. Additional research is needed to determine whether the confounding by age and BMI (or other unmeasured confounders such as thyroid disease) in diabetes favors eGFR$_{cr}$, eGFR$_{cys}$, or perhaps a combination of the two. Additionally, a single random sample of urine was used to quantify albuminuria. Next, despite being

nationally representative, the subset of NHANES with diabetes was relatively small, with a short duration of follow-up for mortality outcomes. Some of the vascular complications were self-reported, and insofar as reporting may vary by level of eGFR, this may lead to bias. Finally, persons with more severe kidney disease are likely underrepresented in NHANES, thus limiting accuracy in the very low ranges of GFR.

In summary, this study demonstrates that using cystatin C to classify kidney function among persons with diabetes results in a higher prevalence of reduced kidney function yet the same or stronger associations with vascular complications and mortality. Future studies are needed to determine whether incorporating cystatin C measurement into clinical care and kidney function estimation would improve outcomes in persons with diabetes.

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