An Overview of Errors and Flaws of Estimated GFR versus True GFR in Patients with Diabetes Mellitus

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Key Words
Estimated GFR · Type 2 diabetes mellitus · Glomerular filtration rate · Formulas

Abstract
The determination of renal function is crucial in patients with type 2 diabetes (T2DM), a population at risk for chronic kidney disease (CKD). Glomerular filtration rate (GFR) can be measured (mGFR) with gold standard methods or estimated (eGFR) with formulas. Since 1957, when Effersoe published the first formula, more than 50 equations have been developed to estimate GFR. In this review, we examined the studies that compared mGFR and eGFR in patients with T2DM to analyze the performance of those formulae in this population. In cross-sectional studies, the average error of eGFR was ±30% of mGFR. Thus, in a patient with mGFR of 60 mL/min, eGFR may vary from 42 to 78 mL/min. Moreover, many patients were misclassified according to CKD stages. Formulas failed to detect glomerular hyperfiltration. In longitudinal studies, eGFR poorly reflected real GFR decline over time. All studies showed that eGFR decline was slower than mGFR decline. Notably, no major improvement in accuracy and precision has been observed since 1957 despite the use of cystatin-c. Thus, formulas are not reliable indicators of GFR in patients with T2DM. In clinical studies, where GFR is the main outcome measure of the study, eGFR should be avoided.

Cross-Sectional Studies
Beauvieux et al. [4] evaluated a series of creatinine- or cystatin-c-based equations in 124 patients in whom GFR was measured with 51Cr-EDTA (Table 1). The proportion

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Table 1. Cross sectional and longitudinal studies that evaluated the agreement between mGFR with a gold standard method and eGFR using formulas. Limits of agreement were calculated with the Bland and Altman test.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
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<td><strong>Cross-sectional</strong></td>
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<td>Beauvieux et al. [4]</td>
<td>124</td>
<td>Creatinine: MDRD, CG, Rule Cystatin-C: Arnal-Dade, Mclsaac, Tan, Rule</td>
<td>Percentage of eGFR included within ±30% of mGFR: creatinine: MDRD: 50%, CG: 68%, Rule: 62%; cystatin-C: Arnal-Dade: 64%, Mclsaac: 55%, Tan: 59%, Rule: 67% 40–50% of eGFR showed an error &gt;30% of mGFR</td>
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<td>Iliadis et al. [5]</td>
<td>460</td>
<td>Creatinine: MDRD, CKD-EPI Cystatin-C: Rule, Perkins, Arnal, Tan, Stevens, Mclsaac, Grubb, Tidman, Flodin Creatinine + cystatin-C: Stevens</td>
<td>Percentage of eGFR included within ±30% of mGFR: creatinine: MDRD: 79%, CKD-EPI 81%; cystatin-C: Rule: 53%, Perkins: 21%, Arnal: 45%, Mclsaac: 46%, Stevens: 54%, Tan: 79%, Grubb: 69%, Tidman: 40%, Flodin: 43%; creatinine + cystatin-C: Stevens: 70% 20–80% of eGFR showed an error &gt;30% of mGFR</td>
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<td>Rigalleau et al. [6]</td>
<td>200</td>
<td>Creatinine: MDRD, CG, Rule</td>
<td>Limits of agreement (mL/min): MDRD: –50 to +35; CG: –45 to +55; Rule: –35 to +45 Wide limits of agreement for all creatinine based formulas</td>
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<td>MacIsaac et al. [7]</td>
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<td>Creatinine: MDRD, CKD-EPI</td>
<td>Percentage of eGFR included within ±30% of mGFR: creatinine: MDRD: 86%, CKD-EPI 90% Limits of agreement (mL/min): MDRD: –34 to 31; CKD-EPI: –30 to 27 10–15% of eGFR showed an error &gt;30% of mGFR</td>
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<td>Silveiro et al. [8]</td>
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<td>Creatinine: MDRD, CKD-EPI</td>
<td>Percentage of eGFR included within ±30% of mGFR: creatinine: MDRD: 64%, CKD-EPI 67% 30–40% of eGFR showed an error &gt;30% of mGFR</td>
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<td>Maple-Brown et al. [9]</td>
<td>224</td>
<td>Creatinine: CKD-EPI</td>
<td>Percentage of eGFR included within ±30% of mGFR: creatinine: MDRD: 79%, CKD-EPI 87% CG: 71% 15–20% of eGFR showed an error &gt;30% of mGFR</td>
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<td>Inker et al. [10]</td>
<td>1,726</td>
<td>Creatinine: CKD-EPI</td>
<td>Percentage of eGFR included within ±30% of mGFR: ~90% for all the formulas 10% of eGFR showed an error &gt;30% of mGFR</td>
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<td><strong>Longitudinal</strong></td>
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<td>Rossing et al. [11]</td>
<td>383</td>
<td>Creatinine: CG, MDRD (follow-up: 6.5 years)</td>
<td>GFR baseline: Limits of agreement (mL/min): CG: –59 to 33; MDRD: –66 to 25 GFR decline: Limits of agreement (mL/min): CG: –8.15 to 6.8; MDRD: –8.5 to 6.3 eGFR decline slower than mGFR decline</td>
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<td>Fontseré et al. [12]</td>
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<td>MDRD, CG, 24h cr-cl, 100/SCr (follow-up: 10 years)</td>
<td>GFR decline: Normal renal function: mGFR: –3 ± 2 mL/min/year; MDRD: –1 ± 2; CG: –0.9 ± 1; 24h cr-cl: 0.1 ± 5. Hyperfiltration: mGFR: –5 ± 5 mL/min/year; MDRD: –0.8 ± 2; CG: –1 ± 2.5; 24h cr-cl: 2 ± 9 CKD 2–3: mGFR: –1.4 ± 1.8 mL/min/year; MDRD: –1.4 ± 1.3; CG: –1 ± 0.9; 24h cr-cl: 2 ± 8.1 eGFR decline slower than mGFR decline</td>
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<td>Wood et al. [13]</td>
<td>152</td>
<td>CKD-EPI (follow-up: 11 years)</td>
<td>mGFR decline: 2.6 mL/min/year eGFR decline: 1.6 mL/min/year</td>
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<td>Gaspari et al. [14]</td>
<td>600</td>
<td>Creatinine: CG, MDRD, CKD-EPI, Rule, Ibrahim, Mawer, Hull, Davis–Chandler, Gates, Walser, Effersöe, Edwards–Whyte, Jelliffe 1, Jelliffe 2, Björnsson (follow-up: 4 years)</td>
<td>GFR baseline: TDI: % from 32 (Rule) to 92 (Jelliffe-2); CG: 51, CKD-EPI: 41; MDRD: 52; Effersöe: 55 CCC from 0.21 (Jelliffe-2) to 0.52 (Rule); CG: 0.43, CKD-EPI: 0.43; MDRD: 0.38; Effersöe: 0.31. Hyperfiltration was not diagnosed by any formula in 75% of the cases GFR decline. CCC from –0.21 (Effersöe) to 0.36 (Hull); CG: 0.35, CKD-EPI: 0.28; MDRD: 0.32 eGFR decline slower than mGFR decline</td>
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<td>Perkins et al. [16]</td>
<td>30</td>
<td>Creatinine: CG, MDRD</td>
<td>GFR decline: (% of annual decline): mGFR –4.4 ± 10.3% CG: –3.4 ± 8.4%; MDRD: –2.8 ± 10.3% eGFR decline slower than mGFR decline</td>
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eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CG, Cockroft-Gault; MCQ, Mayo Clinic Quadratic equation; 24h cr-cl, 24 h creatinine clearance; TDI, total deviation index; CCC, concordance correlation coefficient.
of eGFR values within ±30% of mGFR ranged from 50% (Cockroft-Gault, CG) to ~70% (Rule and Modification of Diet in Renal Disease, MDRD; Table 1), indicating poor agreement between these formulae and mGFR. The boundary of ±30% of mGFR, which is a standard method to evaluate the performance of eGFR, is certainly a wide margin of error. For example, in a patient with mGFR of 60 mL/min, eGFR may range from 42 to 78 mL/min. Moreover, when 70% are included within this range, 30% of the estimations (one case in 3) have an even greater variability, that is, eGFR <42 and >78 mL/min for the above example. Such variability is clearly unacceptable from a clinical perspective.

Iliadis et al. [5] evaluated renal function in 460 patients with 51Cr-EDTA and 12 creatinine- or cystatin-c-based formulae. The proportion of eGFR values within ±30% of mGFR ranged from 21% (Perkins) to 81% (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI; Table 1). Rigalleau et al. [6] compared the CG, MDRD, and Rule equations with mGFR (51Cr-EDTA) in 200 patients. According to the Bland and Altman plot, formulae showed extreme limits of agreement with mGFR, from ~50 to 55 mL/min. As a consequence of this bias, 35% of the cases were misclassified based on chronic kidney disease (CKD) stages.

The lack of accuracy and precision of formulae have also been observed in patients with normal renal function. MacIsaac et al. [7] compared CKD-EPI and MDRD equations with mGFR (diethylenetriamine pentaacetic acid, DTPA) and observed wide limits of agreement, from ~30 to 30 mL/min. Also, 80–90% of eGFR values fell within the wide limits of ±30% of mGFR. In the same line, Silveiro et al. [8] observed that both CKD-EPI and MDRD underestimated mGFR by about 20 mL/min.

In indigenous Australians, comparison between eGFR (CKD-EPI, CG, and MDRD) and mGFR (plasma clearance of iohexol) in a population at high risk for T2DM showed that 71–87% of the estimations fell within ±30% of mGFR [9]. This error was similar in patients with and without impaired renal function.

Of note, this error was also evident in the original studies that described the formulae for the first time. Inker et al. [10] developed equations based on cystatin-c alone or in combination with creatinine in a subgroup of patients with diabetes. However, the P30 for the CKD-EPI equations with creatinine and or cystatin-c was similar, that is, ~90%.

Based on the above evidence, it seems clear that formula-derived estimations are grossly inaccurate in reflecting real renal function in patients with CKD or normal renal function. This wide error of ±30% would be unacceptable for other measurements of risk factors like body mass index or blood pressure. Thus, standard thresholds of agreement used to validate a formula, that is, ±30% of mGFR are too ample to be useful from a clinical point of view, since they lead to the acceptance of extreme variability between estimations and real renal function.

Longitudinal Studies with Repeated Measurements of GFR

One of the consequences of the errors in formulae is that they do not detect changes in GFR over time. Rossing et al. [11] evaluated 383 patients with T2DM and microalbuminuria or overt nephropathy. GFR was measured annually with 51Cr-EDTA and estimated CG and MDRD formulas during a mean follow-up of 6.5 years. At baseline, both formulas showed wide limits of agreement with mGFR, that is, from ~66 to 31 mL/min. During follow-up, mean mGFR decline was ~4–5 mL/min/year while eGFR decline was ~1 mL/min slower. Also, eGFR decline showed wide limits of agreement compared with mGFR decline (Table 1). Fontseré et al. [12] evaluated 87 T2DM patients with normal renal function, glomerular hyperfiltration and CKD using mGFR (iothalamate) and eGFR with CG, MDRD, and 24-h creatinine clearance every 24 months during 10 years. As in the previous study, eGFR decline was slower than the real GFR decline. In general, GFR decline assessed by CG or MDRD only reflected 25% of real decline, that is, ~4 mL/min/year (mGFR) vs. ~1 mL/min/year (eGFR). In patients with CKD, mGFR and eGFR decline were similar, but the decrease in the number of patients (n = 13) limits the interpretation of this result. Finally, 24-h creatinine showed stable GFR decline or even improvement of renal function over time compared with mGFR decline. A slower renal function decline when evaluated with eGFR than mGFR in patients with T2DM has also been described for the CKD-EPI equation [13].

Gaspari et al. [14] evaluated the performance of 15 creatinine-based formulae in 600 patients with T2DM in whom GFR was measured by plasma clearance of iohexol (mGFR) every 6 months during a mean follow-up of 4 years. The authors evaluated the bias between eGFR and mGFR with specific statistics of agreement for continuous variables: the concordance correlation coefficient (CCC), the total deviation index (TDI), and the coverage probability (CP) [15]. In brief, CCC simultaneously combines accuracy and precision, and it is scored from 0 to 1, and a value >0.90 reflects excellent concordance. TDI captures a large proportion of data within a boundary for
allowed differences between estimations and measurements. This is considered the best approach to evaluate the agreement between eGFR and mGFR [15]. The results of this study are discouraging. At baseline, TDI for the 15 formulae was ~40%, which means that 90% of the estimations fell within ±40% of mGFR. This was observed in patients with CKD, normal renal function, or glomerular hyperfiltration. Also, these formulae failed to detect hyperfiltration in most cases. Renal function decline was slower when estimated with formulas than when measured with the gold standard, that is, mean mGFR decline -3.37 mL/min/year vs. eGFR decline which ranged from -1.34 to 0.34 mL/min/year. Accordingly, eGFR showed low concordance with mGFR decline (CCC <0.40 for all the formulae). The first equation that was developed to estimate renal function (Effersoe 1957) showed a bias comparable to that of more recent formulae like MDRD, CKD-EPI, or even cystatin-based equations (Table 1). Thus, from a historical perspective, no improvement has been observed in the last 50 years in the estimation of GFR, despite the availability of more than 50 formulae and the use of cystatin-c. Finally, the error of eGFR was similar between the formulae that were adjusted or unadjusted for body surface area. The above studies consistently showed that eGFR decline is slower than mGFR decline, making these equations unacceptable for monitoring kidney function in patients with T2DM.

### Clinical Examples

Evaluation of clinical cases is complementary to the analysis of the agreement between mGFR and eGFR. Table 2 shows the performance of 3 formulas of the CKD-EPI “family”: creatinine-, cystatin-, and creatinine-cystatin-based equations in patients with T2DM with diverse degrees of renal function, in whom GFR was measured by plasma clearance of iohexol at Hospital Universitario de Canarias (Tenerife, Spain). Of note, none of these patients had extreme obesity, anorexia, severe sarcopenia, cirrhosis, renal or liver transplantation, or other diseases that could influence creatinine or cystatin-c metabolism. All 3 formulas underestimated true GFR in patient 1 and overestimated true GFR in patient 2, despite a difference of only 9 mL/min between the 2 patients. In patients 1 and 5, all the formulae underestimated the real GFR. On the other hand, these formulae showed one of the following: an acceptable error (<10%), underestimation, or overestimation of GFR in the same patient (cases 3, 4, 6, and 7). For the patients with hyperfiltration (cases 8 and 9), all but one equation reflected the real GFR properly. These cases illustrate a major characteristic of the bias of eGFR, that is, the error is random, not systematic, and therefore unpredictable.

### Conclusions

Patients with T2DM are at risk for major complications like CKD, cardiovascular events, blindness, peripheral neuropathy, and cancer. Many sophisticated methods have been developed to evaluate these diseases. However, renal function, a major outcome in this population is still estimated with an unreliable tool, namely, the eGFR. In patients with T2DM, the estimation of renal function using formulae, either creatinine- or cystatin-based, shows a wide margin of error, which averages ±30% of real GFR, observed in several cross-sectional and longitudinal studies. This error leads to frequent misclassification of CKD, which limits the risk prediction for disease progression. Also, eGFR is not suitable to detect ear-
ly stages of the disease (hyperfiltration) and monitor renal function over time. Importantly, no improvement in the accuracy and precision of eGFR has been observed in the last 5 decades. Use of eGFR in clinical research should be avoided whenever renal function is the main outcome measure of the study. New methods to assess renal function with sufficient accuracy and precision are urgently needed [17]. Finally, the comparison between eGFR and mGFR represents a wide margin of error and should therefore be avoided.

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Search Strategy

We searched PubMed for articles published in English with the terms “glomerular filtration rate,” “estimated glomerular filtration rate,” “measured glomerular filtration rate,” “type 2 diabetes,” “iohexol,” “DTPA,” “iothalamate,” “Cr-EDTA,” “glomerular hyperfiltration,” “diabetic nephropathy,” and “GFR decline.” No date restrictions were placed on searches.

Disclosure Statement

The authors have no conflicts of interest to declare.

References