Are prediction equations for glomerular filtration rate useful for the long-term monitoring of type 2 diabetic patients?

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Abstract
Background. The aim of this study was to compare the accuracy of prediction equations (modification of diet in renal disease (MDRD), simplified MDRD, Cockcroft–Gault (CG), reciprocal of creatinine and creatinine clearance) in a cohort of patients with type 2 diabetes.

Methods. A total of 525 glomerular filtration rates (GFRs) using 125I-iothalamate were carried out over 10 years in 87 type 2 diabetic patients. Accuracy was evaluated at three levels of renal function according to the baseline values obtained with the isotopic method: hyperfiltration (GFR: >140 ml/min/1.73 m²; 140 isotopic determinations in 27 patients), normal renal function (GFR: 140–90 ml/min/1.73 m²; 294 isotopic determinations in 47 patients) and chronic kidney disease (CKD) stages 2–3 (GFR: 30–89 ml/min/1.73 m²; 87 isotopic determinations in 13 patients). The annual slope for GFR (change in GFR expressed as ml/min/year) was considered to ascertain the variability in the equations compared with the isotopic method during follow-up. Student’s t-test was used to determine the existence of significant differences between prediction equations and the isotopic method (P < 0.05 with Bonferroni adjusted for five contrast tests).

Results. In the subgroup of patients with hyperfiltration, a GFR slope calculated with 125I-iothalamate −4.8 ± 4.7 ml/min/year was obtained. GFR slope in patients with normal renal function was −3.0 ± 2.3 ml/min/year. In both situations, all equations presented a significant underestimation compared with the isotopic GFR (P < 0.01; P < 0.05). In the subgroup of CKD stages 2–3, the slope for GFR with 125I-iothalamate was −1.4 ± 1.8 ml/min/year. The best prediction equation compared with the isotopic method proved to be MDRD with a slope for GFR of −1.4 ± 1.3 ml/min/year (P: NS) compared with the CG formula −1.0 ± 0.9 ml/min/year (P: NS). Creatinine clearance presented the greatest variability in estimation (P < 0.001).

Conclusions. In the normal renal function and hyperfiltration groups, none of the prediction equations demonstrated acceptable accuracy owing to excessive underestimation of renal function. In CKD stages 2–3, with mean serum creatinine ≥133 μmol/l (1.5 mg/dl), the MDRD equation can be used to estimate GFR during the monitoring and follow-up of patients with type 2 diabetes receiving insulin, anti-diabetic drugs or both.

Keywords: CKD stages 2–3; glomerular filtration rate; hyperfiltration; normal renal function; prediction equations; type 2 diabetic patients

Introduction

Data from the US Renal Data System predict that the number of patients registered with end-stage renal disease (ESRD) in 1997 will have doubled by 2010, leading to approximately 700 000 patients with ESRD and 2.2 million patients in 2030 [1]. According to the current epidemiological data, type 2 diabetes is considered to be one of the most frequent causes of terminal chronic renal insufficiency and inclusion in renal substitution programmes. Simple, purified monitoring of renal function is of vital importance in this subgroup of patients for therapeutic measures aimed at reducing associated comorbidity factors to be applied early.

Isotopic determination of the glomerular filtration rate (GFR) would be the gold standard method for determining renal function; however, it is an expensive option and not often used in clinical practice.
The Cockcroft–Gault formula (CG) is probably one of the most widely used prediction equations for the follow-up of renal function and for the dose adjustment of potentially nephrotoxic drugs [2]. The CG formula is an estimate of creatinine clearance originally developed in a population of 236 Canadian patients (209 males) with normal renal function and chronic kidney disease (CKD) stages 2–3 (creatinine clearance: 114.9–37.4 ml/min). The modification of diet in renal disease (MDRD) equation is the newest equation, used in demographic, biochemical and nutritional studies [3]. The MDRD formula was developed as an estimation of $^{125}$I-iothalamate renal clearance-based GFR measurement in a population of 1628 patients, with CKD stages 3–4 (mean GFR: 39.8 ml/min/1.73 m$^2$). Both equations have been validated and analysed in large patient populations with chronic renal insufficiency, although their predictive capacity has been analysed little in other levels of renal function during the long-term follow-up of type 2 diabetes mellitus (DM) patients [3].

The aim of our study was to compare renal function and annual slope for GFR determined with the isotopic method and the different prediction equations [MDRD, simplified MDRD (sMDRD), CG and reciprocal of creatinine] and with the measurement of creatinine clearance using 24 h urine collection during the follow-up in a cohort of patients with type 2 diabetes.

**Subjects and methods**

**Study population**

A total of 525 isotopic determinations of GFR were carried out between October 1989 and November 2003 in 87 patients with type 2 DM (53 women/34 men). All patients included in the study fulfilled the American Diabetes Association diagnostic criteria for type 2 DM, and were followed at the out-patient clinic of a third-level hospital. Mean initial age of the study group was 54±8.5 years (range: 31–69) and mean known years of type 2 DM evolution 10.7±7.2 years (range: 1–31). Initially, 40.7% were under insulin treatment and 60% in the final period. The control mean using the isotopic technique was 10.2 years (range: 7–15). Renal function was monitored in each patient using isotopic GFR determination calculated by $^{125}$I-iothalamate during the ambulatory follow-up period. Simultaneously with each isotopic determination, demographic (age and sex), anthropometric (height, weight and body surface) and biochemical (serum and urinary creatinine, urea nitrogen and albumin) data were collected during the follow-up period with the aim of establishing the estimation and calculation of renal function using each of the prediction equations of different levels. Data of all diabetic patients at baseline and the last observation during the follow-up period are summarized in Table 1.

According to the baseline values obtained with the isotopic GFR, patients were divided into three study subgroups: normal renal function [GFR between 140 and 90 ml/min/1.73 m$^2$ (294 isotopic determinations during the follow-up period in 47 type 2 DM patients)]; hyperfiltration [GFR >140 ml/min/1.73 m$^2$ (144 isotopic determinations during the follow-up period in 27 type 2 DM patients)] defined according to the results obtained in our previous study [4] and CKD stages 2–3 [GFR between 89 and 30 ml/min/1.73 m$^2$ (87 isotopic determinations during the follow-up period in 13 type 2 DM patients)].

**Study design and methods**

Isotopic GFR was measured every 24 months (range: 12–36 months) by a single-shot clearance technique using an intravenous injection of 30–50 μCi $^{125}$I-iothalamate [5]; blood was drawn at timed intervals and values were corrected for body surface area of 1.73 m$^2$. Preparation of the dose administered to each patient was carried out using an analytical balance and measurement of the tracer in an activity meter. To obtain the standard samples of $^{125}$I-iothalamate in each patient, the tracer was diluted in a 250 ml matrix, taking three 1 ml aliquots using a 1000 μl micropipette. A 19 G peripheral catheter was inserted in each patient for blood sample collection. Blood was extracted at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180 and 240 min.

In each study subgroup, the GFR value obtained with the isotopic method was compared with the following prediction equations:

(i) CG [2]

(a) Men: (140 age) × weight (kg)/72 × SCr.

(b) Women: [(140 age) × weight (kg)/72 × SCr] × 0.85.

(ii) MDRD [3]: $170 \times (SCr)^{-0.996} \times (age)^{-0.176} \times (BUN)^{-0.170} \times (Alb)^{0.318} \times (0.762)$ female sex.

**Table 1.** Clinical and analytical data of 87 type 2 DM patients at baseline and the last observation during the follow-up period

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>28.9±5.5 (17.3–42.0)</td>
<td>30.9±5.6 (21.1–46.4)</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>142.6±25.7 (90–210)</td>
<td>144.9±22.2 (100–198)</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>77.5±11.9 (60–110)</td>
<td>74.1±8.1 (58–100)</td>
</tr>
<tr>
<td>Hb A1c (%)</td>
<td>7.3±1.9 (5.5–13.6)</td>
<td>7.5±1.4 (5.6–12.5)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.4±0.5 (3.3–5.1)</td>
<td>4.1±0.3 (2.7–4.7)</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>85.7±26.5 (55–198)</td>
<td>99.8±45 (59.2–396.9)</td>
</tr>
<tr>
<td>UAER (mg/24h)</td>
<td>259.0±603.2 (2–3600)</td>
<td>387.8±1131.3 (2–3600)</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m$^2$)</td>
<td>118.9±36.9 (38.7–208.8)</td>
<td>91.5±35.1 (30–225)</td>
</tr>
</tbody>
</table>

UAER, urinary albumin excretion rate; GFR, glomerular filtration rate calculated with $^{125}$I-iothalamate.

All data are expressed as mean±SD (minimum–maximum).
where SCr, serum creatinine (mg/dl): UCr, 24 h urinary creatinine (mg/dl): Vo, urine volume: BUN, blood urea nitrogen [urea (mg/dl)/2.14] and Alb, serum albumin (g/dl).

Blood samples were obtained simultaneously with the GFR measurement. Biochemical parameters (glucose, albumin, urea nitrogen concentration) were measured using an autoanalyser (Technicon Autoanalyzer, Tarrytown, New York, USA). Hb A1c was first measured by chromatography (Biosystem, Barcelona, Spain; normal range: 5.0–6.7%) and, since 1995, with a glycated haemoglobin analyser using ion-exchange chromatography HPLC (Hitachi L-9100; normal range: 3.3–5.0%). Urinary albumin analyser using ion-exchange chromatography HPLC an autoanalyser (Technicon Autoanalyzer, Tarrytown, New York, USA), 24 h urinary creatinine measurements were used to guarantee reliability and validity of the results.

Blood pressure was measured in the right arm with the sphygmomanometer. Subjects rested for 15 min prior to the blood pressure recording, which was taken twice (mean recorded).

### Statistical analysis

In each of the three study subgroups (normal renal function, hyperfiltration and CKD stages 2–3), the annual slope for GFR (change in GFR expressed as ml/min/year) was used to assess the variability of the prediction equations compared with the isotopic method during the follow-up period. This parameter was determined in each isotopic GFR control for each prediction equation, and compared with respect to its basal values obtained at the start of follow-up. Student’s t-test was used to determine the existence of significant differences between prediction equations and the isotopic method (P < 0.05 with Bonferroni adjusted for five contrast tests). Pairwise comparisons between the estimation of predictive equations and the isotopic method were made by the method of Bland and Altman [7]. The SAS v 8.2 software (Ref: SAS v 8.2, SAS Institute Inc.; Cary, NC, USA) was used for the statistical analysis.

### Results

The cohort of patients with type 2 diabetes was followed using isotopic determination of GFR for a mean of 10.2 ± 2.2 years (range: 7–15). A mean of six isotopic GFR (range: 4–8) was determined during the follow-up period in all patients. The mean value of GFR with $^{125}$I-iothalamate during the follow-up period was $101.8 \pm 35.6 \text{ ml/min/1.73 m}^2$ (range: 30–225). The accuracy of the prediction equations expressed as the slope for GFR (ml/min/year) in each of the three groups (normal renal function, hyperfiltration and CKD stages 2–3) is summarized in Tables 2 and 3.

#### Table 2. Comparison of prediction equations in normal renal function and hyperfiltration groups of type 2 DM patients during the follow-up period

<table>
<thead>
<tr>
<th>Method of GFR estimation</th>
<th>Mean baseline value</th>
<th>Slope for GFR$^b$ (ml/min/year)</th>
<th>P-value$^c$</th>
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</thead>
<tbody>
<tr>
<td><em>Normal renal function</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{125}$I-iothalamate$^a$</td>
<td>115.3 ± 14.0</td>
<td>−3.0 ± 2.3</td>
<td>–</td>
</tr>
<tr>
<td>MDRD</td>
<td>67.7 ± 15.0</td>
<td>−1.0 ± 1.9</td>
<td>0.0005</td>
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<tr>
<td>sMDRD</td>
<td>69.1 ± 15.0</td>
<td>−0.7 ± 1.5</td>
<td>0.0005</td>
</tr>
<tr>
<td>CG</td>
<td>74.1 ± 14.0</td>
<td>−0.9 ± 1.4</td>
<td>0.0005</td>
</tr>
<tr>
<td>100/SCr</td>
<td>102.2 ± 17.2</td>
<td>−0.3 ± 1.9</td>
<td>0.0005</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>78.1 ± 40.1</td>
<td>+0.1 ± 4.9</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Hyperfiltration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{125}$I-iothalamate$^a$</td>
<td>159.0 ± 18.6</td>
<td>−4.8 ± 4.7</td>
<td>–</td>
</tr>
<tr>
<td>MDRD</td>
<td>78.2 ± 16.8</td>
<td>−0.8 ± 2.3</td>
<td>0.0010</td>
</tr>
<tr>
<td>sMDRD</td>
<td>88.5 ± 31.9</td>
<td>−1.0 ± 2.5</td>
<td>0.0010</td>
</tr>
<tr>
<td>CG</td>
<td>98.0 ± 25.3</td>
<td>−1.2 ± 2.5</td>
<td>0.0015</td>
</tr>
<tr>
<td>100/SCr</td>
<td>122.5 ± 37.9</td>
<td>−0.9 ± 3.1</td>
<td>0.0005</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>77.3 ± 31.4</td>
<td>+1.8 ± 9.2</td>
<td>0.0345</td>
</tr>
</tbody>
</table>

$^a$GFR by $^{125}$I-iothalamate clearance (ml/min/1.73 m$^2$).

$^b$Slope for GFR (change/year) calculated as ml/min/1.73 m$^2$/year.

$^c$Student’s t-test: GFR slopes obtained with different methods compared with $^{125}$I-iothalamate [the reference method (Bonferroni adjusted)].

$^d$MDRD, simplified MDRD equation (ml/min/1.73 m$^2$); sMDRD, simplified MDRD equation (ml/min/1.73 m$^2$); CG, Cockcroft-Gault formula (ml/min/1.73 m$^2$); 100/SCr, reciprocal of creatinine [100/SCr (mg/dl)] and creatinine clearance (ml/min/1.73 m$^2$).

$^e$Normal renal function: 294 $^{125}$I-iothalamate determinations during the follow-up period in 47 type 2 DM patients. **Hyperfiltration: 144 $^{125}$I-iothalamate determinations during the follow-up period in 27 type 2 DM patients. All data are expressed as mean ± SD.
In the normal renal function group [GFR: 140–90 ml/min/1.73 m² (294 125I-iothalamate determinations during the follow-up period in 47 type 2 DM patients)], the mean baseline value of isotopic GFR was 115.3 ± 14 ml/min/1.73 m² (range: 90–140), with a mean age of 58 ± 8.5 years (31–77 years; 33 women/14 men) and a mean SCr value during the follow-up period of 90.1 ± 19.4 μmol/l (range: 53.4–191.8). In this group, the slope for GFR was −3.0 ± 2.3 ml/min/year. As shown in Table 2, all the prediction equations were inaccurate compared with the isotopic GFR and differed statistically and significantly (P < 0.01).

In the hyperfiltration group [GFR > 140 ml/min/1.73 m² (144 125I-iothalamate determinations during the follow-up period in 27 type 2 DM patients)], the mean baseline value of isotopic GFR was 159 ± 18.6 ml/min/1.73 m² (range: 140–208.8), with a mean age of 52 ± 9.2 years (31–71 years; 14 women/13 men) and a mean SCr value during the follow-up period of 81.3 ± 17.6 μmol/l (range: 35.3–142.3). In this group, the slope for GFR during the follow-up period was −4.8 ± 4.7 ml/min/year. As shown in Table 2, all the prediction equations were inaccurate compared with the isotopic GFR and differed statistically and significantly (P < 0.01).

Finally, in CKD stages 2–3 group [GFR: 89–30 ml/min/1.73 m² (87 125I-iothalamate determinations during the follow-up period in 13 type 2 DM patients)], the isotopic GFR value obtained was 71.2 ± 13.9 ml/min/1.73 m² (range: 30–87), with a mean age of 63 ± 7.9 years (44–79 years; 6 women/7 men) and a mean SCr value during the follow-up period of 133.4 ± 50.3 μmol/l (range: 51.2–302.3). In this group, the slope for GFR during the follow-up period was −1.4 ± 1.8 ml/min/year. As shown in Table 3, none of the prediction equations, except creatinine clearance, presented statistically significant differences compared with the isotopic technique (P > 0.05). In this situation, the best result during the follow-up period was obtained with the MDRD equation, which presented a slope for GFR of −1.4 ± 1.3 ml/min/year (P: NS) compared with the CG formula −1.0 ± 0.9 ml/min/year (P: NS).

### Discussion

The main aim of this study was to evaluate the accuracy of different prediction equations for the ambulatory follow-up of a cohort of patients with type 2 DM. From the results obtained, it can be concluded that the application of these equations is inadequate in situations of normal renal function and hyperfiltration. Only in CKD stage 2 levels (GFR < 90 ml/min/1.73 m²) can they be used (except creatinine clearance) in the ambulatory accurate control of this group of patients.

Isotopic GFR is considered to be the gold standard for estimating renal function. At present, its determination using 125I-iothalamate is impossible since it is not available on the market. However, it is not always convenient to apply this method in clinical practice owing to its high cost and lack of availability in primary care centres. For this reason, several prediction equations have been developed for the estimation of GFR from parameters easily measured in the clinic. These equations have been applied in different patients with diverse grades of renal function [8,9]. Very few studies have evaluated the use of these equations in patients with type 2 diabetes. In the study by Levey et al. [3], in the validation of the MDRD equation some of the 558 patients had chronic renal insufficiency caused by type 2 diabetes, although the exact number is not specified. Furthermore, those authors suggested the need to conduct studies aimed at evaluating the application of that prediction equation in type 2 diabetic patients. There are very few published studies that analyse the monitoring of renal function using the application of prediction equations. One notable study was that conducted in 30 Pima Indians with type 2 diabetes during a 4 year follow-up and GFR > 120 ml/min/1.73 m² at baseline.
examination [10]. Among the conclusions, the authors suggested the use of measurements of serum cystatin C (100/cystatin C) during the follow-up of type 2 diabetic patients with normal or elevated GFR, since it is the best method for detecting early function decline. In contrast, some studies have shown that cystatin C may have significant limitations as a marker of kidney function in certain diseases [11]. Unfortunately, at the start of the study, cystatin C was not available at our centre for us to be able to estimate GFR during the follow-up of our cohort of type 2 DM patients. Recent studies [12], conducted in hypertensive patients,
Accuracy of prediction equations in patients with diabetes

conclude that the mean renal extraction of cystatin C was equal to the mean renal extraction of $^{125}$I-iothalamate. However, the authors discuss the application and use of cystatin C as a GFR marker, owing to a lower glomerular sieving coefficient and possible modifications subject to the action of some antihypertensive agents (such as angiotensin converting enzyme inhibitors or angiotensin II antagonist) also widely used in patients with diabetic nephropathy.

The estimation of renal function from the SCR concentration is associated with numerous errors, e.g., it is dependent on production proportional to muscle mass, is influenced by age and sex and by variable tubular secretion and reabsorption, is not very sensitive to the initial reductions in glomerular filtration and is subject to a minimal extrarenal elimination (intestinal). The interference of chromogens [13] in the determination of SCr deserves special mention. Substances such as glucose and ketone bodies can cause false elevation in plasma concentrations up to 20%, resulting in underestimation of creatinine clearance.

For all these reasons, we believe it is of interest to study the behaviour of these equations in patients with type 2 diabetes. From our work, which concurs with those of the other authors [14], we believe creatinine clearance to be the equation with less accuracy and greater variability in the estimation of GFR during the follow-up period [Figure 1], including the CKD stages 2–3 group (Table 3). This variability in estimation may be attributed to problems in the collection of samples and inter-hospital differences in calibration methods, which result in over- and underestimation of renal function [15].

As in previous studies [16], we showed the hyperfiltration situation, with a greater slope for GFR compared with normal filters, to be a marker of poor evolution and worse renal function deterioration in type 2 diabetic patients. As in the abstract published by Rossing et al. [17] and according to our results (Table 2 and Figure 1), we believe these prediction equations in hyperfiltration and normal renal function to be inaccurate in normal clinical practice, since they significantly underestimated the isotopic method during the follow-up period ($P < 0.05$).

In accordance with the study by Viktorsdottir et al. [18] conducted in non-diabetic patients, we believe the predictive capacity of those equations to be limited when kidney failure is absent. For this reason, their application in the design of epidemiological studies aimed at establishing the stratification of the different CKD stages (published in the K/DOQI guidelines) [19], and their correlation with different cardiovascular risk factors, could lead to significant methodological errors being made.

Our results coincide with those of Poggio et al. [20] who proposed using the MDRD equation to monitor diabetic patients with moderate-to-advanced kidney disease. This premise is based on the cross-sectional analysis made in the subgroup of 249 diabetic patients with a GFR calculated with $^{125}$I-iothalamate of $24 \pm 21 \text{ml/min/1.73 m}^2$ (thus nearly classifiable as CKD stage 4). In view of our results, we consider the MDRD equation to be the best prediction equation for the ambulatory monitoring of type 2 diabetic patients. Furthermore, we consider it necessary to conduct European multicentre studies with this kidney function range.

As shown in Table 3, it is from CKD stage 2 (GFR: $<90 \text{ml/min/1.73 m}^2$) that, with the exception of creatinine clearance, the prediction equations can be started to be used for the ambulatory monitoring of this group of patients. During the follow-up period, no statistically significant differences ($P > 0.05$) were observed regarding the slope for GFR (change/year) obtained using $^{125}$I-iothalamate. Figure 1 graphically demonstrates how creatinine clearance proves to be the equation with greater variability and inaccuracy, even in situations of CKD stages 2–3. With respect to reciprocal of creatinine, we believe it excessively overestimates the GFR and, in more advanced stages of chronic renal insufficiency, could lead to severe errors being made in the application of therapeutic measures aimed at programming substitution renal treatment.

In conclusion, based on our results, the use of the prediction equations during the follow-up period of type 2 diabetic patients proved inaccurate in cases of hyperfiltration and normal renal function. It is in situations of CKD stages 2–3 (GFR: 89–30 ml/min/1.73 m$^2$), with mean SCr levels ≥133 μmol/l (1.5 mg/dl), that the MDRD equation can be started to be used for GFR estimation during the monitoring and follow-up of patients with type 2 diabetes receiving insulin and/or oral anti-diabetic drugs.

Acknowledgements. The authors wish to thank Ms. Christine O’Hara for help with the English version of the manuscript.

Conflict of interest statement. None declared.

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Received for publication: 24.11.05
Accepted in revised form: 29.3.06