Creatinine Excretion Rate and Mortality in Type 2 Diabetes and Nephropathy

Steef J. Sinkeler, md[1]
Arjan J. Kwakernaak, md[1]
Stephan J.L. Bakker, md, phd[1]
Shahnaz Shahinfar, md, phd[2]
Enric Esmatjes, md, phd[3]
Dick de Zeeuw, md, phd[4]
Gerjan Navis, md, phd[1]
Hiddo J. Lambers Heerspink, pharmd, phd[4]

OBJECTIVE—The creatinine excretion rate (CER) is inversely associated with mortality in the general and renal transplant population. The CER is a marker for muscle mass. It is unknown whether the CER is associated with outcome in diabetes. We therefore investigated whether the CER is a determinant of all-cause mortality in diabetic patients.

RESEARCH DESIGN AND METHODS—We used data from the combined Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) studies. A total of 1,872 patients (58% of the overall population) with type 2 diabetes and nephropathy with valid 24-h urinary creatinine excretion data were included. The primary end point of the analyses was all-cause mortality.

RESULTS—Mean age was 60 ± 8 years and median CER was 1,407 (total range 400–3,406) mg/day. Body surface area, hemoglobin, black race, and albuminuria were positive independent determinants of the CER, whereas female sex and age were inverse independent determinants of the CER. During a median follow-up of 36 (29–45) months, 300 patients died. In a Kaplan-Meier analysis of sex-stratified tertiles of the CER, risk for all-cause mortality increased with decreasing CER ($P < 0.001$). In a multivariable Cox regression analysis, lower CER (as a continuous variable) was independently associated with increased risk for all-cause mortality (hazard ratio 0.39 [95% CI 0.29–0.52], $P < 0.001$). Adjustment for potential collection errors did not materially change these associations.

CONCLUSIONS—Lower CER was strongly associated with increased all-cause mortality in patients with type 2 diabetes and nephropathy. As the CER can be considered a proxy for muscle mass, this puts renewed emphasis on physical condition and exercise in this population.

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Diabetes is associated with an increased risk for premature mortality and end-stage renal disease. This increased risk is particularly high in patients with overt diabetic nephropathy (1). Insulin resistance has been identified as one of the determinants of the increased risk for mortality (2).

Recent data show that a low creatinine excretion rate (CER) is independently associated with increased mortality in the general (3) and renal transplant population (4). The mechanisms underlying this association are probably multifactorial, but likely include the fact that the CER serves as a proxy for muscle mass (3,4). Muscle mass is associated with insulin sensitivity, physical activity, nutritional status, and BMI and, as such, is a possible determinant of risk for mortality and adverse events (5). Diabetes is a strong determinant of a reduced CER (5–8), but it is unknown whether a low CER is associated with mortality in diabetes. In the current study, we therefore investigated whether the CER is associated with all-cause mortality in patients with type 2 diabetes and nephropathy.

RESEARCH DESIGN AND METHODS

Study design

The current study is a post hoc analysis of the combined databases of the Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) studies. Both trials investigated the efficacy of angiotensin II receptor blocker (irbesartan in IDNT and losartan in RENAAL) on cardiorenal outcomes in patients with type 2 diabetes and nephropathy. The detailed design, rationale, and outcome parameters for these trials have been published previously (9,10).

Study participants

The combined database consists of a total of 3,228 adult patients with type 2 diabetes and nephropathy. The patient characteristics of both trials separately and of the combined database have been reported previously (11). Although there were minor differences in the inclusion criteria between both trials, the patient characteristics were generally similar. The mutual inclusion criteria were age between 30 and 70 years and the presence of diabetic nephropathy, defined as serum creatinine levels between 1.0 and 3.0 mg/dL and the presence of proteinuria. The presence of proteinuria was defined as a 24-h urinary protein excretion >500 mg or as a urinary albumin-to-creatinine ratio of >300 mg/g in the RENAAL trial, and as a 24-h urinary protein excretion of >900 mg in the IDNT trial. History of cardiovascular disease (CVD) was defined as a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischemic attack, or cerebrovascular accident. The exclusion criteria for both trials were type 1 diabetes and nondiabetic renal disease.

From the [1]Division of Nephrology, Department of Medicine, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [2]The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; the [3]Hospital Clinico y Provincial, Barcelona, Spain; and the [4]Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.
Corresponding author: Gerjan Navis, g.j.navis@umcg.nl.
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S.J.S. and A.J.K. contributed equally to this study.

Of all participants included in the RENAAL and IDNT trials, data on the CER were available in 2,360 patients. In the RENAAL trial, a single baseline 24-h urine collection was available, whereas in the IDNT trial, two 24-h urine collections were available. In the IDNT trial, we used the mean of the two 24-h urine collections. The coefficient of variation between the two 24-h urine collections for the CER of IDNT trial patients was 14%.

In the combined database, we excluded patients of non-Caucasian and nonblack race (Asian, $n = 126$; Hispanic, $n = 271$; other, $n = 71$) because the CER estimation formula, which we used in secondary analyses, was not validated in these subgroups (12). According to the literature (12), CER <350 or >3,500 mg/day was regarded as representing an inaccurate 24-h urine collection. These patients were also excluded from the analyses (CER <350, $n = 6$; CER >3,500, $n = 11$), leaving a total of 1,872 patients eligible for analyses.

Follow-up assessments and measurements

Urinary creatinine concentration was determined using the Jaffé colorimetric assay. The CER was calculated as urinary creatinine concentration multiplied by urine volume of the 24-h urine collection. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (13). BMI, as a measure of overall obesity, was calculated by dividing body weight by height squared (kg/m^2). Body surface area (BSA) was calculated using the DuBois and DuBois formula (14). Mean arterial pressure was calculated as diastolic pressure plus one-third of pulse pressure.

Outcome parameters

All-cause mortality was the primary end point for the present analyses. We also analyzed the association of the CER with cardiovascular and noncardiovascular mortality. End points were adjudicated by a blinded end-point committee using rigorous guideline definitions. The specific causes of cardiovascular and noncardiovascular death were not recorded.

Statistical analysis

Data with a normal distribution are presented as mean ± SD, and data with a skewed distribution are presented as median with interquartile range. Differences over sex-stratified tertiles of the CER were tested for statistical significance with one-way ANOVA for normally distributed variables, Kruskal-Wallis for skewed variables, and χ^2 test for categorical variables. Multivariable linear regression analyses were performed to study independent associations with the CER. In these analyses, age, sex, and race were forced into the models, because of their known relationship with the CER. Different models with the additional inclusion of BSA, BMI, or both height and weight combined were then built. In further models, variables with a $P < 0.10$ in univariate linear regression analyses for associations with the CER were selected for multivariate analysis. Initial prospective analyses were performed by means of a Kaplan-Meier plot of sex-stratified tertiles of the CER for mortality, and significance was assessed using the log-rank test. After this, univariable and multivariable Cox regression analyses were performed to further evaluate the association of the CER with mortality. For these analyses, the CER was log-transformed because the risk distribution appeared nonlinear. To allow for the assessment of the hazard ratio (HR) per doubling of the CER, log-transformation was performed according to the base of two. In sensitivity analyses, we defined two cutoff values (>50 or >30% deviation from estimated CER values) to determine the impact of stricter exclusion criteria for inaccurate 24-h urine collections (compared with the original CER of <350 mg/day or >3,500 mg/day) on the association of the CER with mortality. To allow for these secondary analyses, we used a recently developed CER estimation formula (12).

Statistical computations were performed using SPSS, version 18.0 software (SPSS, Inc., Chicago, IL). A P value of ≤0.05 was considered statistically significant.

RESULTS—The characteristics of the 1,872 patients included in the current study matched the characteristics of the overall RENAAL and IDNT population (Table 1). The mean age of patients included in the current study was 60 ± 8 years and the median CER was 1,407 (total range, 400–3,406) mg/day. Patients with the highest CER were younger, more often black, taller, and heavier, and thus had a higher BMI (Table 1). Patients with a higher CER also had lower systolic blood pressure (BP) but higher diastolic BP, higher hemoglobin levels, higher eGFR, diabetes for a relatively shorter amount of time, and less often a history of CVD. Albuminuria was positively associated with the CER.

We performed multivariable linear regression analyses to identify independent determinants of the CER (Table 2). The model with the best fit included BSA ($R^2 = 0.367$), whereas models including BMI ($R^2 = 0.330$) or both height and weight ($R^2 = 0.364$) had lower fits. BSA, hemoglobin, black race, and albuminuria were positive independent determinants of the CER, whereas female sex and age were inverse independent determinants of the CER.

During a median follow-up of 36 (29–45) months, 300 patients died (85 in RENAAL and 215 in IDNT). Of these, 177 deaths were classified as of cardiovascular origin. In a Kaplan-Meier analysis for sex-stratified tertiles of the CER, the risk for all-cause mortality increased according to decreasing CER ($P < 0.001$ across tertiles) (Supplementary Fig. 1).

In a univariate Cox regression analysis, survival worsened across decreasing tertiles of the CER (HR 1.56 [95% CI 1.13–2.16], $P = 0.006$ for the middle tertile vs. the highest tertile; 2.66 [1.98–3.57], $P < 0.001$ for the lowest tertile vs. the highest tertile). In multivariable Cox regression analyses for the CER as a continuous variable, the CER remained strongly and inversely associated with all-cause mortality, independent of body dimensions, classical cardiovascular risk factors, renal function, and diabetic parameters (Table 3). Furthermore, in the final model, the CER was independently and inversely associated with both cardiovascular (0.49 [0.33–0.73], $P < 0.001$) and noncardiovascular mortality (0.27 [0.17–0.42], $P < 0.001$).

In sensitivity analyses, we respectively excluded patients who deviated >50% or >30% from the estimated CER, as calculated by anthropometric data (12). If patients with a deviation of >50% from the estimated value of the CER ($n = 116$) were excluded, 1,756 patients remained for analysis. If patients with a deviation of >30% from the estimated value of the CER ($n = 450$) were excluded, 1,422 patients remained for analysis. Both exclusions did not materially change the association of the CER with all-cause mortality (full model HRs of 0.34 [95% CI 0.23–0.50], $P < 0.001$, and 0.36 [0.19–0.70], $P = 0.002$, respectively).

To visualize the number of patients at risk in relation to the risk for end points, the distribution of the CER as a histogram along with the curve showing HRs over

Table 1—*Characteristics of all RENAAL and IDNT study participants, characteristics of participants included in the current study, and characteristics of included participants according to sex-stratified tertiles of the CER*

Characteristics	Unit	Overall RENAAL and IDNT participants	Included in current analysis	Tertiles of CER			*P*
				Lowest	Middle	Highest	
		n = 3,228	*n* = 1,872	*n* = 624	*n* = 623	*n* = 625	
CER	mg/day	1,407 ± 655	1,450 ± 493	1,012 ± 239	1,412 ± 234	1,926 ± 444	<0.001
Demographics							
Male (%)	*n* (%)	2,096 (65)	1,252 (67)	418 (67)	418 (67)	419 (67)	—
Age	years	59 ± 8	60 ± 8	61 ± 7	60 ± 7	58 ± 8	<0.001
Black race (%)	*n* (%)	458 (14)	354 (19)	74 (14)	92 (15)	178 (29)	<0.001
Body composition							
Height	m	1.67 ± 0.1	1.69 ± 0.1	1.66 ± 0.1	1.69 ± 0.1	1.71 ± 0.1	<0.001
Weight	kg	85 ± 20	89 ± 19	81 ± 17	89 ± 18	97 ± 19	<0.001
BMI	kg/m^2	30.3 ± 6.0	31.2 ± 5.9	29.1 ± 5.4	31.2 ± 5.7	33.2 ± 5.7	<0.001
BSA	m^2	1.93 ± 0.25	1.98 ± 0.23	1.88 ± 0.22	1.98 ± 0.22	2.08 ± 0.22	<0.001
Cardiovascular risk factors							
Diabetes duration >5 years (%)	*n* (%)	2,903 (90)	1,675 (89)	562 (90)	573 (92)	539 (86)	<0.001
History of CVD (%)	*n* (%)	795 (25)	490 (26)	183 (29)	165 (26)	142 (23)	0.02
Current smoking (%)	*n* (%)	573 (18)	340 (18)	133 (21)	102 (16)	105 (17)	0.09
Systolic BP	mmHg	156 ± 20	157 ± 20	160 ± 21	156 ± 19	156 ± 20	0.001
Diastolic BP	mmHg	85 ± 11	85 ± 11	85 ± 11	85 ± 11	87 ± 11	0.003
Laboratory							
HbA_{1c}	%	8.3 ± 1.7	8.2 ± 1.7	8.2 ± 1.8	8.2 ± 1.7	8.3 ± 1.7	0.7
Serum creatinine	mg/dL	1.8 ± 0.5	1.7 ± 0.6	1.8 ± 0.6	1.7 ± 0.5	1.7 ± 0.5	<0.001
eGFR	$mL/min/1.73\ m^2$	44 ± 17	46 ± 17	44 ± 18	46 ± 17	48 ± 17	<0.001
Albuminuria	mg/day	1,757 (901–3,405)	1,736 (886–3,292)	1,665 (891–2,956)	1,780 (908–3,397)	1,802 (867–3,524)	0.001
Serum triglycerides	mg/dL	223 ± 191	219 ± 187	206 ± 170	219 ± 168	233 ± 218	0.04
Total cholesterol	mg/dL	228 ± 57	224 ± 55	223 ± 60	225 ± 52	226 ± 53	0.2
Hemoglobin	mg/dL	12.7 ± 1.9	12.9 ± 1.9	12.6 ± 1.9	12.8 ± 1.8	13.2 ± 1.8	<0.001
Medication							
Diuretics use (%)	*n* (%)	1,685 (52)	950 (51)	322 (52)	314 (50)	315 (50)	0.8
Insulin use (%)	*n* (%)	1,901 (59)	1,083 (58)	347 (56)	360 (58)	376 (60)	0.1

Data with a normal distribution are presented as mean ± SD, and data with a skewed distribution are presented as median with interquartile range (IQR).

Table 2—*Determinants of the CER in a multivariable linear regression analysis*

	β	95% CI	Standardized β	*P*
BSA	650.2	555.9 to 744.4	0.31	<0.001
Sex	−294.3	−342.2 to −246.38	−0.28	<0.001
Hemoglobin	43.43	31.02 to 55.83	0.17	<0.001
Race	144.9	94.1 to 195.8	0.12	<0.001
Age	−5.483	−8.285 to −2.681	−0.08	<0.001
Albuminuria	0.014	0.005 to 0.023	0.06	0.003
History of CVD	−42.37	−86.56 to 1.83	−0.04	0.06
Smoking	−47.64	−97.69 to 2.40	−0.04	0.06
Diabetes duration	−38.15	−100.90 to 24.60	−0.02	0.2
Systolic BP	−0.655	−1.642 to 0.332	−0.03	0.2
eGFR	0.479	−0.797 to 1.756	0.02	0.5
Triglycerides	−0.017	−0.124 to 0.090	−0.01	0.8

R^2 of the model = 0.367.

the range of CERs is shown in Fig. 1. This figure illustrates that the CER-associated risk for mortality is not limited to extremes of the CER but that risk varies over the full range of the CER.

CONCLUSIONS—In this post hoc analysis in patients with type 2 diabetes and nephropathy, the CER was a strong inverse determinant of risk for all-cause mortality, with a more than twofold increased risk for mortality per halving of the CER. As visualized in Fig. 1, an increased risk was already present in patients with a CER around median values, indicating that a large part of the population carried an increased risk in association with a lower CER. To our knowledge, this is the first time the CER was reported to be inversely associated with mortality in diabetic patients.

Table 3—*Cox regression analyses for doubling of the CER as determinant of all-cause mortality*

	All-cause mortality	
	HR (95% CI)	*P*
Model 1	0.49 (0.40–0.61)	<0.001
Model 2	0.41 (0.31–0.53)	<0.001
Model 3	0.40 (0.30–0.52)	<0.001
Model 4	0.39 (0.29–0.53)	<0.001
Model 5	0.39 (0.29–0.52)	<0.001

Model 1: crude; model 2: model 1 + adjustment for age, sex, race, height, and weight; model 3: model 2 + adjustment for eGFR, albuminuria, and treatment allocation; model 4: model 3 + adjustment for smoking status, total cholesterol, HDL cholesterol, systolic BP, and history of CVD; model 5: model 4 + adjustment for diabetes duration and HbA_{1c}.

In the current study, the HR for mortality increased more than twofold per halving of the CER. In a prior study in the general population, the HR increased about twofold per halving of the CER (3). Muscle mass is associated with insulin resistance, nutritional status, and physical activity. As these factors are even more important in diabetic patients, this would also explain the strong inverse association of the CER with mortality in this specific population when compared with the general population.

Several mechanisms can be hypothesized to underlie the inverse association of the CER with mortality in this diabetic population. First of all, muscle mass may materially determine insulin resistance, which is linked to adverse outcomes (3,4). In conditions of impaired insulin production or increased insulin resistance, glucose levels become more dependent on uptake in muscles (15). As such, muscle mass is an important determinant of insulin resistance. Unfortunately, more detailed markers for insulin sensitivity, such as homeostasis model assessment or fasting insulin levels, were not available in our study.

Another potential explanation for the inverse association of the CER with mortality might lie in protein malnutrition. Malnutrition leads to muscle wasting in a variety of conditions, including chronic kidney disease and diabetes (5,7,8), and is associated with adverse outcomes (16,17). In fact, this association may also be influenced by insulin resistance. Apart from its effect on glucose uptake, insulin promotes protein uptake and inhibits proteolysis in muscles (18). As such, resistance to the physiological actions of insulin may lead not only to impaired glucose metabolism but also to muscle wasting and loss of muscle mass (7).

Furthermore, the CER may reflect physical activity and, as such, good health. Interestingly, body weight was inversely associated with mortality in diabetes, possibly related to the age-related loss of lean muscle mass (19). It has extensively been shown that physical activity not only increases muscle mass and strength but also improves insulin sensitivity (20), BP (21), fat mass (22), HDL cholesterol (23), and, ultimately, mortality (24,25). Additionally, increased physical activity and higher muscle mass are associated with lower inflammatory parameters (26), which are associated with a worse outcome in diabetic nephropathy (27). Unfortunately, data on inflammatory markers such as CRP were not available for our study.

Our results underpin the importance of 24-h urine collections for gathering clinically relevant parameters. Although not considered the gold standard for the assessment of muscle mass (that would be computerized tomography or magnetic resonance imaging), a 24-h urine collection is a cheap and relatively fast measurement for various relevant parameters, including proteinuria and sodium excretion (reflecting sodium intake), in addition to the CER. Although in Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, spot morning urine is now proposed for the assessment of albuminuria and proteinuria (28), 24-h urine collection is deemed more accurate (29,30) and allows for the measurement of additional nutritional parameters in addition to the CER.

For the estimation of muscle mass, midarm and midthigh circumference measurements are sometimes considered, but they do not properly reflect muscle mass as measurements may be obscured by edema, intramuscular fat, and other tissues. It has been shown that even computerized tomography and magnetic resonance imaging may suffer from these drawbacks (31,32).

Urine collection errors are considered a major drawback of 24-h urine collection data. To minimize the effect of inaccurate collections on our results, we performed additional sensitivity analyses. Based on a formula developed by Ix et al. (12), whereby the CER is estimated according to anthropometric data, patients who deviated >50 or >30% from their estimated value were deemed inaccurate collections and excluded in the sensitivity

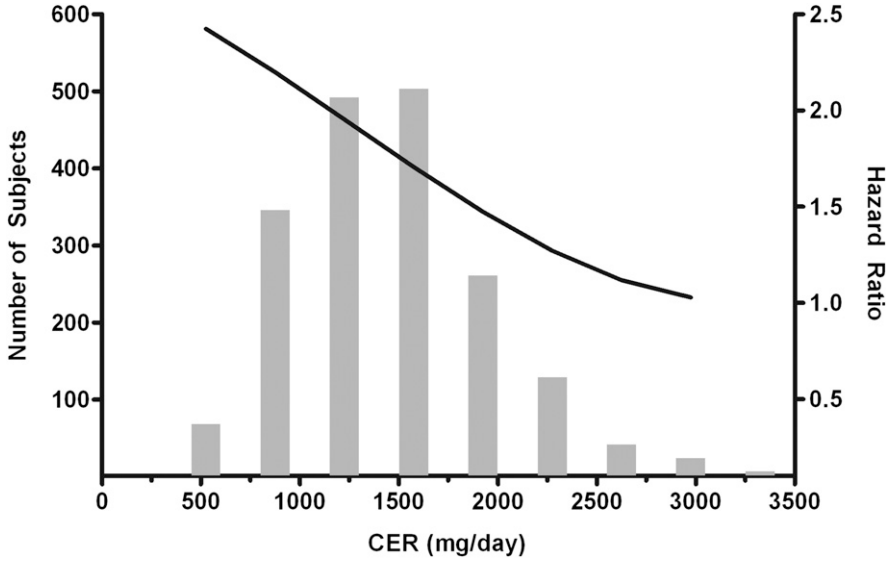

Figure 1—*Histogram of the CER combined with HRs for all-cause mortality plotted over the total range of the CER (smoothed second-order polynomial curve). The gray bars represent the number of patients, and the black line represents the smoothed HR plot over the CER range.*

analyses. This did not materially change our results, which indicates that collection errors did not significantly influence our main findings. However, errors in urine collections cannot be fully accounted for because extremely low or high values of the CER may reflect collection errors but may also reflect extremes in body composition. Furthermore, 24-h urine collections were only available in 58% of the patients in the trials under investigation. This could have induced some bias, but if characteristics of the patients included in the current study were compared with the overall population included in the RENAAL and IDNT trials, no important differences were apparent.

To establish the causes of the association of the CER with mortality, the assessment of the determinants of the CER is useful, as this might guide the search for the causal pathways. Data on insulin resistance and physical activity, unfortunately, were unavailable. Since insulin resistance and physical activity may play an important role in the relationship of the CER with mortality, the roles of insulin resistance and physical activity need to be further elucidated.

In conclusion, the CER, which serves as a surrogate marker for muscle mass, was inversely associated with all-cause mortality in diabetic patients with nephropathy, thus indicating that the CER can be used as a risk marker in this population. It would be of interest to see whether halting the loss of muscle mass seen in diabetes (8) by physical activity may improve outcomes. Further research is needed to gain more insight into the exact relationship between muscle mass and mortality.

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S.J.S. and A.J.K. analyzed the data and wrote the manuscript. S.J.L.B., S.S., E.E., and D.d.Z. reviewed the manuscript. G.N. and H.J.L.H. provided substantial intellectual contribution by revising the final version of the paper. S.J.S. and A.J.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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