Serum Concentration of Cystatin C and Risk of End-Stage Renal Disease in Diabetes

Andrzej S. Krolewski, MD, PhD 1,2
James H. Warram, MD, ScD 1
Carol Forsblom, DMSc 3,4
Adam M. Smiles, MS 1
Lena Thorn, MD, DMSc 3,4
Jan Skupien, MD, PhD 1,2
Valma Harjuutsalo, PhD 3
Robert Stanton, MD 1,3
John H. Eckfeldt, MD, PhD 6
Lesley A. Inker, MD, MS, FRCP(C) 7
Per-Henrik Groop, MD, DMSc 3,4

OBJECTIVE—Patients with diabetes have a high risk of end-stage renal disease (ESRD). We examined whether prediction of this outcome, according to chronic kidney disease (CKD) staging by creatinine-based estimates of the glomerular filtration rate (eGFRcreat), is improved by further staging with serum cystatin C–based estimates (eGFRcyst).

RESEARCH DESIGN AND METHODS—Patients with diabetes in CKD stages 1–3 were selected from three cohorts: two from Joslin Diabetes Center, one with type 1 diabetes (N = 364) and one with type 2 diabetes (N = 402), and the third from the Finnish Diabetic Nephropathy (FinnDiane) Study of type 1 (N = 399). Baseline serum concentrations of creatinine and cystatin C were measured in all patients. Follow-up averaged 8–10 years and onsets of ESRD (n = 246) and death unrelated to ESRD (n = 159) were ascertained.

RESULTS—Although CKD staging by eGFRcyst was concordant with that by eGFRcreat for 62% of Joslin patients and 73% of FinnDiane patients, those given a higher stage by eGFRcyst than eGFRcreat had a significantly higher risk of ESRD than those with concordant staging in all three cohorts (hazard ratio 2.3 [95% CI 1.8–3.1]). Similarly, patients at a lower stage by eGFRcyst than by eGFRcreat had a lower risk than those with concordant staging (0.30 [0.13–0.68]). Deaths unrelated to ESRD followed the same pattern, but differences were not as large.

CONCLUSIONS—In patients with diabetes, CKD staging based on eGFRcyst significantly improves ESRD risk stratification based on eGFRcreat. This conclusion can be generalized to patients with type 1 and type 2 diabetes and to diabetic patients in the U.S. and Finland.

C onsiderable effort has been devoted toward developing an accurate estimate of the glomerular filtration rate (eGFR) based on an easily assayed endogenous biomarker (1–3). The most widely used method is based on serum creatinine and a formula developed in the Modification of Diet in Renal Disease (MDRD) Study and designated here as eGFRmdrd (4). Recently, the Chronic Kidney Disease (CKD)-Epidemiology Collaboration (EPI) Group developed a second formula that is more accurate in the normal range and designated here as eGFRcreat (5). These two formulas are the foundation for staging CKD and guiding clinical practice (6,7).

An alternative endogenous serum biomarker, cystatin C, has been proposed for estimating renal function. Cystatin C is a 13-kDa protein that is freely filtered at the glomerulus and almost completely reabsorbed in proximal tubules and catabolized by epithelial cells. Its synthesis is believed to be constant and independent of muscle mass and diet (8). Stevens et al. (9) developed an eGFR formula based on cystatin C (eGFRcyst).

Evaluation of eGFRcyst and eGFRcreat against a measurement standard, iothalamate clearance, found no major advantage of one over the other (10,11). However, a more cogent standard for comparing eGFRcyst and eGFRcreat is their ability to predict end-stage renal disease (ESRD), the clinically important outcome addressed in this study. A potentially complicating factor is that cystatin C may carry information about disease processes beyond its role in estimating GFR. In the elderly, for example, eGFRcyst predicts death from cardiovascular disease (CVD) more accurately than eGFRcreat (12). If true, predictions could be biased because the risk of death from CVD competes with the risk of ESRD. Moreover, eGFRcyst improves identification of nondiabetic subjects in CKD stage 3 (based on eGFRcreat) at risk for complications (13). Similar studies have not been performed in patients with diabetes, a population of particular interest because of its high risk of ESRD and death unrelated to ESRD. Thus, in this report, we examine whether the predicted risk of ESRD and the competing risk of death based on eGFRcreat are refined by determination of eGFRcyst. To examine whether our findings could be generalized to all patients with diabetes, we studied groups that differed by nationality and type of diabetes.

RESEARCH DESIGN AND METHODS—We used data from three long-term follow-up studies of the risk of ESRD: two previously published studies of patients with type 1 diabetes (T1D) and
proteinuria (14,15) and one study of patients with type 2 diabetes (T2D) (16). From each study, we included only patients with CKD stages 1–3 as determined by serum creatinine concentration and the CKD-EPI formula (eGFRcreat). The protocols and consent procedures for each study were approved by the relevant institutional review board. Written informed consent was obtained from each participating patient. A brief description of each study follows.

Joslin cohorts
The Joslin Clinic is a large center for the treatment of patients of all ages with diabetes, regardless of type. Patient care includes control of diabetes and treatment of the late complications. Most patients come to the clinic within 5 years of diagnosis, and many remain with the clinic for decades, receiving integrated care from endocrinologists, nephrologists, and ophthalmologists. About one-fourth of the 16,000 patients under the care of the clinic have T1D.

Joslin T1D cohort. Between 1991 and 2004, we recruited 423 patients with T1D and proteinuria for studies of the genetics of diabetic nephropathy. Details of the selection, examination, and follow-up of this cohort were provided in a previous publication (14). The analysis in this report includes the 364 Caucasian patients with CKD stage 1–3 at baseline. These patients were monitored through 2008 for the occurrence of ESRD or death unrelated to ESRD.

Joslin T2D cohort. Between 1991 and 1995, we recruited 560 patients with T2D (half with normoalbuminuria and half with microalbuminuria or proteinuria) for studies of the genetics of diabetic nephropathy. Details of the selection, examination, and follow-up of this cohort were provided in a previous publication (16). The analysis in this report includes 402 patients (93% Caucasian) with CKD stage 1–3 at baseline for whom baseline serum was available for biochemical measurements. The cohort was monitored through 2008 for the occurrence of ESRD or death unrelated to ESRD.

Finnish Diabetic Nephropathy (FinnDiane) T1D cohort. The cohort used in this study is part of the ongoing nationwide, multicenter FinnDiane Study. The patients included in the present study had their baseline examination between 1995 and 2006. Those with proteinuria at baseline were included in a study of the risk of ESRD and death unrelated to ESRD, the results of which were recently reported (15). The analysis in this report includes 399 Caucasian patients with CKD stage 1–3 at baseline, for whom baseline serum was available for biochemical measurements. The cohort was monitored through 2008 for the occurrence of ESRD or death unrelated to ESRD.

Baseline characteristics
Enrollment examinations were performed by trained recruiters in all studies and included a structured interview about medical history, blood pressure measurements, and anthropometric measurements. Blood and urine were collected for biochemical studies. The data obtained at the baseline examination were supplemented with clinical data from medical records (14–16). Baseline characteristics are reported in Table 1.

Determination of serum creatinine and cystatin C
In 2009 and 2010, creatinine and cystatin C were assayed in stored baseline serum samples from the three cohorts in the Finnish Diabetic Nephropathy (FinnDiane) study and the Joslin T1D and T2D study. Details of the methods are given in the Supplemental Methods. Determination of serum creatinine was based on the EPI equation (eGFRcreat). The GFR was then estimated by 1.12 (17). The GFR was then estimated by regularly measuring National Institute of Standards and Technology Standard Reference Material (NIST SRM) No. 967. The GFR was estimated from the serum concentration of creatinine in milligrams per deciliter with the eGFRcreat formula (4) and the eGFRmdrd formula (4).

Serum cystatin C was measured with a particle-enhanced immunonephelometric assay using reagents from Siemens-DadeBehring on a BN ProSpec (Siemens Healthcare Diagnostics, Inc., Deerfield, IL). Serum cystatin C assay was standardized by traceability to higher-order primary reference materials by multiplying the values obtained at the University of Minnesota Laboratory by 1.12 (17). The GFR was then estimated.

Table 1—Baseline characteristics of the three cohorts with diabetes

| Cohort     | Joslin T1D | FinnDiane T1D | Joslin T2D |
|------------|------------|---------------|------------|
| n          | 364        | 399*          | 402        |
| Male (%)   | 55         | 56            | 56         |
| Caucasian (%) | 100       | 100           | 94         |
| Age at diabetes diagnosis (years) | 13.3 ± 8.3 | 11.5 ± 8.0 | 42.5 ± 9.1 |
| Duration of diabetes (years) | 24.9 ± 8.4 | 29.1 ± 8.3 | 13.3 ± 7.9 |
| BMI (kg/m²) | 26.6 ± 5.8 | 26.2 ± 4.1 | 29.9 ± 6.3 |
| HbA₁c (%) | 9.1 ± 1.7 | 9.0 ± 1.6 | 8.5 ± 1.7 |
| Blood pressure (mmHg) | 132 ± 18 | 142 ± 19 | 135 ± 18 |
| Systolic | 78 ± 10 | 82 ± 10 | 79 ± 10 |
| Diastolic | 1.6 ± 8.5 | 29.9 ± 13.3 | 11.5 ± 8.0 |
| Renoprotection (ACE inhibitor/ARB) (%) | 68 | 86 | 48 |
| Albumin-to-creatinine ratio (mg/g creatine) | 774 (467, 1,387) | 382 (154, 959) | 18 (5, 159) |
| 24-h albumin excretion rate (mg/dL) | 1.16 ± 0.45 | 1.20 ± 0.42 | 0.83 ± 0.27 |
| Serum creatinine (mg/L) | 2.01 ± 0.45 | 2.11 ± 0.40 | 0.94 ± 0.32 |
| eGFRcreat (mL/min) | 80 ± 29 | 75 ± 27 | 93 ± 22 |
| eGFRmdrd (mL/min) | 74 ± 30 | 68 ± 26 | 94 ± 30 |
| eGCRcyst (mL/min) | 71 ± 32 | 76 ± 32 | 89 ± 33 |
| Follow-up (person-years) | 2,818 | 3,111 | 3,826 |
| ESRD cases (n) | 114 | 80 | 52 |
| ESRD incident rate (per 100 person-years) | 4.0 | 2.6 | 1.4 |
| Deaths unrelated to ESRD (n) | 29 | 47 | 83 |
| Mortality rate (per 100 person-years) | 1.0 | 1.5 | 2.2 |

Data are mean ± standard deviation or median (25th, 75th percentiles); ARB, angiotensin-receptor blocker; NA, not applicable. *2 additional patients (including 16 who developed ESRD) were not used in the study due to lack of sera for cystatin C determinations.
from the serum concentration of standard-
ized cystatin C in milligrams per liter using the
published eGFRcyst formula (9,17):
\[ \text{eGFRcyst} = 127.7 \times (0.105 + 1.13 \times \text{standardized cystine})^{-1.17} \times \text{age}^{-0.13} \times (0.91 \text{ if female}) \times (1.06 \text{ if black}). \]

**Determination of onset of ESRD and death**

**Joslin cohorts.** Patients enrolled were monitored for the development of ESRD or death by matching the study roster against the medical records of the Joslin Clinic, the United States Renal Data System and the National Death Index. The onset of ESRD was recorded as the date of the first renal transplant (if it was preemptive kidney transplant) or renal dialysis. The most recent query took place in October 2010 and covered all incident cases of ESRD between 1991 and the end of 2008. Living subjects who were free of ESRD were contacted during 2009. We were able to ascertain the status (alive, ESRD, or death) of 98% of the subjects through 2008.

**FinnDiane cohort.** Deaths, regardless of cause, were identified by a search of the Finnish National Death Registry and center databases through 24 March 2009. Cause of death was confirmed by death certificate. ESRD was defined as a requirement for dialysis or kidney transplant and identified via a search of renal registries and center databases and verified in medical records.

**Statistical analyses**

Characteristics of patients were summarized by means and SDs or medians and quartiles. Cumulative risks of ESRD were calculated by actuarial methods. Covariate effects on time-to-events were evaluated in Cox regression models. Statistical significance was set at a value of \( P < 0.05 \). Analyses were conducted in SAS 9.2 software (SAS Institute, Cary, NC).

**RESULTS**—Demographic clinical characteristics of the two T1D cohorts were similar, whereas those of the Joslin T2D cohort were quite different. Age at diabetes diagnosis was almost 30 years older; current age was older, and duration of diabetes was shorter. Body weight and blood pressure were higher, whereas urinary albumin excretion (measured as the albumin-to-creatinine ratio) was lower and eGFR was higher. Moreover, the incidence rate of ESRD was lower and the mortality rate due to death unrelated to ESRD was higher than in the T1D cohorts.

The three cohorts differed to some degree in endogenous markers of renal function. In the FinnDiane cohort, the concentration of creatinine was higher than in the T1D Joslin cohort, whereas the concentration of cystatin C was lower. As a consequence of these differences, mean eGFRcreat and eGFRmdrd were slightly lower in the FinnDiane cohort \((P = 0.02)\) than in the Joslin cohort \((P = 0.01)\) and mean eGFRcyst was higher \((P = 0.02)\). As expected, serum concentrations of creatinine and cystatin C in the Joslin T2D cohort were substantially lower than in the T1D cohorts.

The distributions of patients in each cohort according to CKD stage defined by eGFRcreat and then partitioned by eGFRcyst stage are reported in Table 2. Concordant staging (numbers along the main diagonal) predominated in all cohorts. For example, in the Joslin T1D cohort, those numbers \((87 + 55 + 75)\) add to 217, which is 60% of the cohort \((n = 364)\). Concordance was similar in the Joslin T2D cohort \((65\%)\) and somewhat higher in FinnDiane \((73\%)\). However, discordant staging in the FinnDiane cohort differed from that in the Joslin cohorts. It was symmetric in the FinnDiane cohort (eGFRcyst stage higher for 16% and lower for 11%) but very asymmetric in both Joslin cohorts (eGFRcyst stage was higher than eGFRcreat stage for 35% and lower for only 3%). This difference in the pattern of discordant classification in the Joslin and FinnDiane cohorts was highly significant \((P < 0.0001)\).

We determined the ESRD incidence rate in each cell of Table 2 to assess what effect the partitioning of eGFRcyst stages according to eGFRcyst stages had on the risk of ESRD. The incidence rates are reported in Table 3. The partitioning produced subgroups within each eGFRcyst stage with a gradient of increasing ESRD risk; moreover, the gradient was very similar within each of the three cohorts. Thus, despite the differences among the cohorts, staging each eGFRcyst stage by eGFRcyst stage, consistently, added information about the risk of ESRD. By contrast, the partitioning of eGFRcyst (along the columns) of patients within an eGFRcyst stage did not result in comparable gradients.

The incidence rates of ESRD during follow-up that were reported in Table 3 can also be summarized by actuarial methods as 10-year cumulative risks of ESRD (Fig. 1). This representation of ESRD risk is probably easier for clinicians and patients to interpret when considering prognosis. Figure 1 shows the combined results from a stratified modeling of the Joslin and the FinnDiane T1D cohorts. Relative to the subgroups where the eGFRcyst and eGFRcyst stages agree (■ bars), the 10-year risks were lower (□ bars) if the eGFRcyst stage was lower than the eGFRcyst stage, and higher (△ bars) if the eGFRcyst stage was higher. For T2D, the 10-year risks were also higher if the eGFRcyst stage was higher than the eGFRcyst stage, but if it was lower, the 10-year risk could not be estimated because no
ESRD occurred among the few patients there (data not shown). The analyses in Tables 2 and 3 were repeated using CKD stages based on eGFR<sub>mdrd</sub> and the pattern of ESRD risk was the same (Supplementary Tables 1 and 2).

We tested the statistical significance of differences presented in Table 3 using a Cox proportional hazard model of time to ESRD with adjustment for cohort differences in urine albumin excretion and ACE inhibitor/angiotensin receptor blocker use. Because the results within each cohort were similar (Table 4), we tested for significant heterogeneity of the hazard ratios (HRs) across cohorts in a joint model and found none; therefore, the cohorts were combined for the final analysis. For patients with concordant staging by both eGFR<sub>cyst</sub> and eGFR<sub>creat</sub>, the summary HR for a one-step increase in CKD stage was linear (3.3 [95% CI 2.7–4.0]). For patients with discordant staging, the risk of ESRD for patients with an eGFR<sub>cyst</sub> stage higher than their eGFR<sub>creat</sub> stage was significantly higher than for those with concordant stages (summary 2.3 [1.8–3.1]). Similarly, the risk for patients with an eGFR<sub>cyst</sub> stage lower than their eGFR<sub>creat</sub> was significantly lower than that for those with concordant stages (summary 0.30 [0.13–0.68]).

Table 3—Incidence rate of ESRD in each cohort according to CKD stage defined by eGFR<sub>creat</sub> and partitioned by CKD stage defined by eGFR<sub>cyst</sub>

| CKD stage by eGFR<sub>creat</sub> | 1 (−90 mL/min) | 2 (89–60 mL/min) | 3 (59–30 mL/min) | 4 (29–15 mL/min) |
|--------------------------------|----------------|------------------|------------------|------------------|
| 1 (−90 mL/min)                 | −90 mL/min     | 59–30 mL/min     | 29–15 mL/min     | 1 (−90 mL/min)   |
| Joslin T1D                     | 1.5            | 2.4              | —                | —                |
| FinnDiane T1D                  | 0.8            | 1.9              | —                | —                |
| Joslin T2D                     | 0.1            | 1.0              | —                | —                |
| FinnDiane T2D                  | 0.7            | 1.4              | 2.2              | —                |
| Joslin T2D                     | 0.0            | 1.5              | 5.3              | —                |
| FinnDiane T2D                  | —              | 2.9              | 9.9              | 25.3             |
| Joslin T1D                     | —              | 1.3              | 5.1              | 16.6             |
| FinnDiane T1D                  | —              | 0.0              | 9.4              | 13.5             |

CONCLUSIONS—Patients with diabetes have a very high risk of developing ESRD as well as a high risk of dying without developing ESRD. In this report, we show for the first time that, for young or middle-aged diabetic patients in CKD stages 1–3 (based on routine measurements of serum creatinine), a secondary assessment of renal function based on serum cystatin C significantly improves ESRD risk stratification. This finding applies to Caucasian patients with T1D and T2D in Boston as in Finland and is true regardless of whether the initial CKD stage is based on the CKD-EPI or MDRD Study formulas.

CKD staging by both eGFR<sub>creat</sub> and eGFR<sub>cyst</sub> resulted in significant discrepancies in approximately 25–35% of patients. In the Joslin cohorts, the predominant discordance was a higher CKD stage by eGFR<sub>cyst</sub> than by eGFR<sub>creat</sub>. This is consistent with the evidence that cystatin-based formulas underestimate GFR in the normal range. Therefore, it is the symmetric pattern of discordant staging in the FinnDiane cohort that is unexpected. Although the reason for this difference is unclear, we hypothesize that the modestly higher serum cystatin in the FinnDiane cohort was responsible. Factors other than GFR are known to influence serum cystatin, so population differences most likely exist. They may be due to differences in muscle mass or diet and do not necessarily imply population differences in kidney function. The MDRD and CKD-EPI formulas were calibrated in Caucasian Americans. Estimates based on a population with a different distribution of serum creatinine concentrations, such as the FinnDiane cohort, will be biased. If the higher creatinine in FinnDiane is due to something other than GFR (as seems most likely), the CKD-EPI formula underestimates their GFR and overestimates their CKD stage. This would counter the tendency of eGFR<sub>creat</sub> to underestimate renal function and result in the symmetric pattern of discordance in the FinnDiane cohort.

Although the difference between the distributions of serum creatinine concentrations in the Joslin and FinnDiane cohorts raises concerns about the applicability of the MDRD and CKD-EPI formulas across diverse populations, the significantly improved ESRD risk stratification provided by a secondary assessment of renal function based on serum cystatin C is robust against these population differences. The partitioning of each eGFR<sub>creat</sub> stage by eGFR<sub>cyst</sub> stage distinguishes a significant gradient of risk, with the risk increasing as eGFR<sub>cyst</sub> stage increases. Interestingly, although the pattern of discordant CKD stages depends on whether the eGFR<sub>creat</sub> (CKD-EPI) or eGFR<sub>mdrd</sub> (MDRD) formula is used, the pattern of a risk gradient with eGFR<sub>cyst</sub> stage within each eGFR<sub>mdrd</sub> stage persists (data not shown).

Should measurement of serum cystatin C replace measurement of serum creatinine in clinical settings or supplement it in selected patients is a question that arises. Several considerations influence the answer. First, one must take into account that patients with diabetes have a much higher risk of ESRD than the general population and may require special consideration. Second, although CKD staging based on the serum creatinine concentration and the MDRD or CKD-EPI formula is inexpensive and already in routine clinical use, secondary CKD staging based on serum cystatin C concentration in patients with normal or nearly normal GFR improves stratification of ESRD risk and limits the extra expense to the subset of patients who can benefit most. Whether this extra expense is justified depends on the cumulative risk of ESRD (as illustrated in Fig. 1) and the value of improved detection of patients at high risk of ESRD. The latter depends on the availability of effective interventions to prevent this outcome.
The question deserves a formal cost-benefit analysis, which is beyond the scope of this report.

It is unclear that we can attribute the ability of eGFRcyst to refine a prediction of ESRD based on eGFRcreat simply to an improved estimate of renal function and, hence, a more accurate determination of how much renal function must be lost to reach ESRD. Only a marginal difference between eGFRcreat and eGFRcyst has been found in cross-sectional comparisons of them with a direct measurement of GFR (iothalamate clearance) in nondiabetic individuals (9–11). Another possibility is that serum cystatin C concentration carries additional information about the risk of other adverse outcomes. In the elderly general population, for example, the serum concentration of cystatin C is a more accurate predictor of death due to CVD than serum creatinine (12). Possibly, variation in serum cystatin C reflects a mechanism or risk factor involved in CVD that is unrelated to renal function (18). The Multi-Ethnic Study of Atherosclerosis (MESA) and Cardiovascular Health Study (CHS) demonstrated that for patients with CKD stages ≥3 according to the creatinine-based CKD-EPI equation, an adverse prognosis was limited to the subset of patients who had CKD stages ≥3 according to eGFRcyst (13). The adverse outcomes included death, cardiovascular event, heart failure, and kidney failure. In a recent analysis of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study of middle-aged individuals, adding cystatin C to measures of creatinine and urinary albumin excretion improved the predictive accuracy for all-cause mortality and ESRD (19).

There is general agreement between our results and those obtained in these other studies, namely, that measurement of serum cystatin C has value in assessing risk of ESRD and death. The studies in nondiabetic patients with CKD ≥3 (by eGFRcreat) showed that eGFRcyst is a predictor of ESRD and death. Our study in patients with diabetes showed that discordant CKD staging by eGFRcreat and eGFRcyst added particularly to the prediction of ESRD risk, the principal risk for this population. Thus, its utility is not diminished by the fact that the relationship of serum cystatin C with mortality risk in diabetes, so well documented in nondiabetic subjects (12,13,19), is only marginally confirmed in our diabetic cohorts. In summary, the risk of ESRD increases with each stage of CKD, but partitioning of each eGFRcreat stage by eGFRcyst stage distinguishes a significant gradient of risk, with the risk

Table 4—Analysis of time to onset of ESRD in each cohort according to CKD stage defined by eGFRcreat and partitioned by eGFRcyst stage

| CKD stages | Joslin T1D | FinnDiane T1D | Joslin T2D |
|------------|------------|---------------|------------|
| eGFRcyst higher than eGFRcreat stage* | 2.2 (1.5–3.9) | 2.2 (1.3–3.8) | 3.2 (1.8–5.9) |
| Stages the same | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| eGFRcyst lower than eGFRcreat stage† | 0.4 (0.1–1.3) | 0.3 (0.1–0.9) | Indeterminate |

Data are HR (95% CI) unless otherwise indicated. Adjusted for CKD stage and albumin-to-creatinine ratio and albumin excretion rate. *P < 0.001 for Joslin, P = 0.0025 for FinnDiane. †P = 0.1 for Joslin T1D, P = 0.03 for FinnDiane.
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increasing as eGFRcyst stage increases. The information gained from discordant CKD staging can be important clinically for advising patients about their risk of ESRD or to tailor interventions to their level of risk. This finding applies to Cauca-
sian patients with T1D and T2D in Boston as in Finland and is true regardless of whether the initial CKD stage is based on the CKD-EPI or MDRD Study formulas.

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