Serial Measurements of Cystatin C Are More Accurate Than Creatinine-Based Methods in Detecting Declining Renal Function in Type 1 Diabetes

EROSHA PREMARATNE, MBBS, FRACP[1]
RICHARD J. MACISAAC, PHD, MBBS, FRACP[1]
SUE FINCH, PHD[2]
SIANNA PANAGIOTOPOULOS, PHD[1]
ELIF EKINCI, MBBS[1]
GEORGE JERUMS, MBBS, FRACP, MD[1]

OBJECTIVE — Cystatin C– and creatinine-based methods were compared with ^{99m}-technetium-diethylene-triamine-penta-acetic acid (^{99m}Tc-DTPA) plasma clearance (isotopic glomerular filtration rate [iGFR]) for detecting declining renal function.

RESEARCH DESIGN AND METHODS — Glomerular filtration rate (GFR) was monitored over a mean of 10.1 years in 85 subjects with type 1 diabetes (with an average of 5.6 measurements per individual). Baseline mean ± SD iGFR of the cohort was 106.1 ± 2.6 ml/min per 1.73 m^2. The rates of decline in GFR (ΔGFR) were derived using linear regression.

RESULTS — In 19 of 85 subjects with declining renal function (i.e., ΔiGFR >3.3 ml/min per 1.73 m^2 per year), ΔGFR (ml/min per 1.73 m^2 per year) was 6.5 by iGFR, 4.2 by 10^4/creatinine, 3.6 by Cockcroft-Gault formula, 3.4 by the Modification of Diet in Renal Disease (MDRD)-6 equation, and 3.5 by the MDRD-4 variable equation ($P < 0.01$ vs. iGFR). In comparison, ΔGFR was 6.1 using the formula Cys-GFR = (86.7/cystatin C concentration) − 4.2 (not significant).

CONCLUSIONS — Cystatin C was more accurate in detecting decline in renal function than creatinine-based methods in this population of subjects with type 1 diabetes and a normal mean baseline GFR.

Diabetes Care 31:971–973, 2008

Monitoring trends in renal function via glomerular filtration rate (GFR) is of critical importance in managing patients with diabetes. Gold-standard methods for determining GFR employing plasma clearance techniques are cumbersome and not adaptable to routine clinical practice. Limitations of serum creatinine– and creatinine-based equations for estimation of GFR are well known (1,2). Cystatin C concentration has been proposed as an endogenous marker of GFR superior to creatinine (3,4).

We compared serum cystatin C, creatinine, Cockcroft-Gault formula, and the Modification of Diet in Renal Disease (MDRD)-4 and -6–variable equations with direct measurement of renal function employing ^{99m}-technetium-diethylene-triamine-penta-acetic acid (^{99m}Tc-DTPA) plasma clearance (isotopic GFR [iGFR]) in longitudinal monitoring of GFR in 85 subjects with type 1 diabetes with baseline GFR values predominantly in the normal range. In particular, the accuracy of the above methods for identifying subjects with progressively declining renal function was examined.

RESEARCH DESIGN AND METHODS

— A search of our database located 85 subjects with type 1 diabetes attending the Diabetes Clinics at Austin Health (a tertiary referral center) in Melbourne, Australia, in whom at least two iGFR measurements had been performed 3 or more years apart between 1987 and 2004. Subjects with nondiabetic renal disease were excluded. All subjects were Caucasian, except for one who was of Chinese ethnicity.

GFR measurements utilizing ^{99m}Tc-DTPA plasma clearance (iGFR) were routinely performed (5,6) on all clinic attendees two to three times yearly, irrespective of renal function or albuminuria status.

At baseline, mean ± SEM age of the 85 subjects (n = 85, 49 male) was 38.4 ± 1.3 years (range 14–72) and the mean ± SEM disease duration was 13.7 ± 1.1 years (range 0.2–48.6). On average, 5.6 iGFR measurements had been performed on each individual (range 2–11). The initial mean ± SEM iGFR was 106.1 ± 2.6 ml/min per 1.73 m^2, which declined to 90.4 ± 3.4 ml/min per 1.73 m^2 after 10.1 ± 0.3 years (range 3.0–15.7) of follow-up. The initial iGFR was >120 in 27%, 90–120 in 54%, and <90 ml/min per 1.73 m^2 in 19% of the subjects. From these 85 subjects, those with a rate of decline in iGFR >3.3 ml/min per 1.73 m^2 per year were defined as having a declining renal function ("decliners," n = 19) based on longitudinal data from the Baltimore Longitudinal Study of Aging (7).

Serum for creatinine and cystatin C was collected on the same morning as the corresponding iGFR measurement. Creatinine assays were determined by the Jaffe alkaline picrate method in the same laboratory, using a Parallel American Monitor (1987–1993), a Hitachi 747 instrument (1994–1997), or a Hitachi 917 automatic analyzer (1998–2004). There was no difference between GFR estimates obtained with the three creatinine methods and the corresponding iGFR measurements when analyzed by the Bland-Altman method. The latter assay produced creatinine values that fell within ±15% of the reference MDRD method, an accuracy that has been en-

From the [1]Endocrine Centre, Austin Health, University of Melbourne, Melbourne, Australia; and the [2]Statistical Consulting Centre, University of Melbourne, Melbourne, Australia.
Corresponding author: Dr. Erosha Premaratne, Endocrine Centre, Austin Health, Studley Road, Heidelberg, Victoria 3084, Australia. E-mail: erosha@aanet.com.au.
Received for publication 11 August 2007 and accepted in revised form 28 January 2008.
Published ahead of print at http://care.diabetesjournals.org on 4 March 2008. DOI: 10.2337/dc07-1588.
Abbreviations: GFR, glomerular filtration rate; iGFR, isotopic GFR; MDRD, Modification of Diet in Renal Disease; ^{99m}Tc-DTPA, ^{99m}-technetium-diethylene-triamine-penta-acetic acid.

dorsed by the Australian Creatinine Consensus Working Group on automatic reporting of estimated GFR (8). The intra- and interassay coefficients of variation (CVs) for serum creatinine were 2.3 and 6.7%, respectively, using the Hitachi 917 analyzer. Cystatin C was measured from stored serum samples in a single batch in 2004 using an automated particle-enhancing immunonephelometric assay on a BN II instrument (Dade Behring, Marburg, Germany). The intra- and interassay CVs for cystatin C were 2.58 and 3.95%, respectively, at a concentration of 1.54 mg/l.

The following techniques were used to estimate GFR: creatinine was transformed to a GFR value (Cr-GFR) using the equation 10^4/serum creatinine (μmol/l). Cystatin C was transformed to a GFR equivalent using the equation Cys-GFR = (86.7/cystatin C concentration) − 4.2 (3). Standard formulas were used to derive GFR from Cockcroft-Gault formula (CG-GFR) (9) and MDRD equations (1). For each individual, the trends of GFR (ΔGFR) were derived from linear regression from each method. The regression line for all except one subject with declining GFR was statistically significant ($P < 0.05$). Statistical analysis was performed using Minitab 14 statistical software.

RESULTS — The baseline and final iGFR in the group of decliners ($n = 19$) was mean ± SEM 105.1 ± 7 and 51.6 ± 7 ml/min per 1.73 m^2, respectively, compared with 106.3 ± 3 and 101.5 ± 3 ml/min per 1.73 m^2 in the nondecliners. Decliners had a greater baseline A1C than nondecliners ($P < 0.05$). The median baseline and final albumin excretion rates were18 and 150 μg/min, respectively, in decliners and 9 and 10 μg/min, respectively, in nondecliners. Thus, both baseline and final albumin excretion rate was higher in decliners than nondecliners ($P < 0.02$).

The mean ΔiGFR in the 19 decliners was 6.5 (range 3.3–26.2) ml/min per 1.73 m^2 per year. All of the creatinine-based methods significantly underestimated the decline in iGFR, i.e., 4.2 for Cr-GFR ($P < 0.01$ vs. ΔiGFR), 3.6 for CG-GFR ($P < 0.01$), 3.4 for MDRD-4–GFR ($P < 0.01$), and 3.5 for MDRD-6–GFR ($P < 0.01$). In contrast, there was no difference between rates of decline observed with iGFR and those observed with cystatin C, i.e., ΔCys-GFR 6.1 ml/min per 1.73 m^2 per year (Fig. 1). The sensitivity and specificity for each of the four creatinine-based methods for identifying the 19 subjects with declining iGFR were 42 and 100%, respectively, compared with 84 and 100%, respectively, for Cys-GFR.

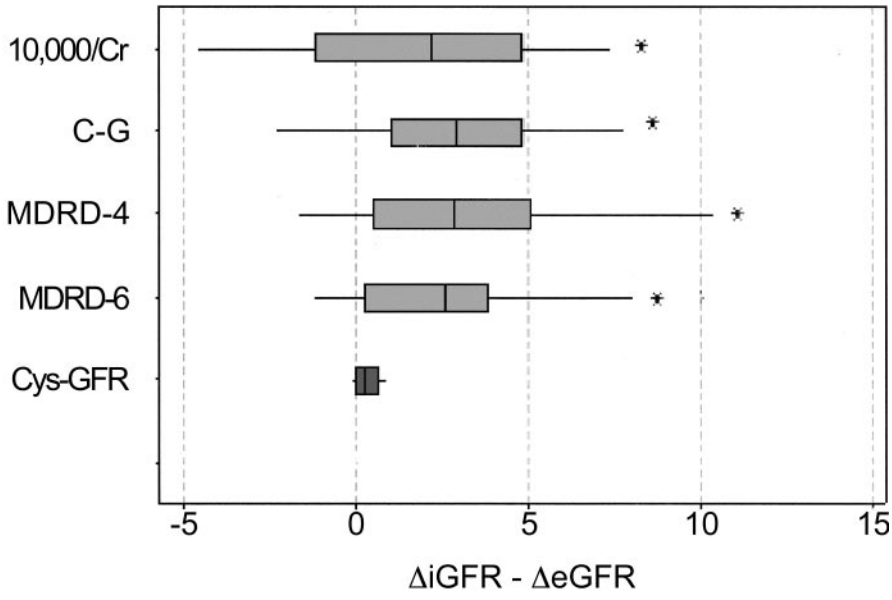

Figure 1— *Comparison of the difference between the rates of decline in GFR (ml/min per 1.73 m^2 per year) as measured by ^{99m}Tc-DTPA clearance (ΔiGFR) and the various indirect estimates of GFR (ΔeGFR) in "decliners," i.e., subjects with a ΔiGFR >3.3 ml/min per 1.73 m^2 per year* (n = *19). Cr-GFR, 10^4/serum creatinine; C-G, Cockcroft-Gault formula; Cys-GFR, (86.7/serum cystatin C concentration) − 4.2 (3). The line in the box represents the median and the boxes represent the interquartile range. Asterisks indicate whether (ΔiGFR − ΔeGFR) is significant* ($P < 0.05$).

CONCLUSIONS — This study demonstrates that estimates of renal function derived from serum cystatin C accurately portray long-term changes in GFR when compared with serial iGFR measurements in a cohort of subjects with type 1 diabetes with declining renal function. In contrast, creatinine-based estimates such as the Cockcroft-Gault formula and MDRD-4 and -6 variable equations and 1/creatinine significantly underestimated the decline in iGFR in this population.

Thus serial measurements of serum cystatin C may facilitate early identification of patients at risk of developing renal failure. Cystatin C has the potential to be employed more widely for monitoring of GFR, given its advantages of availability of a simple and accurate automated assay and the ability to directly use the reciprocal of cystatin C level as a GFR equivalent.

Acknowledgments— This study was supported by grants from the Pfizer Cardiovascular Lipid Grant Scheme and the Austin Hospital Medical Research Foundation and by Melbourne University Postgraduate Research grants.

This study was presented in abstract form at the 67th annual meeting of the American Diabetes Association, Chicago, Illinois, 22–26 June 2007.

References

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 130:461–470, 1999
2. Rossing P, Rossing K, Gaede P, Pedersen O, Parving HH: Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. *Diabetes Care* 29:1024–1030, 2006
3. MacIsaac RJ, Tsalamandris C, Thomas MC, Premaratne E, Panagiotopoulos S, Smith TJ, Poon A, Jenkins MA, Ratnaike SI, Power DA, Jerums G: Estimating glomerular filtration rate in diabetes: a comparison of cystatin C- and creatinine-based methods. *Diabetologia* 49:1686–1689, 2006
4. Perkins B, Nelson R, Ostrander BE, Blouch KL, Krolewski AS, Myers BD, Warram JH: Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. *J Am Soc Nephrol* 16:1404–1412, 2005
5. Houlihan C, Jenkins M, Osicka T, Scott A, Parkin D, Jerums G: A comparison of the plasma disappearance of iohexol and 99mTc-DTPA for the measurement of

glomerular filtration rate (GFR) in diabetes. *Aust NZ J Med* 29:693–700, 1999
6. Brochner-Mortensen J: A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* 30:271–274, 1972
7. Linderman RD, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 33:278–285, 1985
8. Mathew T, the Australian Creatinine Consensus Working Group: Chronic disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 183:138–141, 2005
9. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976