Monitoring kidney function in diabetic nephropathy

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Summary Progression in diabetic nephropathy is usually determined by repeated measurements of glomerular filtration rate and expressed as rate of decline in glomerular filtration rate. Our aim was to evaluate the agreement between rate of decline in glomerular filtration rate estimated from the Cockroft–Gault formula: (140-age)*K*body weight*(1/S-creatinine) and measured by the plasma clearance of ^{51}Cr-EDTA. All insulin-dependent diabetic patients with diabetic nephropathy followed-up for at least 5 years with at least 5 simultaneous measurements of glomerular filtration rate, s-creatinine, and weight were included in the study. Forty-three patients (32 male/11 female), age 31 (18–61) years were enrolled. Observation period: 6.6 (5.1–9.9) years and number of investigations per patient 6 (5–16) (median(range)). Baseline glomerular filtration rate (ml/min) was 97 (30) measured and 107 (37) estimated (mean(SD))($p < 0.001$) and the 95 % limits of agreement were −42.0 to 20.8 ml/min. Measured and estimated glomerular filtration rate correlated significantly ($r = 0.91, p < 0.00001$). Rate of decline in kidney function ml · min^{-1} · year^{-1} was 4.7 (3.3) measured and 4.8 (3.5) estimated (mean(SD)) (NS), but the 95 % limits of agreement showed a wide range −3.9 to 3.5 ml · min^{-1} · year^{-1}. A significant correlation between rate of decline in measured and estimated glomerular filtration rate was present ($r = 0.84$, $p < 0.00001$). In conclusion, glomerular filtration rate is overestimated by the Cockroft–Gault formula. The mean rates of decline in glomerular filtration rate are comparable, but the limits of agreement are wide, which make the Cockroft–Gault method unacceptable for clinical purposes, i.e. monitoring progression in kidney function in the individual patient. However, the estimated glomerular filtration rate may be used for comparison of groups in observational studies and in clinical trials with a long observation period. [Diabetologia (1994) 37: 708–712]

Key words Insulin-dependent diabetes mellitus, diabetic nephropathy, glomerular filtration rate, creatinine clearance, progression of renal disease.

Diabetic nephropathy is characterized by persistent albuminuria, a rise in blood pressure and a decline in GFR [1–3]. Since rate of decline in kidney function is used to assess the prognosis and the efficacy of therapy on the progression of renal disease, a valid method for

determination of GFR is essential. The plasma disappearance of ^{51}Cr-EDTA followed for 4 h or longer is an accurate and precise technique [4]. Unfortunately, it is time consuming, expensive, requires radiation exposure, and repeated blood sampling. Cross-sectional data suggest that the formula described by Cockroft and Gault [5] for estimating creatinine clearance: (140-age)*K*body weight*(1/p-creatinine [μmol/l]), K = 1.23 for men, 1.05 for women, gives an accurate estimate of GFR in diabetic nephropathy [6]. This lead the authors to suggest that the method may be of clinical use for assessing renal function in patients with diabetic nephropathy. However, it has not been demonstrated whether the rate of decline in GFR can be ac-

curately determined from the rate of decline in estimated creatinine clearance. To evaluate this suggestion we compared rate of decline in measured GFR (^{51}Cr-EDTA) and rate of decline in estimated GFR from the Cockroft–Gault formula, in IDDM patients with diabetic nephropathy followed-up for at least 5 years.

Subjects and methods

Subjects. We examined the records of all patients with IDDM suffering from diabetic nephropathy followed-up at Hvidöre Hospital between 1984 and 1992. As part of the routine care and monitoring programme for these patients, GFR was determined approximately yearly. Forty-three patients followed-up for at least 5 years undergoing at least five simultaneous measurements of GFR, weight and serum creatinine were included in the study (Table 1). The observation period was 6.6 (5.1–9.9) years and number of investigations per patient 6 (5–16) (median (range)). All developed diabetes before the age of 40, and were dependent on insulin from the time of diagnosis, and all received at least two daily injections of highly purified insulin. They had a normal diabetic diet containing 45–55 % carbohydrate, 30–35 % fat and 15–20 % protein. None of the patients had their intake of salt or protein restricted. Nephropathy was diagnosed clinically according to previously described criteria [7]. All patients, except two who were normotensive, were treated with antihypertensive medication throughout the entire observation period. The study was approved by the local ethical committee, and the patients gave their fully informed consent to the investigations.

Methods. All investigations were carried out on one day between 08.30 and 13.00 hours. Patients had their normal breakfast and morning dose of insulin before the investigations, during which they rested supine and stood up only to pass urine. They drank 150–200 ml tap water per hour during the study period.

The GFR was measured after a single intravenous injection of edetic acid labelled with 3.7 MBq sodium chromate-51 at 09.00 hours, by determining the radioactivity in venous blood samples taken from the other arm 180, 200, 220, and 240 min after the injection [4, 8]. The small underestimation (10 %) of ^{51}Cr-EDTA clearance vs inulin clearance was corrected for by multiplying the ^{51}Cr-EDTA clearance by 1.10. Extra renal loss was corrected for by subtracting 3.7 ml per min. The mean day-to-day coefficient of variation in the GFR of each patient was 4 %. Serum creatinine was measured using a time reaction technique which reduces the interference from pseudo-creatinines [9].

All the patients visited the clinic at 2–4 month intervals. At each visit the postprandial blood glucose concentration was measured along with urinary glucose excretion, blood pressure and body weight, and the dose of insulin and antihypertensive treatment were adjusted.

Statistical analysis

Values are given as mean (SD) or geometric mean (antilog SE). Paired *t*-test was used to compare estimated creatinine clearance and GFR at baseline. Linear regression analysis (least squares method) was used to determine the rate of decline in estimated creatinine clearance and GFR for each patient. The rates of decline were compared with paired *t*-test. Univariate linear regression analysis was used to examine agreement between the two methods. The stochastic variation was calculated as the residual

Table 1. Clinical characteristics of 43 IDDM patients with diabetic nephropathy followed-up with simultaneous measurements of GFR (^{51}Cr-EDTA) and estimated GFR by the Cockroft–Gault formula

Sex (F/M)	11/32
Age (years)	31 (18–61)
Duration of diabetes (years)	22 (8)
Retinopathy (background/proliferative)	13/30
Body mass index (kg/m^2)	23.7 (2.7)
Serum creatinine (µmol/l)	88 (28)
Albuminuria (µg/min)	539 (1.2)
Blood pressure (mm Hg)	142 (17)/88(9)

Values are mean (SD), for albuminuria: geometric mean (antilog SE)

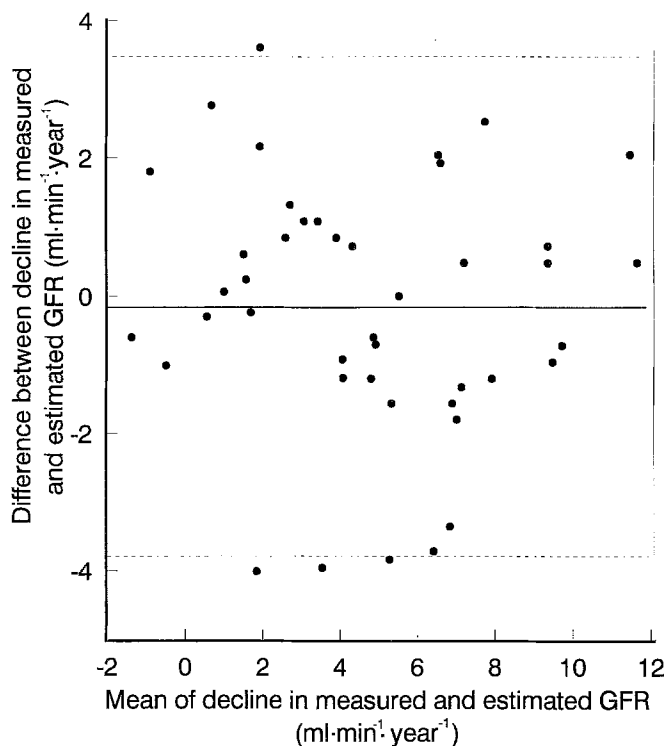**Fig. 1.** Difference between measured GFR (^{51}Cr-EDTA) and estimated GFR (Cockroft–Gault formula) vs mean of the two methods at baseline in 43 IDDM patients with diabetic nephropathy. Mean difference (——), and 95 % limits of agreement (-----) are indicated

SD and expressed as a percentage of the corresponding value. The difference between the two methods was then plotted against the average of the two methods for each patient to give a further estimate of the agreement between the methods (Bland–Altman plot) [10]. Limits of agreement were calculated as mean difference ± 1.96·SD of the differences. All calculations were made using Statgraphics (STSC, Rockville M.D., USA). A *p* value of < 0.05 was considered significant (two tailed).

Results

GFR at baseline. GFR (^{51}Cr-EDTA) at baseline was 97 (30) ml/min and estimated GFR (Cockroft–Gault) was 107 (37) ml/min (*p* = 0.0001). The average difference
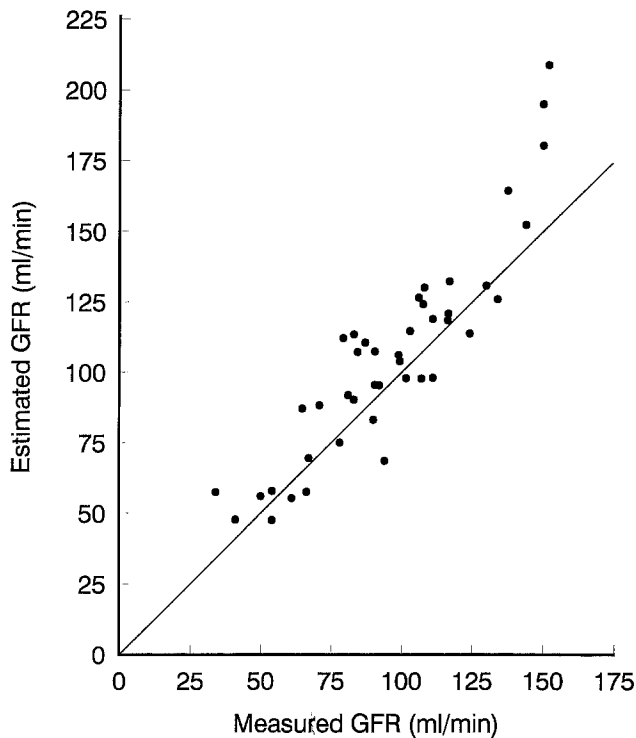
Fig. 2. Correlation between estimated GFR (Cockroft–Gault formula) and measured GFR (^{51}Cr-EDTA) at baseline in 43 IDDM patients with diabetic nephropathy ($r = 0.91, p < 0.0001$). The identity line is indicated
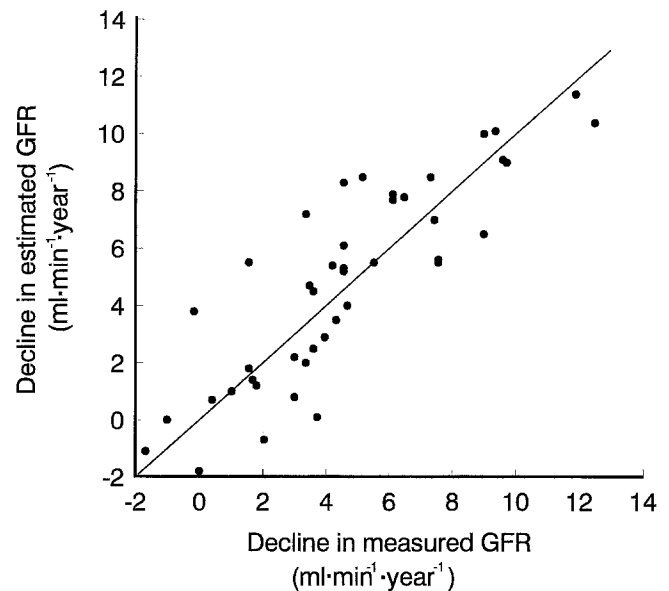
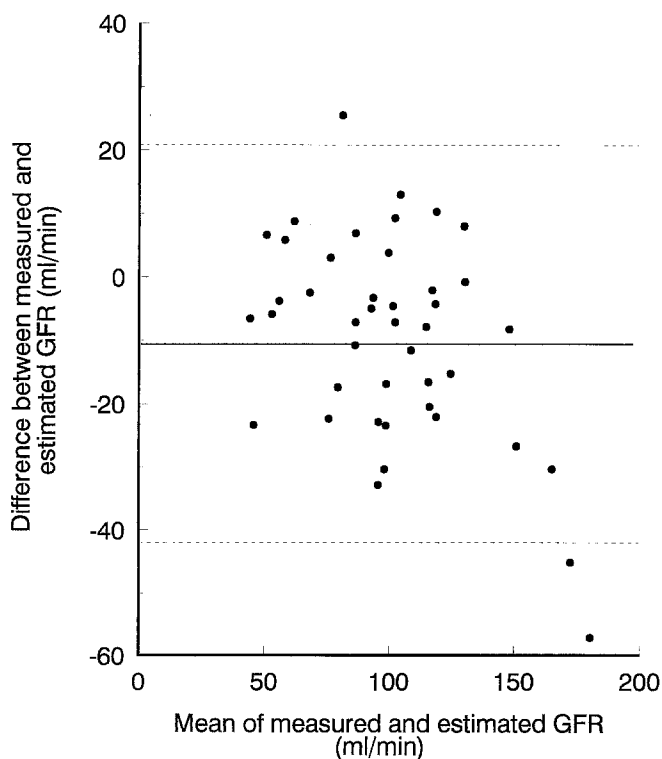**Fig. 4.** Correlation between rate of decline in estimated GFR (Cockroft–Gault formula) and rate of decline in measured GFR (^{51}Cr-EDTA) in 43 IDDM patients with diabetic nephropathy ($r = 0.84, p < 0.0001$). The identity line is indicated

between these two methods (the bias) was –10.6 ml/min. The 95 % limits of agreement are –42.0 to + 20.8 ml/min (Fig. 1). The differences between the two methods are significantly correlated with the mean values ($r = -0.47, p < 0.01$), indicating increasing overestimation by the Cockroft–Gault formula with increasing GFR. Linear regression analysis of estimated creatinine clearance on GFR reveals a highly significant correlation ($r = 0.91, p < 0.00001$, Fig. 2). The residual SD was 13 % of mean GFR.

Rate of decline in GFR. The measured rate of decline in GFR was 4.7 (3.3) ml·min^{-1}·year^{-1} compared to a rate of 4.8 (3.5) ml·min^{-1}·year^{-1} based on estimated GFR (NS). The mean difference between the two methods (the bias) was –0.2 ml·min^{-1}·year^{-1} (95 % confidence interval for the bias:–0.8 to 0.4). The 95 % limits of agreement were –3.9 to + 3.5 ml·min^{-1}·year^{-1} (Fig. 3). There was no significant correlation between the differences between the two methods and the mean values ($r = -0.12$, NS). There was a significant correlation between the two methods for determination of the progression rate ($r = 0.84, p < 0.00001$, Fig. 4). The residual SD was 41 % of mean rate of decline in GFR.

Since several clinical studies (observational and clinical trials) are of shorter duration than our study the agreement between the two methods was evaluated using a 3-year observation period in a subgroup of our patients with at least five measurements of GFR and serum creatinine. Nineteen patients were identified with 7 (6–8) investigations during the first 3 years. The rate of decline in GFR was 5.9 (4.1) ml·min^{-1}·year^{-1}

Fig. 3. Difference between rate of decline in measured GFR (^{51}Cr-EDTA) and estimated GFR (Cockroft–Gault formula) vs mean of the two methods in 43 IDDM patients with diabetic nephropathy. Mean difference (——), and 95 % limits of agreement (-----) are indicated

compared to 7.2 (6.1) ml·min^{-1}·year^{-1} using estimated GFR values (p = 0.21, n = 19). The mean difference between the two methods was -1.4 ml·min^{-1}·year^{-1} and the 95% limits of agreement varied widely from -10.5 to +7.8 ml·min^{-1}·year^{-1}. For these 19 patients the mean difference between the two methods was -0.1 ml·min^{-1}·year^{-1} using the whole observation period of 6.8 (5.8–7.2) years with 95% limits of agreement of -3.3 to +3.1 ml·min^{-1}·year^{-1}.

Discussion

Our cross-sectional study showed a close correlation between GFR determined with ^{51}Cr-EDTA and estimated from the formula by Cockroft and Gault using serum creatinine, weight, age and sex in patients with IDDM and diabetic nephropathy with GFR ranging from 34 to 152 ml/min. Despite the close correlation the Cockroft–Gault formula significantly overestimated the GFR (lack of accuracy), and the limits of agreement were wide (lack of precision). In the longitudinal part of our study we found a highly significant correlation between the rate of decline in GFR (^{51}Cr-EDTA) and rate of decline in estimated GFR (Cockroft–Gault formula) in patients with a rate of decline of 4.7 (3.3) ml·min^{-1}·year^{-1} and followed-up for at least 5 years (6.6 (5.1–9.9) years). On average there was no significant difference between the two methods, but the limits of agreement were wide compared to the average rate of decline in GFR. If the observation period was only 3 years the limits of agreement were more than doubled, indicating reduced precision with shorter follow-up periods. It is likely that a better agreement could have been obtained with more frequent measurements of s-creatinine.

Several cross-sectional studies have compared the GFR measured using inulin or radioactive labelled filtration markers to endogenous creatinine clearance, the inverse of the serum creatinine or estimated creatinine clearance by the formula of Cockroft and Gault in patients with diabetic nephropathy [6, 11–15] and non-diabetic kidney diseases [16–19]. The correlations are often stronger between estimated creatinine clearance or 1/creatinine and GFR (r values approximately 0.80) than between endogenous creatinine clearance and GFR (r values from 0.60 to 0.70). The mean difference between GFR and estimated creatinine clearance is small but the variability is considerable. In diabetic patients without nephropathy the correlations between estimated creatinine clearance by Cockroft and Gault's formula and GFR is weaker (r values approximately 0.50) [12, 14].

The major advantages of estimating GFR from the Cockroft–Gault formula are the rapidity with which results can be obtained (1–2 h) requiring only a knowledge of the patients age, body weight, sex and a single blood sample, the reduced cost, and the avoidance of

timed urine collections (compared to renal clearance techniques), which often leads to errors, especially in diabetic patients as many patients have residual urine due to diabetic cystopathy [20].

Many factors apart from the glomerular filtration influence serum creatinine, therefore the use of the inverse of the serum creatinine and estimated creatinine clearance as indices of GFR has been questioned. These factors include: tubular secretion of creatinine [16,19,21,22], impact of skeletal muscle mass and meat intake on creatinine generation, extra renal clearance of creatinine [21, 23] and the inhibiting effect of medication on the tubular secretion of creatinine (e.g. cimetidine) [23, 24]. Furthermore, the tubular secretion of creatinine and the extrarenal clearance of creatinine increases with deteriorating kidney function and the rate of changes are highly variable among patients [16, 19]. Therefore, discrepancies between rate of decline in measured GFR and rate of decline in estimated GFR could be expected, but only few longitudinal studies comparing the rate of change in GFR and the inverse of the serum creatinine are available, and to our knowledge no longitudinal studies have used the Cockroft–Gault formula.

Two longitudinal studies have compared the slope of the inverse of the serum creatinine to the slope of measured GFR in IDDM patients with diabetic nephropathy. In 13 patients studied for up to 53 months a weak correlation was found (r = 0.37), if patients with GFR in excess of 48 ml·min^{-1}·1.73 m^{-2} were excluded the correlation improved to r = 0.83 [25]. The other study found a correlation between Log serum creatinine and Log GFR in 18 patients followed-up for up to 70 months (r = -0.51) [26]. Patients with various glomerulopathies demonstrated a decline in GFR of 48% after one year, while the inverse of the serum creatinine only decreased 29% [16]. In the feasibility phase of the Modification of Diet in Renal Disease study including patients with non-diabetic chronic renal failure, the effect of increasing duration of follow-up was demonstrated, as the correlation between rate of decline in GFR and rate of decline in the inverse of the serum creatinine increased from -0.29 at 3 months of follow-up to 0.74 at 15 months of follow-up [27]. Furthermore, it was possible to demonstrate that the rate of tubular secretion and total renal excretion of creatinine varied among patients and changed over time thus contributing to the variability in the rate of decline in the reverse of the serum creatinine not explained by the variability in the rate of decline in GFR [19].

The agreement between two methods is often evaluated by calculating the correlation coefficient (r) between the two methods as has been done in several of the previous studies comparing measured GFR and estimated GFR. However, r measures the strength of a relation between two variables, not the agreement. The correlation depends on the range of values included in the analysis, and data which seem to be in poor agree-

ment can produce quite high correlations as also found in our study. It has therefore been suggested to plot the difference between the two methods against their mean (Bland–Altman plot), and calculate the limits of agreement from the mean difference and the SD of the differences [10]. The acceptable limits of agreement will be a question of judgement. When monitoring kidney function the limits of agreement should be small compared to the mean rate of decline.

In conclusion, in patients with IDDM and diabetic nephropathy GFR is overestimated by the Cockroft–Gault formula. The mean rates of decline in GFR are comparable, but the limits of agreement are wide, which makes the Cockroft–Gault formula unacceptable for clinical purposes, i.e. monitoring progression of renal failure in the individual patient. However, the Cockroft–Gault formula may be used for comparison of groups in observational studies and in clinical trials with a long observation period.

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