Serial Measurements of Cystatin C are More Accurate than Creatinine-based Methods in Detecting Declining Renal Function in Type 1 Diabetes

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ABSTRACT

Objective: Cystatin C and creatinine-based methods were compared with $^{99m}$Tc-DTPA plasma clearance (isotopic Glomerular Filtration Rate or iGFR) for detecting declining renal function.

Research Design and Methods: GFR was monitored over a mean of 10.1 years in 85 subjects with type 1 diabetes (average of 5.6 measurements per individual). Baseline mean iGFR of the cohort was 106.1±2.6 ml/min/1.73m$^2$. The rates of decline in GFR (ΔGFR) were derived using linear regression.

Results: In the 19/85 subjects with declining renal function (i.e. ΔiGFR>3.3 ml/min/1.73m$^2$ per year), ΔGFR (ml/min/1.73m$^2$ per year) was: 6.5 by iGFR and 4.2 by $10^4/$creatinine, 3.6 by Cockcroft-Gault formula, 3.4 by MDRD-6-equation and 3.5 by MDRD-4 variable-equation (p<0.01 versus iGFR). In comparison, ΔGFR was 6.1 using the formula Cys-GFR=$(86.7/$cystatin C concentration)-4.2 (ns).

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

Monitoring renal function (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 as well as 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 MDRD-4 and -6 variable equations with direct measurement of renal function employing $^{99m}$Tc-DTPA plasma clearance (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 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, Melbourne (a tertiary referral centre), in whom at least two iGFR measurements had been performed 3 or more years apart, between 1987-2004. Subjects with non-diabetic renal disease were excluded. All subjects were Caucasian, except for one, who was of Chinese ethnicity.

GFR measurements utilizing $^{99m}$Technetium-diethylene-triamine-penta-acetic acid ($^{99m}$Tc-DTPA) plasma clearance (iGFR) were routinely performed (5,6) on all clinic attenders 2-3 yearly, irrespective of renal function or albuminuria status.

At baseline, the mean age of the 85 subjects (n=85, 49 males) was 38.4±1.3 SEM (range 14 to 72) years and the mean disease duration was 13.7 ± 1.1 (range 0.2-48.6) years. On average, 5.6 iGFR measurements had been performed on each individual (range 2-11). The initial mean iGFR was 106.1±2.6 ml/min/1.73m$^2$ which declined to 90.4±3.4 ml/min/1.73m$^2$, after 10.1 ± 0.3 (range 3.0-15.7) years of follow-up. The initial iGFR(ml/min/1.73m$^2$) was >120 in 27% , 90-120 in 54% and <90 in 19% of the subjects. From these 85 subjects, those with a rate of decline in iGFR >3.3 ml/min/1.73m$^2$ per year were defined as having a declining renal function (“decliners”, n=19), based on longitudinal data from the Baltimore Ageing Study (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 3 creatinine methods and the corresponding iGFR measurements when analyzed by the Bland-Altman method. The last mentioned assay produces creatinine values that fell within ±15% of the reference MDRD method, an accuracy that has been endorsed by the Australian working group on automatic reporting of estimated GFR (8). The intra- and inter-assay CV for serum creatinine were 2.3% and 6.7%, respectively using the Hitachi 917 analyzer. Cystatin C was measured on 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 inter-assay CV 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 $10^{3}$/serum creatinine (µmol/L). Cystatin C
was transformed to a GFR equivalent using the equation Cys-GFR=86.7/cystatin C -4.2 (3). Standard formulae 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 1 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 105.1±7 and 51.6±7 ml/min/1.73m² respectively compared with 106.3±3 and 101.5±3ml/min/1.73m² in the non-decliners. Decliners had a greater baseline HbA1c compared to non-decliners (p<0.05). The median baseline and final AER was 18 and 150µg/min respectively in decliners and 9 and 10µg/min in non-decliners. Thus, both baseline and final AER was higher in decliners compared to non-decliners (p<0.02).
The mean ΔiGFR in the 19 decliners was 6.5 (range 3.3-26.2)ml/min/1.73m² per year. All of the creatinine-based methods significantly underestimated the decline in iGFR, i.e., 4.2 for Cr-GFR (p<0.01 versus Δ iGFR), 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 cystatin C; i.e. ΔCys-GFR 6.1 ml/min/1.73m² per year. (Figure 1). The sensitivity and specificity for each of the 4 creatinine based methods for identifying the 19 subjects with declining iGFR were 42% and 100%, respectively, compared with 84% and 100% for Cys-GFR.

CONCLUSION

This study demonstrates that estimates of renal function derived from serum cystatin C accurately portray long-term changes in GFR when compared to 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.

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REFERENCES

FIGURE LEGEND

FIGURE 1. Comparison of the difference between the rates of decline in GFR (ml/min/1.73m² per year) as measured by 99mTc-DTPA clearance (Δ iGFR) and the various indirect estimates of GFR (Δ eGFR) in “decliners” i.e. subjects with a ΔiGFR>3.3ml/min/1.73m² per year (n=19). Cr-GFR= 10⁴/serum creatinine; C-G = Cockcroft-Gault formula; Cys-GFR=(86.7/serum cystain C concentration)-4.2 (3). The line in the box represents the median and the boxes represent the inter-quartile range. Asterisks indicate if (Δ iGFR - Δ eGFR) is significant (p <0.05).
FIGURE 1